“A COMPARATIVE STUDY OF INTRATHECAL DEXMEDETOMIDINE 10mcg AND FENTANYL 25mcg AS ADJUVANTS TO 0.5% HYPERBARIC BUPIVACAINE IN SPINAL ANAESTHESIA WITH A CONTROL GROUP’’.

By Dr. HARISH B G

SDUAHER

DISSERTATION SUBMITTED TO
SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, KOLAR, KARNATAKA

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF MEDICINE

IN

ANAESTHESIOLOGY

Under the guidance of

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. **Dr. HARISH B G**

LIST OF ABBREVIATIONS USED

Abbreviation	Full Form
ASA	American society of Anaesthesiologists
CNS	Central nervous system
cms	Centimeters
CSF	Cerebro spinal fluid
CVS	Cardiovascular system
ECG	Electrocardiogram
HR	Heart Rate
Hrs	Hours
I.V	Intravenous
Kg	Kilogram
L_{3-4}	Lumbar Vertebra
ml	Milliliter
Mg	Milligram
Min	Minutes
mm of Hg	Millimeter of mercury
NIBP	Non Invasive Blood Pressure
PR	Pulse rate
SBP	Systolic blood pressure
SpO_2	Percentage of oxygen saturation
VAS	Visual analogue scale

ABSTRACT

"A COMPARATIVE STUDY OF INTRATHECAL DEXMEDETOMIDINE 10mcg AND FENTANYL 25mcg AS ADJUVANTS TO 0.5% HYPERBARIC BUPIVACAINE IN SPINAL ANAESTHESIA WITH A CONTROL GROUP".

Background and objectives:

To compare the effects of intrathecal dexmedetomidine and fentanyl as adjuvants to hyperbaric bupivacaine with a control group in regards to time of onset of sensory, motor blockade, Duration of sensory, motor blockade, Two segment sensory regression time, Duration of effective post- operative analgesia and incidence of side effects.

Materials and Methods:

A randomized, prospective study, after obtaining ethical committee approval in R.L. Jalappa hospital and research center was done on 90 adult Patients of either sex, aged between 20 to 45 years, of physical status ASA Grade I and Grade II undergoing elective lower abdominal and lower limb surgeries under spinal anaesthesia after obtaining written informed consent. They were divided into 3 groups of 30 each. Group D received 15mg hyperbaric bupivacaine with 10mcg dexmedetomidine in 0.5ml of normal saline. Group F received 15mg hyperbaric bupivacaine with 25mcg fentanyl. Group C received 15mg hyperbaric bupivacaine with 0.5ml of normal saline. The data collected were statistically analyzed using univariate analysis, ANOVA test and post hoc analysis.

Results:

Duration of onset of sensory blockade and motor blockade was (4.04±1.10min), (5±0.55min) in group D, (4.43±0.47 min), (6.10±1.04min) in group F and (5.43±0.53min), (6.40±0.55min) in group C. Duration of motor blockade was (424.67±36.32 min) in group D, (221.83±27.14) in group F and (180.83±24.9) in group C. Two segment sensory regression time was prolonged in group D (168.5±20.68min) compared to group F (103.23±8.82 min) and group C (87.37±5.88min).

CONCLUSION:

Intrathecal Dexmedetomidine is associated with faster onset of sensory and motor blockade, with significantly prolonged sensory, motor blockade and effective post-operative analgesia, hence use of dexmedetomidine as adjuvant to hyperbaric bupivacaine in spinal anaesthesia is an attractive alternative especially in those surgeries requiring long duration compared to fentanyl and control group.

Key words:

$\alpha_{2,}$ adrenoreceptor agonists, bupivacaine, fentanyl, spinal anaesthesia.

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INTRODUCTION

INTRODUCTION

Spinal anaesthesia is a commonly used technique for lower abdominal and lower limb surgeries. It results from the injection of anaesthetic drug into the subarachnoid space. It's a simple technique which is easier to perform with rapid onset of anaesthesia, provide adequate analgesia both intra operatively and post operatively. Polypharmacy and problems associated with airway management of general anaesthesia can be avoided.

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

Spinal anaesthesia can be provided with a wide range of local anesthetics and additives that allow control over the level, time of onset and duration of spinal anaesthesia. Lignocaine was used as local anaesthetic of choice for decades in spinal anaesthesia because of its rapid onset of action, good motor block and shorter duration action. Its implication in causing transient neurological symptoms and cauda equina syndrome following spinal anaesthesia has made its use limited[2].

Hyperbaric bupivacaine 0.5% is three to four times more potent than lignocaine[3], and has prolonged duration of action. Its disadvantages being slow onset of action. Though its duration of action is longer than lignocaine it cannot provide adequate post-operative analgesia.

The discovery of opioid receptors and endorphins in spinal and supraspinal regions soon led to the use of intrathecal opioids. The first opioid used intrathecally to

augment neuraxial block was morphine in 1979. Opioids produce intense and prolonged analgesic action without gross autonomic changes, loss of motor power or impairment of sensation other than pain when injected into subarachnoid space[4].

Morphine a highly hydrophilic agent has slower onset of action. Use of morphine can produce serious side effects like respiratory depression, post-operative nausea and vomiting, pruritus and urinary retention[5].

Fentanyl a highly lipophilic opioid has rapid onset of action and lesser side effects compared to morphine. It has become a very popular intrathecal adjuvant in recent times. Duration of effects of intrathecal fentanyl is dose independent. Side effects include pruritus, nausea and vomiting and rarely serotonin syndrome[6].

Recently intrathecal administration of α-2 adrenoreceptor agonist as adjuvants to local anaesthetics has shown to have sedative, analgesic, hemodynamic stabilizing effect with prolonged duration of spinal block[7].

Clonidine and dexmedetomidine are the two α-2 adrenoreceptor agonists used intrathecally. Dexmedetomidine is a newer drug approved by FDA in 1999 for use in humans for short term sedation (<24hrs) in intensive care unit. It's a highly specific and selective α-2 adrenoreceptor agonist with 8 times more affinity for α-2 adrenoreceptors than clonidine[8].

It's been recently introduced in India and not many studies have been done regarding its use as adjuvant to local anesthetics in intrathecal anaesthesia and study its effect. We have undertaken this study to evaluate and compare the effects of adding dexmedetomidine versus fentanyl to intrathecal hyperbaric bupivacaine with a control group in patients scheduled for elective lower abdominal and lower limb surgeries.

OBJECTIVES

OBJECTIVES OF THE STUDY

To study the effects of adding 10 mcg of dexmedetomidine or 25 mcg of fentanyl to 3 ml of intrathecal bupivacaine for spinal anaesthesia. A control group with plain bupivacaine 3ml with 0.5 ml normal saline is also taken into the study. The objectives of the study are

1. Time of onset of sensory blockade.
2. Time of onset of motor blockade.
3. Time taken for sensory regression by two segments.
4. Duration of sensory blockade.
5. Duration of motor blockade.
6. Duration of effective post-operative analgesia.
7. The incidence of side effects.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

ANATOMY OF VERTEBRAL COLUMN:

The vertebral canal extends from the foramen magnum to the sacral hiatus. It is composed of 33 vertebrae (7 cervical, 12 thoracic, 5 lumbar, 5 fused sacral and 4 coccygeal). With the exception of C1, the cervical, thoracic and lumbar vertebrae consist of body anteriorly, two pedicles that project posteriorly from the body and two laminae that connect the pedicles. These structures form the vertebral canal, which contains the spinal cord, spinal nerves, and epidural space. The laminae give rise to the transverse processes that project laterally and the spinous process that project posteriorly. The pedicles contain a superior and inferior vertebral notch through which the spinal nerves exit the vertebral canal. The superior and inferior articular processes arise at the junction of the lamina and pedicles and form joints with the adjoining vertebrae. The first cervical vertebra ("atlas") differs from this typical structure in that it does not have a body or a spinous process[10].

The vertebral column has four curves, the cervical and lumbar curves are convex anteriorly while the thoracic and sacral curves are convex posteriorly. These curves have significant influence on the spread of local anaesthetics in the subarachnoid space.

The spine of C7 is the first prominent spinous process encountered while running the hand down the back of the neck. The spine of T1 is the most prominent spinous process and immediately follows C7. The 12th thoracic vertebra can be identified by palpating the 12th rib and tracing it back to its attachment to T12. A line drawn between the iliac crests crosses the body of L5 or the 4-5 inter space.

The spinal cord gives rise to 31 pairs of spinal nerves, each composed of an anterior motor root and a posterior sensory root. The nerve roots are in turn composed

of multiple rootlets. The portion of the spinal cord that gives rise to all of the rootlets of a single spinal nerve is called a cord segment. The skin area innervated by a given spinal nerve and its corresponding cord segment is called a dermatome.

Because the spinal cord usually ends between L1 and L2, the thoracic, lumbar, and sacral nerve roots run increasingly longer distances in the subarachnoid space to get from their spinal cord segment of origin to the intervertebral foramen through which they exit. Those nerves that extend beyond the end of the spinal cord to their exit site are collectively known as the cauda equina.

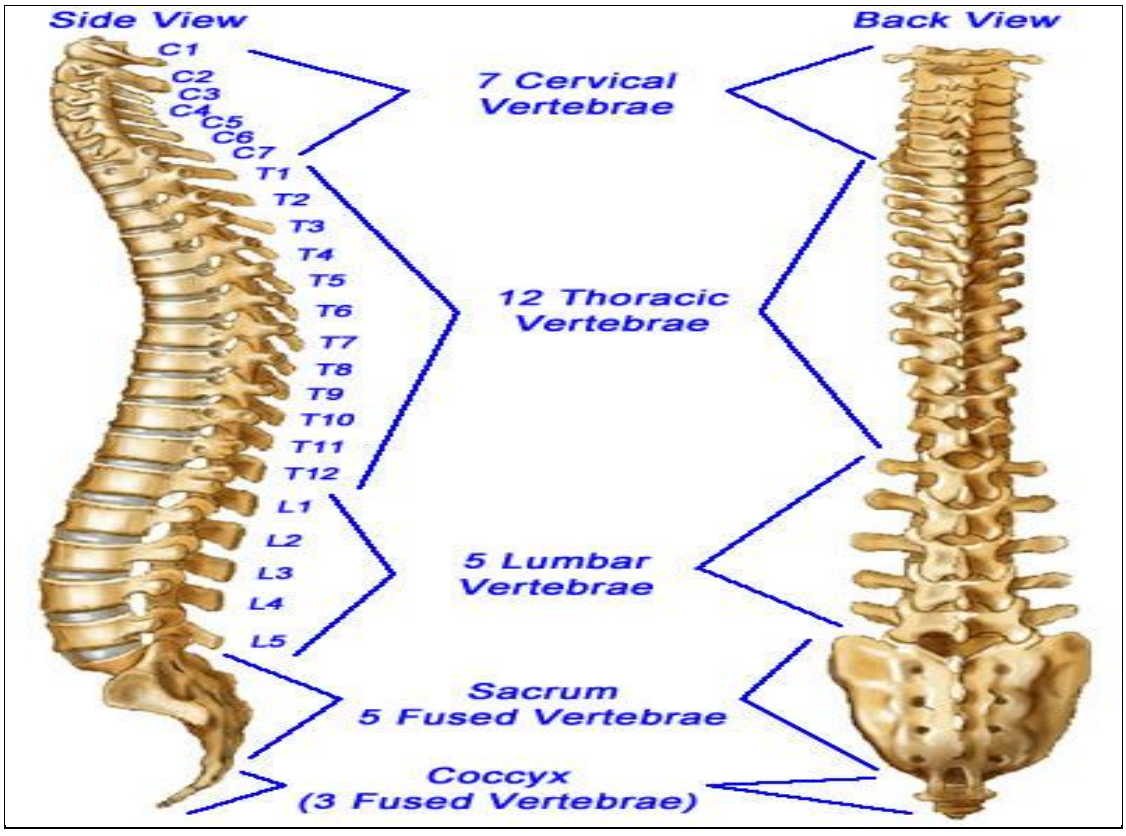


FIGURE 1: CURVES OF THE SPINE

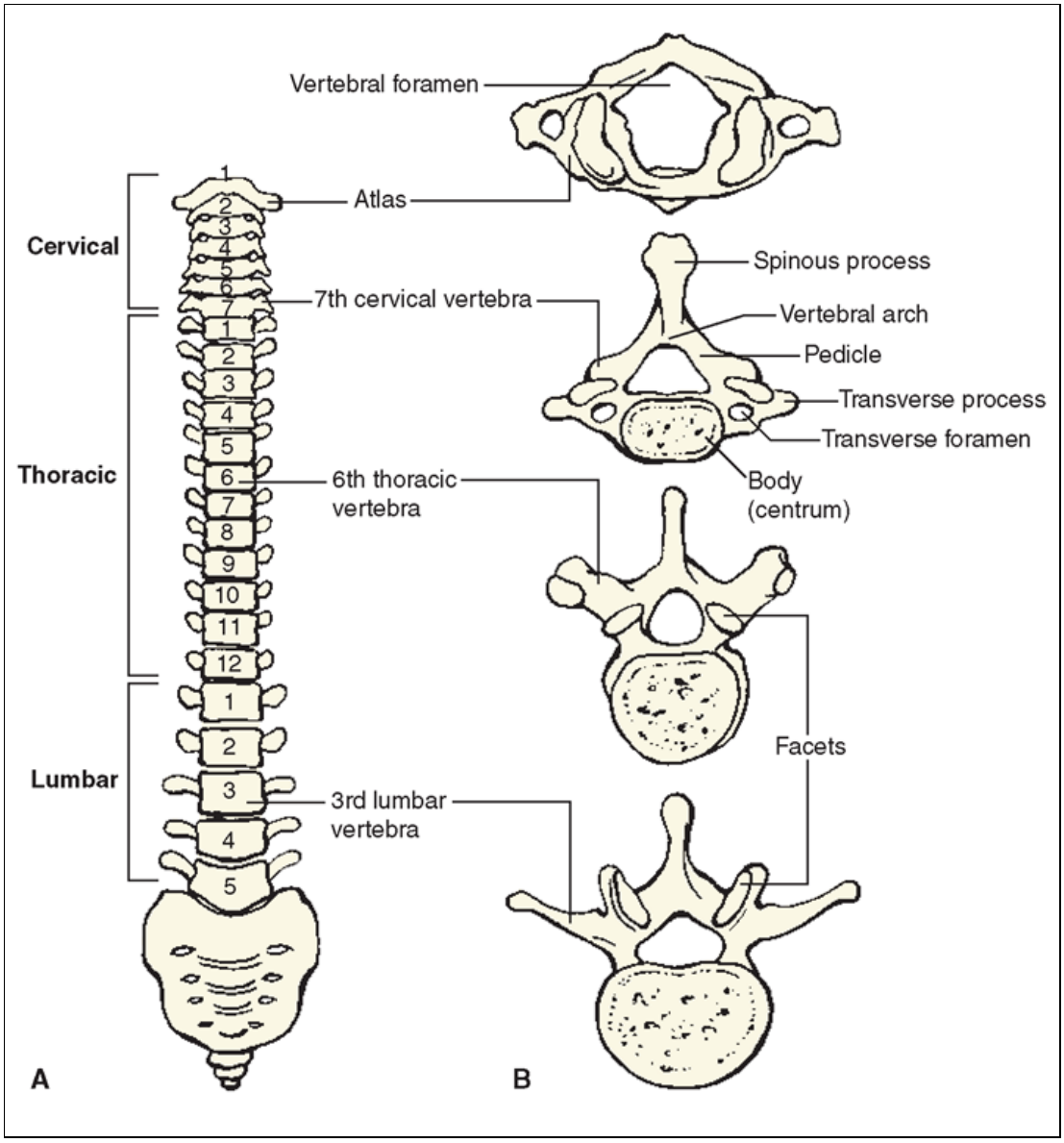


FIGURE 2: VERTEBRAL COLUMN, SUPERIOR VIEW

The vertebral canal is bounded anteriorly by the bodies of vertebrae, intervertebral discs and posterior longitudinal ligament. Posteriorly by the laminae and ligamentum flavum, laterally by the pedicles and laminae. The vertebral canal is narrow at the thoracic level and considerably wider at the cervical and lumbar levels[3, 10].

The vertebral canal is bounded by several ligaments, which give its stability and elasticity.

a) Supraspinous ligament

b) Interspinous ligament

c) Ligamentum flavum

d) Longitudinal ligaments.

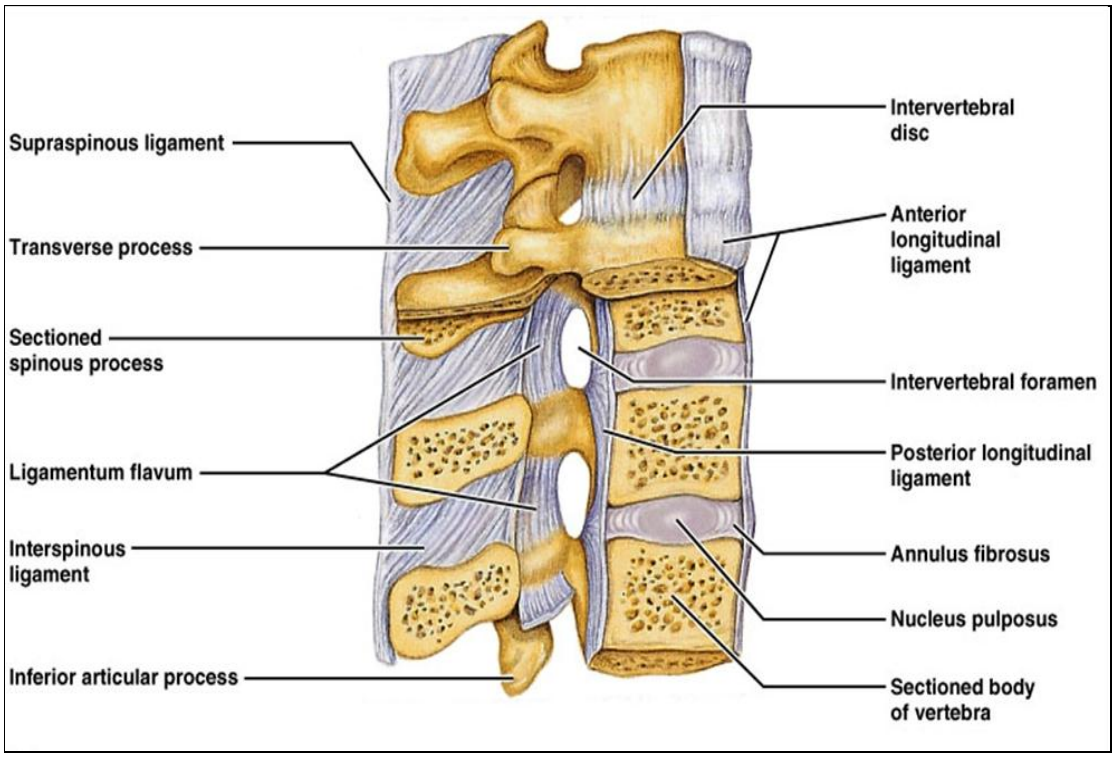


FIGURE 3: LIGAMENTS OF VERTEBRAE

Ligaments of vertebral column[11].

1) **Supraspinous ligament**: It is a strong, thick, fibrous band, connecting the apices of the spines from the seventh cervical vertebra to the sacrum. At the lumbar region it is thick and broad. In the cervical region it blends with neck ligaments to form ligamentum nuchae. Its thickness varies with age and sex.

2) **Interspinous ligament**: The interspinous ligament is a thin fibrous structure, connecting adjacent spines. The fibers are almost membranous and extend from the apex and upper surface of a lower spine towards the root and inferior surface of the next higher vertebra. These ligaments are rectangular in shape. These longitudinal fibers meet the supraspinous ligament posteriorly and tends to blend with the ligamentum flavum in front.

3) **Ligamentum flavum**: This consists of yellow elastic tissue. They extend between lamina from the anterior inferior surface of the upper lamina downwards to the anterior superior surface of the lower lamina. Laterally this ligament begins at the roots of the articular process and extends posteriorly and medially to the point where the laminae join to form the spinous process. Here the two compartments of the ligaments are united thus covering the interlaminar space

The ligament thickness, distance to dura, and skin to dura distance vary with the area of vertebral canal. They constitute slightly more than half of the posterior wall of the vertebral canal. They are thickest and strongest in the lumbar region.

TABLE 1: THICKNESS OF LIGAMENTUM FLAVUM

Characteristics of ligamentum flavum at different vertebral level[1]	
Site	**Thickness of ligament (mm)**
Cervical	1.5-3.0
Thoracic	3.0-5.0
Lumbar	5.0-6.0
Caudal	2.0-6.0

4) **Longitudinal ligaments**: The anterior and posterior longitudinal ligaments bind the vertebral bodies together.

Posterior longitudinal ligament:

Lies within the canal on the posterior surface of bodies of vertebra from which it is separated by basivertebral veins. Ligament is thinnest in cervical and lumbar regions.

Anterior longitudinal ligament:

Runs along the anterior aspect of vertebral bodies.

The cervical, thoracic and lumbar vertebrae have certain differentiating features. Cervical vertebrae differ from thoracic and lumbar vertebrae by the presence of a foramen transversarium in their transverse process for the vertebral artery, spinous process is short and bifid. The thoracic vertebrae differ from cervical and lumbar vertebrae by the presence of articular facets for ribs on their bodies. The lumbar vertebrae differ from thoracic and cervical vertebrae by the presence of large bodies and large vertebral foramen[12].

LUMBAR VERTEBRA:

A typical lumbar vertebrae is made up of the following parts.

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

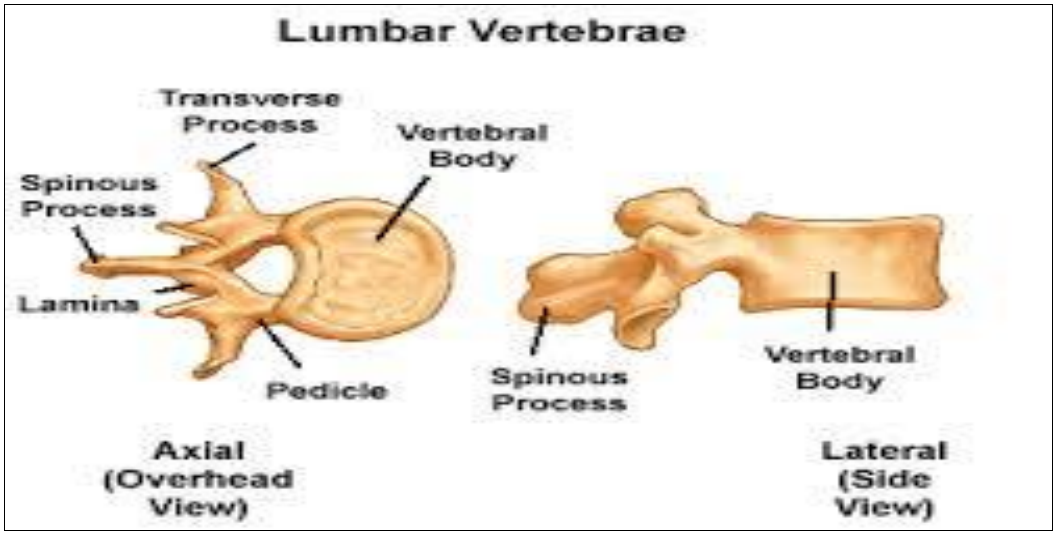


FIGURE 4: TYPICAL LUMBAR VERTEBRAE

BODY:

It is kidney shaped. The flat articular surfaces are covered with hyaline cartilage, which are firmly united to the fibrocartilagenous intervertebral discs. The anterior and posterior longitudinal ligaments reinforce the union between the bodies.

VERTEBRAL ARCH:

Composed of pedicles and laminae which surround and protect the spinal cord and its coverings. Half of each vertebral arch is divided into two parts by the roots the transverse process. Anteriorly the arch is formed by the pedicles, whose function is to transmit stress. Posteriorly it is formed by the lamina. Four articular facets project from the arches, two are directed upwards and two downwards to articulate with similar processes of adjacent vertebrae.

The superior articular processes arise from the junction of pedicles and laminae. They project upwards behind the pedicles and come to lie above the level of transverse processes and the articular facets on their posterior surface facing backwards and medially. The inferior articular processes extend downwards from the

inferolateral aspects of the laminae and lie below the level of transverse processes and the articular facets.

The pedicles arise from the upper part of the posterolateral surface of the body giving rise to two notches between the body and the pedicles (superior and inferior). When two adjacent vertebrae articulate they form an intervertebral foramen on either side through which the mixed spinal nerve of that particular segment issues. The boundaries of the intervertebral foramen are bounded superiorly and inferiorly by the pedicles of adjoining vertebrae, posteriorly the capsules surrounding the articular processes of adjoining vertebrae and anteriorly by the intervertebral disc and the lower part of the body above it.

The posterior surface of the body and the vertebral arch together form the boundaries of the vertebral foramen. These foramina collectively form the vertebral canal, which contain the spinal cord and its covering membranes. The anterior boundary of the vertebral canal is formed by the posterior surface of vertebral bodies and the intervertebral discs covered by the posterior longitudinal ligament. The lateral and posterior wall formed by the vertebral arches are incomplete forming intervertebral foramina laterally through which the segmental spinal nerves passes. Posteriorly the interlaminar foramina through which approach to subarachnoid and epidural space is possible.

Anatomy of the spinal cord[11].

Spinal cord is the continuation of medulla oblongata below the level of foramen magnum terminating as a conical extremity conus medullaris. In first trimester it extends up to the end of sacrum. At birth, the tip of the spinal cord lies at the level of the lower border of L3 and the dural sac at the third sacral vertebrae.

After birth, the lengthening and growth of the cord, as well as the meninges, continue to lag behind the growth of the bony vertebral column. At one year of age, the conus medullaris at the lower border of the second lumbar vertebra and the dural sac ends at the second sacral vertebra. This differential growth rate results in the development of the epidural space and the caudal canal. Between 12-16 years of age, the adult relations are attained, and the spinal cord is located at the lower border of the 1st lumbar vertebrae. This placement is seen in 50% of patient and in about 40% it is located opposite the body of second lumbar vertebrae.

The average length of the spinal cord in males is about 45 cms, and in females it is about 42 cms. The average weight is approximately 30 grams.

Spinal segments:

The spinal cord gives rise to 31 pairs of spinal nerves each containing anterior and posterior sensory roots. The portion of spinal cord giving rise to single nerve is called a cord segment. The skin innervated by a given spinal nerve and its corresponding cord segment is called a dermatome.

There are 31 pair of spinal nerves:

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

Two roots, anterior and posterior join to form a spinal nerve. Sympathetic preganglionic axons arise from cells in the intermediolateral horn of the spinal cord from T1 to L2. Posterior roots are longer than the anterior and the efferent impulses from the whole body including the viscera passes through these roots.

Each posterior root has a ganglion and convey fibers of pain, touch, temperature, 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 line	T4-5
Subcostal	T6-9
Umbilicus	T10
Inguinal region	L4
Perineum	S1-4

Meningeal coverings of the spinal cord[1, 11].

Surrounding the spinal cord in the bony vertebral column are three membranes (from within to the periphery): the pia mater, arachnoid mater, and dura mater.

Dura mater - This layer is the direct extension of the cranial dura mater and extends as spinal dura mater from the foramen magnum to S2, where the filum terminale blends with the periosteum on the coccyx.

Arachnoid mater - this is the middle of the three coverings of the brain and spinal cord. It is a delicate non-vascular membrane closely attached to the dura and ends at the lower border of S2.

Pia mater - this is a delicate, highly vascular membrane, closely investing the spinal cord and brain. Denticulate ligaments are the folds of pia matter that extends laterally along the lines of attachments of the anterior and posterior roots. They act as struts to hold the spinal cord suspended within the subdural space.

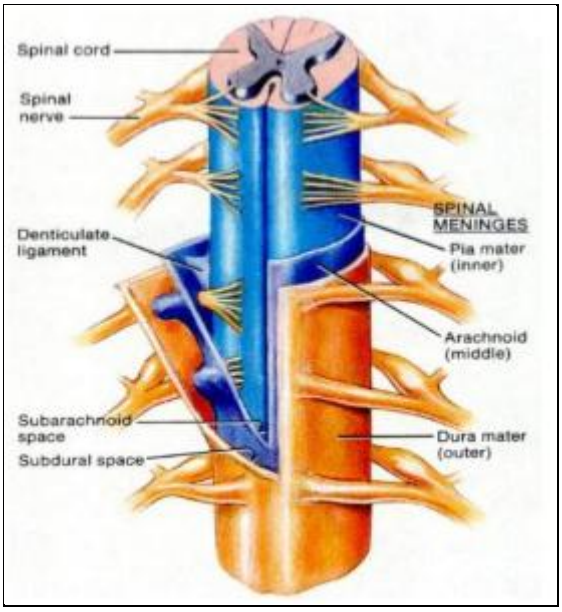


FIGURE 5: MENINGES OF SPINAL CORD

DURAL SPACES[1]:

In the subarachnoid space are the CSF, spinal nerves and blood vessels that supply the spinal cord and the lateral extensions of the pia mater and the dentate ligaments, which supply lateral support from the spinal cord to the dura mater.

Although the spinal cord ends at the lower border of L1 in adults, the subarachnoid space continues to S2. There is a potential space between the dura mater and the arachnoid, the subdural space, which contains only small amounts of serous fluid allowing the dura and arachnoid to move over each other.

Surrounding the dura mater is the spinal epidural space extends from the foramen magnum to the sacral hiatus. The epidural space is bounded anteriorly by the posterior longitudinal ligaments, laterally by the pedicles and the intervertebral foramina, and posteriorly by the ligamentum flavum. Contents of the epidural space include the nerve roots that traverse it from foramina to peripheral locations, as well as fat, areolar tissue, lymphatics, and blood vessels which include the well-organized Batson venous plexus.

CIRCULATION OF THE SPINAL CORD[11].

ARTERIAL SUPPLY TO THE SPINAL CORD.

The principal arterial supply to the spinal cord is derived from one anterior and two pairs of posterior spinal arteries that descend from the level of the foramen magnum.

The anterior spinal artery is formed at the foramen magnum by a branch from the terminal portion of each vertebral artery. This is a large artery and lies in the midline on the anterior median fissure. It descends the entire length of the spinal cord and with contributing arteries, supplies a major portion of the anterior two-thirds of the spinal cord.

The posterior spinal arteries are four longitudinal running vessels—two on each side. One lies in front of the attachment of the dorsal nerve root, and the other or larger artery lies behind the attachment. These arteries are derived at the base of the brain, either directly from the vertebral artery or more often from a primary branch of the posterior inferior cerebellar artery, the largest branch of each vertebral artery. They supply the posterior one third of the spinal cord, i.e., the posterior gray horns and white columns.

Reinforcement of Arterial Supply

Contributing by anastomotic channels to the anterior and posterior spinal cord arteries are a succession of spinal radicular branches arising from local segmental arteries (derived from the aorta) of the vertebral, ascending cervical, posterior intercostal, spinal lumbar and lateral sacral arteries. Each spinal branch divides into an anterior radicular and posterior radicular artery that approaches the spinal cord along the ventral and dorsal roots.

Most of the anterior radicular arteries are small and terminate within the ventral nerve roots or in plexus of the pia around the cord. Frequently, one of these anterior radicular arteries is considerably larger than all the others and is termed the arteria radicularis magna, or the artery of Adamkiewicz. It arises from one of the intersegmental branches of the descending aorta at the lower thoracic or upper lumbar vertebral level usually on the left side (80%). This radicular artery may be responsible for the major blood supply of the lower two-thirds of the spinal cord in about 50% of the population.

The arterial supply to the spinal cord is a delicate system and is quite vulnerable to minor trauma and to vasoconstrictor drugs. Occlusion of the anterior spinal artery produces the anterior spinal artery syndrome denoted by lower limb paralysis without loss of posterior column sensation, i.e, touch, position, vibratory, and joint senses, or cauda equina syndrome denoted by sphincter disturbances.

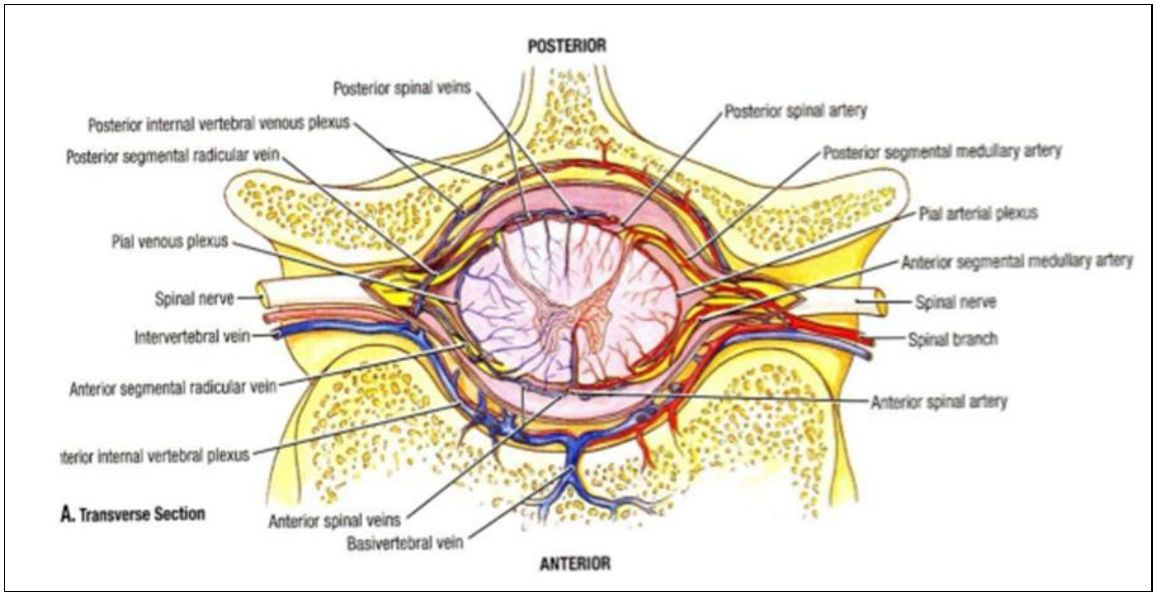


FIGURE 6: BLOOD SUPPLY OF SPINAL CORD

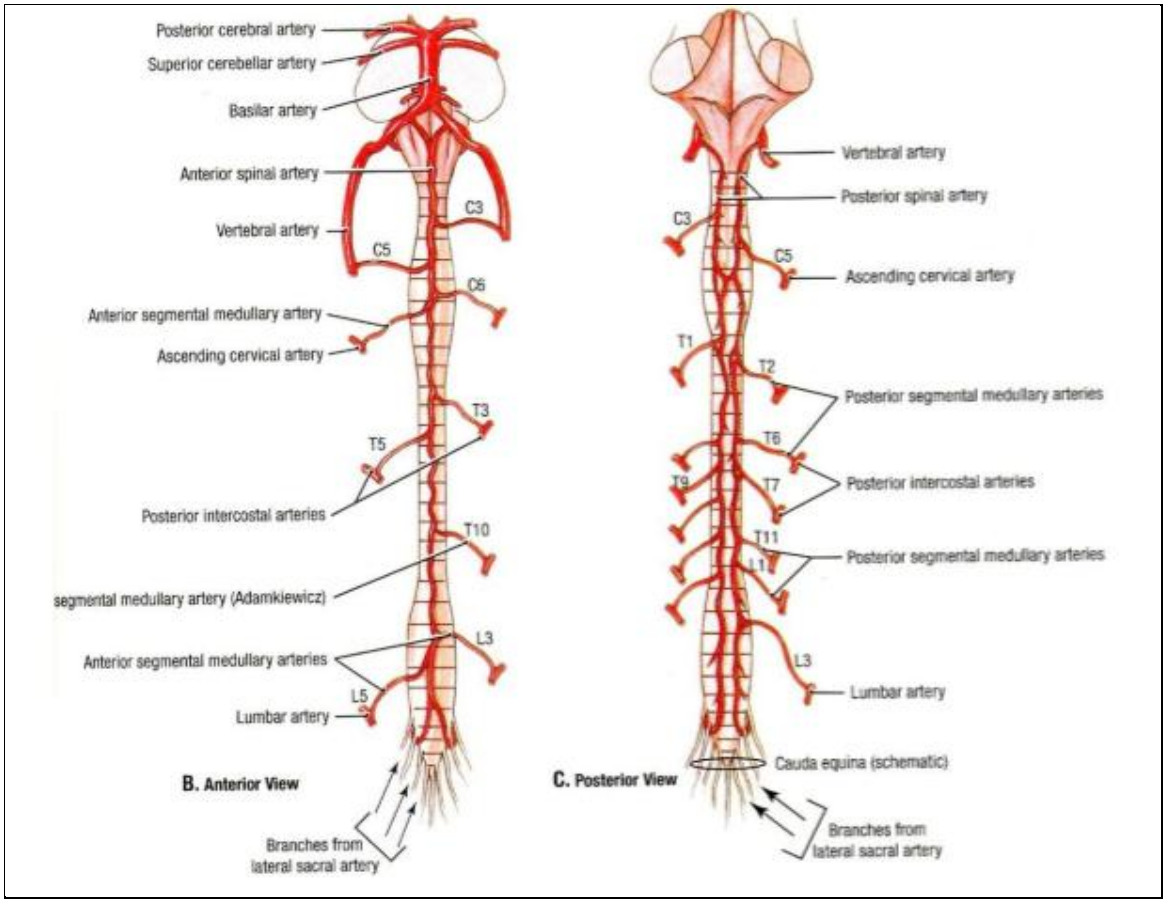


FIGURE 7: BLOOD SUPPLY OF SPINAL CORD

Veins of the spinal cord

The veins of the spinal cord are situated in the pia mater. They are six in number and form longitudinal plexiform channels after draining the parenchyma of the cord. In this plexus, there are (1) two median longitudinal veins, one anterior in the anterior fissure, and the other posterior at the posterior sulcus of the cord, and (2) four lateral longitudinal veins: one pair (posterolateral) runs dorsal to the attachment of the nerve roots and the other pair ventral to the nerve roots (anterolateral). These veins communicate with the internal vertebral plexus, from which blood drains into the intervertebral veins. The intervertebral veins pass out through the intervertebral foramina to the segmental veins and to the external vertebral plexus.

Cerebrospinal Fluid[9, 13].

CSF is a complex solution containing an array of molecules including electrolytes, proteins, glucose, neurotransmitters, neurotransmitter metabolites, cyclic nucleotides, amino acids, among many others. CSF is produced by ultra-filtration of plasma in the choroid plexus and the cerebral/spinal capillaries and by oxidation of glucose, which produces water as a "by-product". The CSF volume is approximately 100 to 160 ml in adult humans and it is produced at the rate of 20 to 25 ml/hr. Consequently, the entire CSF volume is replaced roughly every 6 hours. CSF is removed by arachnoid villi present in the superior sagittal sinus and along many spinal nerve roots.

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

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

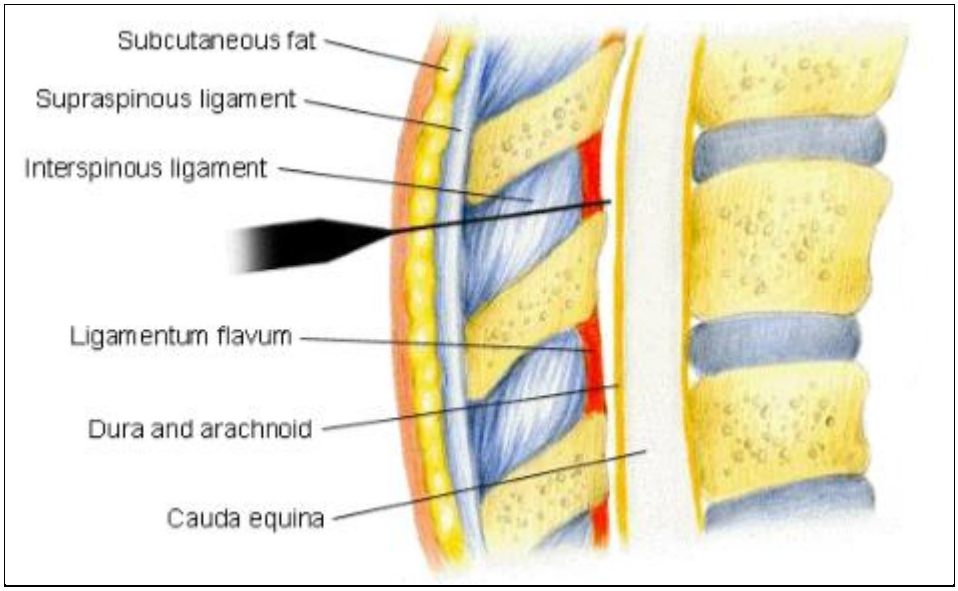


FIGURE 8 STRUCTURES PIERCED DURING SUBARACHNOID BLOCK

PHYSIOLOGY OF SPINAL ANAESTHESIA[1, 14.]

Local anaesthetic deposition in the subarachnoid space leads to loss of sensation and muscle paralysis which is apparent immediately due to direct blocking effects on the transmission of impulses in nerve fibers.

Three sites of action are identified in order of importance.

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

DIRECT EFFECTS:

Primary site of action is specifically on the nerve roots of the spinal cord both anterior and posterior. Blocking effect depends on the size of nerve fiber. Small non medullated sensory fibers of the nerve roots are more sensitive to the anaesthetic agents and motor fibers more resistant

Weaker concentration of local anaesthetic are likely to block sensation without providing motor paralysis. Increased concentration of local anaesthetic blocks both anterior and posterior nerve roots and more intense anaesthesia will be produced with motor paralysis.

Each nerve fiber has differential susceptibility to local anaesthetic action which depends on:

1. Fiber size: small thinly myelinated B fibers carrying sympathetic impulses and non-myelinated C fibers carrying pin prick sensation are easily blocked. Large A fibers carrying motor fibers and medullated proprioceptive fibers has slower onset and shorter duration of block. They are the last to be blocked.

2. The degree of myelination and the distance between the nodes of Ranvier: greater the distance between the nodes and greater the myelination the greater is the resistance to penetration of nerve fiber
3. Functional characteristic: single axon with frequency of impulse transmission are more sensitive to local anaesthetic blockade.

Difference in level of block according to fiber type:

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

Sequence of nerve modality block[11].

1. Vasomotor block - Dilation of skin vessels and increased cutaneous blood flow.
2. Block of cold temperature fibers.
3. Sensation of warmth.
4. Temperature discrimination.
5. Slow pain.
6. Fast pain.
7. Tactile senses.
8. Motor paralysis.
9. Pressure senses.
10. Proprioception and joint senses.

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

Factors determining spread of local anaesthetic solutions within the subarachnoid space[8].

CHARACTERISTICS OF THE LOCAL ANAESTHETIC SOLUTION

Baricity

Local anaesthetic dose

Local anaesthetic concentration

Volume injected

PATIENT CHARACTERISTICS

Age

Weight

Height

Gender

Pregnancy

Patient position

Anatomic configuration of spinal column

TECHNIQUE

Site of injection

Speed of injection

Barbotage

Direction of needle bevel

Addition of vasoconstrictor

Baricity and patient positioning:

Baricity is defined as the ratio of the density (mass/volume) of the local anesthetic solution divided by the density of CSF, which averages 1.0003±0.0003 g/mL at 37°C. Solutions that have the same density as CSF have a baricity of 1.0000

and are termed isobaric. Solutions that are denser than CSF are termed hyperbaric, whereas solutions that are less dense than CSF are termed hypobaric.

Baricity is important in determining local anesthetic spread and thus block height because gravity causes hyperbaric solutions to flow downward in CSF to the most dependent regions of the spinal column, whereas hypobaric solutions tend to rise in CSF. In contrast, gravity has no effect on the distribution of truly isobaric solutions. Thus, the anesthesiologist can exert considerable influence on block height by choice of anesthetic agent and proper patient positioning.

Dose, volume and concentration:

These are interdependent variables affecting block height. When drug dose is held constant, injected volume and drug concentration will not affect block height. Dosage of the drug has a smaller role in determining block height.

Patient characteristics:

Clinical characteristics of a block do not correlate with patient height or age. CSF volume and weight correlate with peak block of height. BMI is a significant predictor of time of onset of sensory block.

Controllable factors:

- Dose (volume x concentration)
- Site of injection
- Baricity of local anaesthetic
- Posture of the patient

Volume and density of cerebrospinal fluid are the two uncontrollable factors determining spread of local anaesthetic.

ACTION ON SPINAL CORD TRACTS:

The main action of local anaesthetic in subarachnoid space is on the nerve roots and nerve root ganglia with subtle effects on the spinal cord tracts.

This is apparent in segmental anaesthesia- segment where the anaesthetic agent is deposited that area is fully blocked and in segment below this, the finer sensation such as touch, temperature and two point discrimination which are conducted by more superficially located fibers in the cord may be blocked. Sensations such as pain, pressure and proprioception which are conducted by ascending fibers located deeper in spinal cord are not blocked.

INDIRECT EFFECTS:

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

Effect on autonomic system:

Blockade of autonomic system varies with the extent of anaesthesia, which is evident by hemodynamic changes. Sympathetic system is usually blocked two segments higher than sensory blockade which will include middle and part of upper splanchnics.

In low spinal (level below T4) lower thoracic and the entire lumbar sympathetics are blocked with significant inactivation of their outflow into superior, middle and inferior splanchnics, thus leading to vagal predominance on splanchnic bed and viscera.

In high spinal (level above T4) most of the sympathetic fibers are blocked. The parasympathetic fibers to the upper part of the body, to the thoracic viscera and most of the abdominal viscera arise from cranial nerves, especially the vagus and remain active.

The consequences of these effects are a number of physiologic disturbances in heart, bronchi and gastrointestinal system.

Cardiovascular system

The cardiovascular effects of spinal anaesthesia are similar in some ways to the combined use of intravenous α1 and β-adrenergic blockers. It decreases heart rate and arterial blood pressure. The sympathectomy that accompanies the technique depends on the height of the block, extending for two to six dermatomes above the sensory level. This results in venous and arterial vasodilatation, but because of the large amount of blood in the venous system (approximately 75% of total blood volume), the venodilation effect predominates because of the limited amount of smooth muscle in venules. Heart rate during high spinal anaesthesia typically decreases as a result of blockade of the cardioaccelerator fibers arising from T1 to T4. The heart rate may decreases as a result of a fall in right atrial filling, which decreases the outflow from intrinsic chronotropic stretch receptors located in the right atrium and great veins on the basis of **"Bainbridge reflex"** (elevation of pressure in great veins or in the atrium produces tachycardia reflexly through stretch receptors, lowering this pressure results in bradycardia).

Within the walls of the ventricles there are nerve endings, which may be activated mechanically either by ventricular distension and stretching or by vigorous and rapid systolic contractions. This reflex is called "**Bezold Jarish reflex"**, which arises from mechano- receptors and chemoreceptors found primarily in the inferoposterior wall of left ventricle. Activation of this reflex results in increased parasympathetic activity and inhibition of sympathetic activity.

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 mins, if left untreated the blood pressure reaches its lowest level in 20-25mins. 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 liters 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 centers in the brainstem. This rare respire tory 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.

Liver

The decrease in hepatic blood flow in spinal anaesthesia parallels with decrease in mean arterial pressure. Liver diseases may interfere with metabolism of local anaesthetic drugs.

Genito urinary function

The decrease in renal blood flow is of little physiological importance following neuraxial blockade. Neuraxial blocks are frequent cause of urinary retention, delaying discharge of outpatients and necessitating catheterization in

patients. S2 and S3 contain small autonomic fibers and their paralysis lasts longer than that of larger sensory and motor fibers. Lower concentration of local anaesthetics are sufficient to cause paralysis of bladder function.

Endocrine effects

Spinal anaesthesia has been shown to inhibit many endocrine metabolic changes associated with stress response. The release of ADH is suppressed during surgery and the spinal block delays the adrenal response to trauma contrary to that of general anaesthesia which shows a rise in blood cortisol levels. It is greater in cases of lower abdominal and lower limb surgeries than in case of upper abdominal and thoracic surgeries due to decrease in afferent sensory input that helps in maintaining stress response.

Body temperature:

Vasodilation favors heat loss. Catecholamine secretion is depressed hence less heat is produced by metabolism.

Fate of injected agents:

Concentration of the local anaesthetic agent decrease immediately following injection into the subarachnoid space. Due to

- Dilution and mixing in CSF
- Diffusion and distribution into neural tissue
- Uptake and fixation by neural tissues
- Vascular absorption and elimination through arachnoid villi or directly from capillary bed of parenchyma.

Complications of spinal anaesthesia[11].

Complications of spinal anaesthesia may be considered as immediate or delayed.

Immediate complications

- Hypotension, bradycardia, cardiac arrest.
- Respiratory impairment
- Difficult spinal puncture
- Traumatic spinal puncture
- Broken needle

Hypotension

Symptoms are related to the tissue hypoxia that results from diminished blood pressure. Hypotension during spinal anaesthesia is because of the physiologic effects of central neuraxial blockade, which is due to two major alterations in cardiovascular systems. First is blockade of sympathetic vasoconstrictor fibers of the arterioles. Arteriolar dilatation results in a decrease in peripheral vascular resistance. The second is actual dilatation of peripheral veins and venules with pooling of blood. This combined with paralysis of skeletal muscle and the loss of muscular milking action plus the interference with the thoracic respiratory pump decreases venous return.

Adequate hydration that is replacement of fluid deficit prior to induction of spinal anaesthesia and proper positioning of the patient after spinal anaesthesia will improve venous return, cardiac output and blood pressure. Once the diagnosis of hypotension is established four procedures are of practical importance.

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

2. Administration of oxygen by simple facemask or nasal catheter will increase oxygen content of blood. This will minimize hypoxia and at the same time relieve dyspnea and ameliorate nausea and vomiting. Occasionally, despite above measures blood pressure will need to be supported with vasopressors.

3. Vasopressors that constrict veins in preference to arterioles provide a more rational method for treating the hypotension. Drugs commonly used are ephedrine, mephentermine, and phenylephrine. The former two have mixed α and β receptor agonist activity and are potent vasoconstrictor whereas the latter is an α receptor agonist and a more potent arteriolar vasoconstrictor.

4. Head down position: About $5\text{-}8^0$ of head low position will increase venous refilling of the heart and the pulmonary blood volume. The result is an increase in stroke volume and cardiac output with a rise in blood pressure. This can only be done after fixation of local anaesthetic.

Respiratory impairment-

This is related to high spinal anaesthetic levels with ascending blockade of the thoracic and the cervical segments, a progressive ascending paralysis of the intercostal muscles and diaphragm ensues. This leads to respiratory insufficiency and apnea. Respiratory arrest may be due to hypoperfusion of respiratory center in brainstem following hypotension.

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

Traumatic spinal puncture:

Repeated attempts to achieve a spinal tap may result in direct trauma to nerves, to periosteum of vertebra, to intervertebral discs and to shearing of spinal nerves. Blood tap tends to neutralize the effectiveness of local anaesthetics while blood in the sub arachnoid space may produce arachnoiditis.

Late complications[11].

Post spinal anaesthesia headache was first documented by August Bier in 1899. Classically, the spinal headache appears on the second or third post-operative day. It is postural in nature, aggravated or appearing with assumption of the erect position and relieved by recumbency. Terms used to describe the headache include the following, roughly in order of frequency: constricting weight of the head, pressure in the head, throbbing sensation; top blowing off; and occasionally a vacuum-like sense.

Post spinal headaches are much more frequent in females especially the young female. The greater frequency of spinal anaesthetic headaches occurs in the age group of 20 to 40 years.

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 – produce 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˚.

Mechanism of post-puncture headache

The pathophysiologic mechanism of this headache is that of an imbalance in CSF dynamics. A continuing loss of spinal fluid occurs, and the rate of this loss is greater than the rate of fluid production. A loss of 30 to 50 ml of spinal fluid may be critical and has been demonstrated to produce headache. As a result of diminished CSF, with a fall in spinal fluid pressure, the brain losses its "water cushion" and sags, especially in the upright position. Traction on pain-sensitive supporting structures, including blood vessels, ensues.

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 coagulopathy, skin or soft tissue infection at the proposed site of needle insertion. Severe hypovolemia, preexisting neurological disease.

PHYSIOLOGY OF PAIN[15]

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), is used to describe the neural response only to traumatic or noxious stimuli. All nociception produces pain, but not all pain results from nociception.

Clinically pain can be categorized into (1) Acute pain, which is primarily due to nociception, and (2) Chronic pain which may be due to nociception but in which psychological and behavioral factors often play a major role.

Acute pain can be defined as pain that is caused by noxious stimulation due to injury, a disease process, or the abnormal function of muscle or viscera. Four physiological processes are involved: transduction, transmission, modulation, and perception. This type of pain is typically associated with a neuroendocrine stress that is proportional to intensity.

Acute pain can be somatic or visceral, which are differentiated based on origin and features. Somatic pain can be further classified as superficial or deep. Superficial somatic pain is due to nociceptive input arising from skin, subcutaneous tissues, and mucous membranes. It is characteristically well localized and described as a sharp, pricking, throbbing, or burning sensation.

Deep somatic pain arises from muscles, tendons, joints or bones. In contrast to superficial somatic pain, it usually has a dull, aching quality and is less well localized.

The visceral form of acute pain is due to a disease process or abnormal function of an internal organ or its covering (e.g. Parietal pleura, pericardium, or peritoneum).

Four subtypes are described: (1) true localized visceral pain, (2) localized parietal pain, (3) referred visceral pain, and (4) referred parietal pain. The visceral pain is dull, diffuse, and usually midline. Parietal pain is typically sharp and often described as a stabbing sensation that is either localized to the area around the organ or referred to a distant site. The phenomenon of visceral or parietal pain referred to cutaneous areas results from patterns of embryological development and migration of tissues, and the convergence of visceral and somatic afferent input into the central nervous system.

Pain pathway[15, 16.]

Pain is conducted along a three neuron pathways that transmit noxious stimuli from the periphery to the cerebral cortex.

Primary afferent neurons are located in the dorsal root ganglia, which lie in the vertebral foramina at each spinal cord level. Each neuron has a single axon that bifurcates, sending one end to the peripheral tissues it innervates and the other into the dorsal horn of the spinal cord. In the dorsal horn, the primary afferent neuron synapses with a second order neuron whose axons cross the midline and ascend in the contralateral spinothalamic tract to reach the thalamus. Second order neurons synapse in thalamic nuclei with third order neurons, which in turn send projections through the internal capsule and corona radiata to the postcentral gyrus of the cerebral cortex.

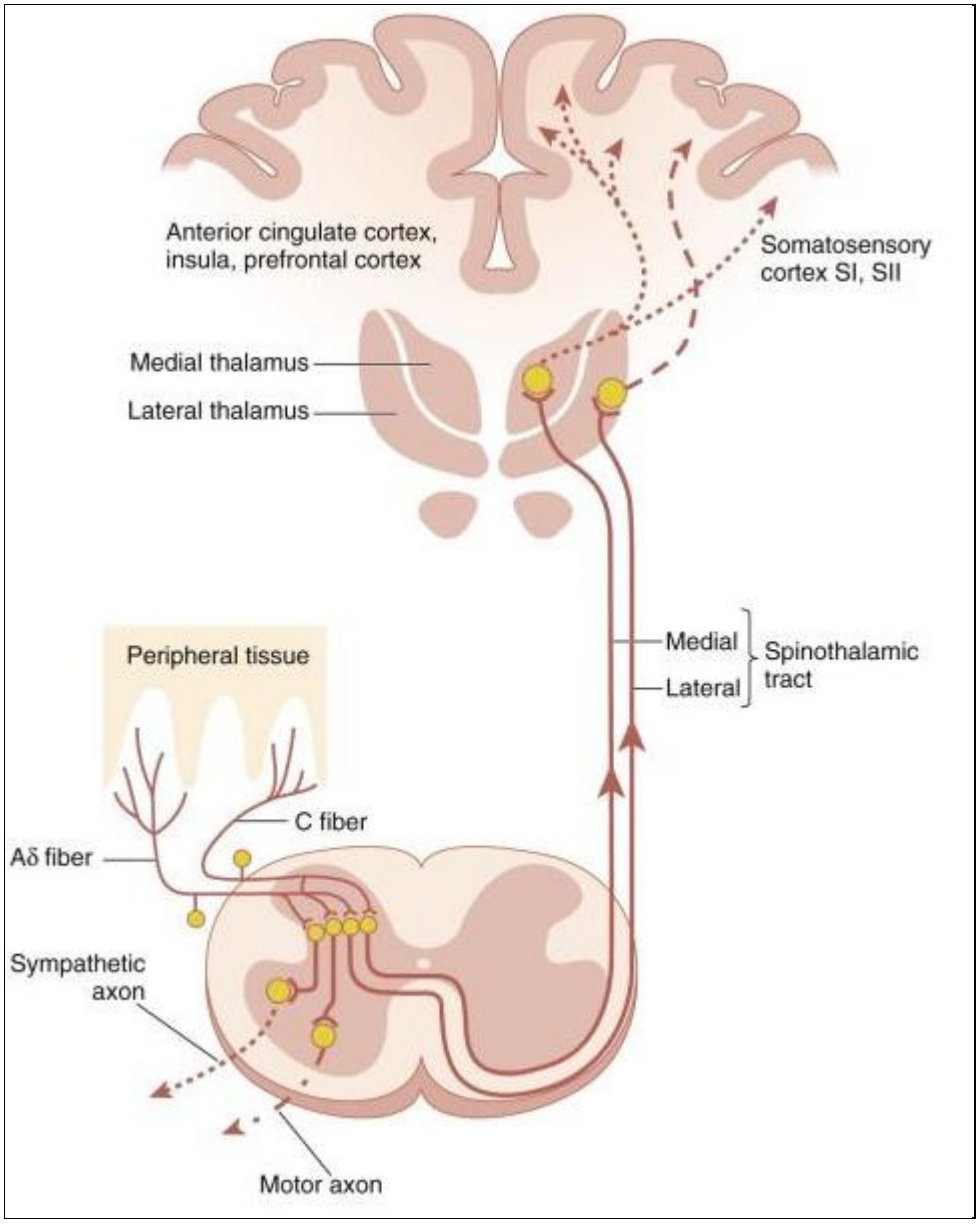


FIGURE 9: PAIN PATHWAY

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) mechano nociceptors, which respond to pinch and pinprick, (2) silent nociceptors, which respond only in the presence of inflammation, and (3) polymodal mechano heat 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 chemo-attractant for leukocytes.

RECEPTORS:

OPIOID RECEPTORS[17, 18]:

Martin and co-workers (1979) proposed three classes of opioid receptors based on radioligand studies and named them according to the prototypic drugs. These receptors are located in the CNS and throughout the Peripheral tissue. These are normally stimulated by endogenous peptides (endorphins, enkephalins and dynorphines). These are G protein coupled receptors. These receptors are located on the presynaptic terminals of the nociceptive C fibers and A delta fibers. Activation of these receptors by opioid agonists will indirectly inhibit voltage gated calcium channel, decreasing the cAMP levels and blocking the release of pain neurotransmitters like glutamate, substance P and calcitonin gene related peptide from the nociceptive fibers resulting in analgesia.

Mu (μ) receptor:

Also called OP3 or morphine opioid receptors. These receptors are located primarily in brain stem and medial thalamus. Stimulation of these receptors causes supraspinal and spinal analgesia, sense of wellbeing, euphoria, respiratory depression, sedation, miosis, reduced gastrointestinal motility and physical dependence. There are 2 subtypes of Mu receptors, Mu1 and Mu2.

Mu1 receptors are related to analgesia, euphoria, and serenity.

Mu2 receptors are related to respiratory depression, pruritus, prolactin release, dependence, anorexia and sedation.

Kappa (κ) receptor:

Also known as OP2 or KOR (kappa opioid receptors). The agonist is ketocyclazocine. Kappa receptors are found in the limbic and other diencephalic

areas, brain stem, and spinal cord, and are responsible for spinal analgesia, sedation, dyspnoea, dependence, dysphoria, and respiratory depression.

Delta (δ) receptor:

Also called OP1 and DOR (delta opioid receptors). The agonist is delta-alanine-delta-leucine-encephalin. Delta receptors are located largely in the brain and their effects are not well studied. They may be responsible for psychomimetic and dysphoric effects.

Sigma (σ) receptor:

The agonist is N-allylnormetazocine. Sigma receptors are responsible for psychomimetic effects, dysphoria, and stress-induced depression. They are no longer considered opioid receptors, but rather the target sites for phencyclidine (PCP) and its analogs.

ALPHA 2 ADRENERGIC RECEPTORS[8, 20]. (α2)

1969- Paton and co-workers found that a subclass of alpha adrenoceptors located presynaptically regulated the release of neurotransmitter. Bylund and co-workers defined three alpha-2 isoreceptors; alpha-2a, alpha-2b and alpha-2c based on their affinity for alpha adrenoceptor ligands. These are G protein coupled receptors.

The subtype A, the predominant subtype in CNS, is responsible for sedation, analgesia, and sympatholytic effect. Subtype B found mainly in peripheral vasculature is responsible for short term hypertensive response and subtype C found in CNS is responsible for anxiolytic effect.

Activation of G_i protein gated potassium channels results in membrane hyperpolarization leading to decreased firing rate in the CNS.

Activation of G_o protein results in reduction of calcium conductance into the cell through the N type voltage gated calcium channels leading to inhibition of neurotransmitter release.

Presynaptic alpha-2 adrenoceptors are present in sympathetic nerve endings and noradrenergic neurones in the central nervous system where they inhibit the release of noradrenaline leading to termination of pain signal. Whereas postsynaptic alpha-2 adrenoceptors are present in liver, pancreas, platelets, kidney, adipose tissue and the eye, these inhibit sympathetic activity causing hypotension and bradycardia. The predominant alpha-2 receptor in spinal cord is alpha-2a subtype.

The locus coeruleus is the largest noradrenergic cell group in the brain and is the major site for the hypnotic action of alpha-2 adrenoreceptors agonists. Nociceptive transmission at a spinal level is decreased via descending fibres in the dorsolateral funiculus tracts.

Activation of **α2** receptors in the brain and spinal cord inhibits neuronal firing, causing hypotension, bradycardia, sedation and analgesia. The response to activation of other areas include decreased salivation, secretions and reduced bowel motility, contraction of vascular and other smooth muscles, inhibition of renin release, increased glomerular filtration and increased secretion of sodium and water in the kidneys; decreased intraocular pressure and decreased insulin release from pancreas.

PHARMACOLOGY

Local anaesthetic drugs:

Local anaesthetic drugs have similar configuration. They have one aromatic lipophilic part (benzene ring) and one hydrophilic part (quaternary ring) connected by an intermediate ring either an ester (-COO-) or an amide (-NHCO-). The lipophilic portion is essential for anaesthetic activity and therapeutically useful local anaesthetics require a delicate balance between lipid solubility and water solubility. Addition of a butyl group to the piperidine nitrogen of mepivacaine results in bupivacaine, which is 35 times more lipid soluble and has a potency and duration of action three to four times that of mepivacaine.

BUPIVACAINE2[20, 21, 22, 23].

Structural Formula

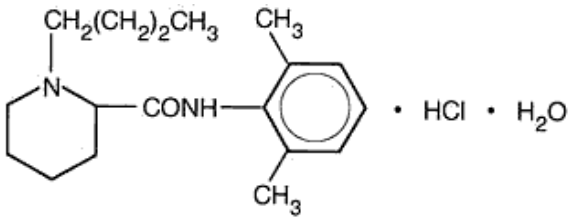


Figure 10: Chemical structure of bupivacaine

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 hrs
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 approximately three to four times more potent than lidocaine.

Bupivacaine, the pipecoloxylidide local anaesthetic is a chiral drug because its molecule possesses an asymmetric carbon atom and it is available for clinical use as racemic mixture of the enantiomers.

Mechanism of action

Local anaesthetics prevent transmission of nerve impulses (conduction blockade) by inhibiting passage of sodium ions through ion selective sodium channels in nerve membranes. Occlusion of open sodium channels by local anesthetic molecules contributes little to overall inhibition of sodium permeability. Failure of sodium ion channel permeability to increase slows the rate of

depolarization such that threshold potential is not reached and thus an action potential is not propagated.

Pharmacokinetics

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

Pharmacodynamics:

The drug is slower in onset of action than other local anaesthetics, but has the longest duration of action of the existing local anaesthetics. The degree of motor block increases with increasing concentration.

Dosage for spinal anaesthesia:

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

Not more than 150mg (30ml of 0.5% solution) should be given at one time or in any 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% solution, 5-20ml for a dose of 12.5-50mg resulting in blockade duration of 180-360 min.

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

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

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

These doses may be repeated in 3-4 hours but 400 mg is the maximum dose in 24 hours. Bupivacaine can be used with or without epinephrine. The addition of Vasoconstrictor produces a very slight increase in the duration of action. However, the peak blood level is significantly reduced, thereby minimizing the system toxicity.

Absorption and distribution

Absorption of local anaesthetic from site of injection into the systemic circulation is influenced by the site of injection and dosage, use of epinephrine, and pharmacologic characteristics of the drug. The ultimate plasma concentration of a local anaesthetic is determined by the rate of tissue distribution and the rate of clearance of the drug.

Lipid solubility is important in redistribution as well as being a primary determinant of intrinsic local anaesthetic potency. Ultimately the local anaesthetic is eliminated from the plasma by metabolism and excretion. Protein binding of local anaesthetic will influence their distribution and excretion.

For bupivacaine, the first pass pulmonary extraction is dose dependent, suggesting that the uptake process becomes saturated rapidly. There may be clinically significant trans-placental transfer of local anaesthetic between the mother and fetus. Plasma protein binding influences the rate and degree of

diffusion of local anesthetics across the placenta. Bupivacaine, which is highly protein bound (approximately 95%) has an umbilical vein-maternal arterial concentration ratio of about 0.32.

Metabolism

They undergo varying rates of metabolism by microsomal enzymes located primarily in the liver. Bupivacaine undergo the slowest metabolism among the amide local anaesthetics. Pathways for metabolism of bupivacaine include aromatic hydroxylation, N-dealkylation, amide hydrolysis and conjugation.

Systemic toxicity

Systemic toxicity of a local anaesthetic is due to an excess plasma concentration of the drug. Plasma concentration is determined by the rate of drug entering into the systemic circulation relative to their redistribution to inactive tissue sites 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 often first evident in the face and extremities and signals the imminence of tonic-clonic seizures. Drowsiness before the onset of seizures. Seizures are classically followed by CNS depression which may be accompanied by hypotension and apnea.

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

Selective cardiac toxicity

After accidental IV injection of bupivacaine the protein binding sites ($alpha_1$ acid glycoprotein and albumin) are quickly saturated, leaving a significant mass of unbound drug available for diffusion into the conducting tissue of the heart. This may result in precipitous hypotension, cardiac dysrhythmias and atrioventricular heart block.

Cardiotoxic plasma concentration of bupivacaine is 8 to 10 µg/ml. The threshold for cardiac toxicity produced by bupivacaine may be decreased in patients being treated with drugs that inhibit myocardial impulse propagation (beta adrenergic blockers, digitalis preparations, calcium channel blockers).

It depresses the maximal depolarization rate of cardiac action potential (V_{max}) by virtue of their ability to inhibit sodium ion influx via sodium channels. Bupivacaine depresses V_{max} considerably more than lidocaine. The resulting slowed conduction of the cardiac action potential manifest on the electrocardiogram as prolongation of the P-R and QRS intervals and reentry ventricular cardiac dysrhythmias. The R enantiomer of bupivacaine is more toxic than the S enantiomer.

Hepatotoxicity

Continuous or intermittent epidural administration of bupivacaine has been associated with increased plasma concentration of liver transaminase enzymes that normalized when bupivacaine infusion was discontinued.

FENTANYL[24, 25, 26].

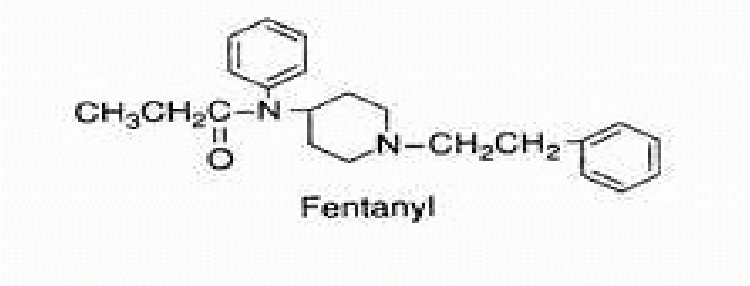


Figure 11: chemical structure of fentanyl

Fentanyl was first synthesized in 1960 by Dr. Paul Jannsen, released into clinical practice in 1963.Fentanyl citrate is a synthetic phenylpiperidine opioid analgesic and chemical congener of the reversed ester of pethidine. It is a powerful, safe and rapidly acting analgesic.

Fentanyl is highly lipid soluble and has a low molecular weight. Fentanyl is widely available for parenteral use and also in buccal, transdermal and aerosolized formulation. Fentanyl provides analgesia and relaxation.

Fentanyl is 1000 times more potent than meperidine, 50-100 times more potent than morphine, 100mcg fentanyl is equal to 10mg morphine.

Presentation:

- As a clear, colorless solution for injection containing 50mcg/ml of fentanyl citrate.
- Transdermal patches which delivers 25/50/75/100 mcg/hr fentanyl over a 72 hour period.
- Fentanyl lollipop- dissolves slowly in mouth, and is available in 6 dosages 200-1600 micrograms in 200mcg increments excluding 1000 and 1400 mcg.

Physiochemical properties:

pK	8.4
% non-ionized	8.5% at pH 7.5
Protein binding	84%
Effect site equilibrium	6.8 min
Elimination half time	3.1-6.6hrs
Context sensitive halflife	260 min

Routes of administration:

- Oral as syrup or lozenges
- Intravenous route
- Epidural route
- Intrathecal route

PHARMACOKINETICS

After I.V. administration, the onset of action of fentanyl is 1-2 minutes with duration of action for about 60 minutes. After epidural route duration is 3-4 hours.

After intrathecal administration onset is within 5 minutes and duration is of 60 minutes.

METABOLISM AND ELIMINATION

Fentanyl is eliminated from body predominantly by the biotransformation in the liver and is metabolized mainly by N. Dealkylation to Norfentanyl, which is pharmacologically inactive. Fentanyl is excreted mainly in urine as metabolites, less than 8% is excreted as unchanged drug.

MECHANISM OF ACTION

Fentanyl is primarily a μ receptor agonist with an analgesic potency greater than morphine, pethidine and alfentanyl. Analgesia is produced principally through interaction with μ receptors at supraspinal sites. It also binds to a much lesser degree to kappa receptors located within the spinal cord. There is evidence now that, the gray matter of the spinal cord also contains opioid receptors and most of them are located in substantia gelatinosa. ie 50% kappa, 40% μ and 10% Delta.

PHARMACOLOGICAL ACTION

1. CARDIOVASCULAR SYSTEM

A. **Heart Rate**

Due to stimulation of central vagus nucleus there is a decrease in the heart rate. It is dependent on dose and speed of injection. It can be effectively prevented by premedication with parasympatholytic agent such as glycopyrolate or atropine. Fentanyl also blocks sympathetic stress response that includes increase in heart rate by decreasing in CNS sympathetic vasoregulatory flow.

Dose of 1mcg/kg→ no significant effect on papillary muscle function

7mcg/kg→ at induction decreases heart rate, but no change in mean arterial pressure

10mcg/kg→ myocardial contractility reduced by 50%

20-25mcg/kg→ decreases heart rate, MAP, systemic and pulmonary vascular resistance and pulmonary capillary wedge pressure by 15% in patients with coronary artery disease.

B. **Blood pressure**

Minor reductions in blood pressure are seen primarily due to a reduction in systematic vascular resistance through centrally mediated reduction in sympathetic tone and often associated with bradycardia.

C. **Cardiac electrophysiological effects**

Fentanyl slows AV conduction, prolongs RR interval, AV node refractory period and the duration of Purkinjie fiber action potential.

2. RESPIRATORY SYSTEM

Fentanyl produces dose related depression of breathing. Resting minute volume, tidal volume and rate is decreased. The ventilatory responses to hypercapnia and hypoxia are blunted.

1-2mcg/kg→ decreases respiratory rate and increase tidal volume

More 3mcg/kg→ deceases respiratory rate, tidal volume and also the ventilatory response to hypoxia and hypercarbia.

3. RIGIDITY

Occurs frequently during I.V. induction of anaesthesia with larger doses. But with intrathecal fentanyl no such complication is seen. In fact fentanyl was used to relieve the spasticity with intrathecal Baclofen. Chest wall rigidity or wooden chest phenomenon is due activation of μ receptors located on GABAnergic interneurons. It can be controlled by early use of muscle relaxants.

4. CEREBRAL BLOOD FLOW AND INTRACRANIAL PRESSURE

Fentanyl produces no change or modest reduction in cerebral blood flow and cerebral metabolic oxygen consumption.

5. GASTROINTESTINAL TRACT

Intestinal motility is decreased and constipation can be a problem. It can increase tone of sphincter of Oddi and produce increased pressure in biliary ducts, occasionally producing pain. The effects are produced by combination or peripheral actions.

Intrathecal action:

"**Selective Spinal Analgesia"**

Intrathecal administration of fentanyl produces selective spinal analgesia by acting on opioid receptors in the substantia gelatinosa of the spinal cord. The major advantage of selective blockade of pain by fentanyl lie in the absence of sympathetic blockade and postural hypotension potentially allowing early ambulation of the patient and avoidance of cardiovascular collapse or convulsion, which are one the major complications of spinal anaesthetic blockade.

Intrathecal dose→10-25µgm.

Duration of action→ 2-6 hrs

1. Drug distribution:

a. After administration of the drug, fentanyl is lost into the epidural space and epidural fat, and thus unavailable at the target tissue site in the spinal cord.
b. The transfer rate constant for CSF to epidural space is same as meningeal permeability co-efficient. Fentanyl octonol: buffer distribution co-efficient is 955 i.e. intermediate hydrophobicity which is less than morphine.
c. Estimated apparent volume of distribution at spinal cord V_{cord} applies to unbound, freely diffusible opioid in CSF. V_{cord} paralleled the drug's octonal: buffering distribution co-efficient and it is 23.58.

d. $V_{epi-fat}$ –Fentanyl highest→ 45.88ml

V_{csf} - 11.08 ml

For this reason fentanyl's low non ionized fraction compared to sufentanyl may lead to great ion trapping.

2. Potency:

It is only 4 times more potent than morphine when administered intrathecally compared to Iv administration. It is a less hydrophobic opioid and has little rostral spread which causes less respiratory depression compared to morphine. Fentanyl by virtue of its high volume of distribution in spinal cord and epidural space results in very low integral exposure within the spinal cord. Addition of vasoconstrictors would be modestly beneficial to exposure because most of the dose is lost into the epidural space.

Relationship between fentanyl plasma concentration and effect.

Plasma Fentanyl concentration (ng/ml)	Pharmacological effect
>1	Slight analgesia, minimal ventilatory depression
1-3	Analgesia; 50% decrease in the ventilatory response to carbon dioxide
4-10	Analgesia for surgery if combined with nitrous oxide
>20	Unconsciousness, satisfactory anesthesia if used as sole agent

6. DRUG INTERACTIONS

Neuraxial administration of opioids in conjunctions with local anaesthetics improves the quality of intraoperative analgesia and prolongs the duration of post-operative analgesia.

Uses:

- Provide analgesic component of balanced anaesthesia for short surgical procedures, dose 2mcg/kg.
- High dose fentanyl anaesthesia (50-100mcg/kg) with nitrous oxide and oxygen or oxygen alone for cardiac surgeries or long surgical procedures. With continued post op ventilation.
- Post-operative pain relief in the loading dose of 50-150mcg and maintenance infusion of 0.5-1.5mcg/kg/hr.
- For sedation and analgesia in the dose of 1-4mcg/kg Iv for patient on mechanical ventilation
- Analgesia for labor and delivery
- As a component of neuroleptanalgesia with droperidol.

ADVERSE EFFECTS:

Bradycardia, Hypotension, Pruritus, Urinary retention, Respiratory depression (Dose related), Hyperalgesia, Neonatal morbidity, Sexual dysfunction, Ocular dysfunction

Anaphylaxis, Shivering, Nausea and vomiting.

The four classical side effects are:

1. Pruritus: incidence 0-100%

   May be generalized or more likely over face, neck and thorax.

The cephalad spread of the drug in the CSF and the subsequent interaction of the opioid in the substantia trigeminal initiates the itch reflex by indirect action on trigeminal nucleus.

2. Nausea and vomiting: incidence 30% more in women compared to men

   Mechanism:

   - Activation of opioid receptors located in area postrema due to cephalad spread of the drug.
   - Sensitization of vestibular system to motion
   - Decreased gastric emptying time.

3. Urinary retention: incidence 0-80% more in young males and is related to dose of opioid dose administered.

   Activation of opioid receptors in the sacral spinal cord causes inhibition of sacral parasympathetic nerves leading to detrusor muscle relaxation, increased urine accumulation and retention of urine.

4. Respiratory depression:

Early onset respiratory depression occurs within 2 hrs of injection, delayed respiratory depression occurs 2 hrs after the administration which is dose dependent and synergistic with concomitant use of other sedatives or respiratory depressant drugs.

THERAPEUTIC EFFICACY

Fentanyl is both potent and safe. Its therapeutic index of 323 is much greater than that of morphine (69) and pethidine (4.8)

CONTRA INDICATION AND CAUTIONS

1. Should not be administered to patients who have taken mono amine oxidase inhibitors within previous 24 hrs.
2. Bronchial Asthma
3. Myasthenia gravis

COUNTER MEASURES FOR ADVERSE EFFECTS

Respiratory depression can be treated with Naloxone and by mechanical ventilation.

Pruritis, nausea and urinary retention can be reversed by Naloxone, antihistaminic, antiemetic and by catheterization

Bradycardia by Atropine or Glycopyrolate.

PHARMACOLOGY OF DEXMEDETOMIDINE

The use of alpha 2 agonists in anaesthesia was started after observations were made on patients receiving clonidine therapy during anaesthesia. Dexmedetomidine was introduced into clinical practice in 1999. It has been used for sedation and analgesia in veterinary medicine for many years. It was approved by FDA for only short term sedation (<24hrs) in mechanically ventilated ICU patients.

Dexmedetomidine hydrochloride, a dextroisomer (s-enantiomer) of medetomidine belongs to imidazole subclass of alpha 2 agonists. It is described chemically as (+)-4-(s) [2 3–(dimethylphenyl) ethyl]-11H-imidazole monohydrochloride. Its empirical formula is $C_{13}H_{16}N_2HCl$ and its molecular weight is 236.7[27].

Dexmedetomidine is a highly selective alpha 2 adrenergic agonist with very high ratio of specificity for alpha 2 receptors (α2: α1: : 1620:1). It is 8 times more specific to alpha 2 receptors compared to clonidine[7]. This selective alpha 2 adrenergic agonism might permit its application in relatively high doses for sedation and analgesia without unwanted vascular effects from activation of alpha 1 receptors.

Abrupt cessation of clonidine infusion is associated with rebound hypertension which is not seen with dexmedetomidine infusion after its discontinuation. Dexmedetomidine is a shorter acting drug than clonidine and has a reversal agent Atipamizole, thus making it a suitable agent for sedation and analgesia during the perioperative period[28].

Structural formula

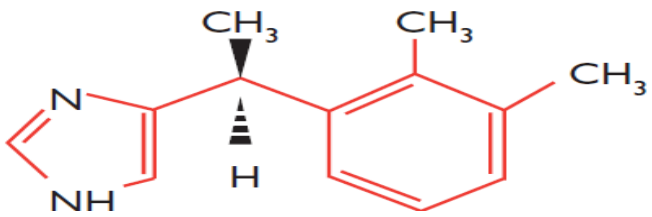


Figure 12: Chemical structure of dexmedetomidine

PHYSIOCHEMICAL PROPERTIES

A white or almost white powder that is freely soluble in water with Pka of 7.1. Partition coefficient in octanol: water at pH 7.4 is 2.89.

Preservative free dexmedetomidine is available in 2ml/1ml (100μg/ml) ampoule as Dexmedetomidine Hydrochloride for intravenous use.

It can also be used for intrathecal and epidural anaesthesia.

MECHANISM OF ACTION OF DEXMEDETOMIDINE

Specific alpha-2 receptor subtypes mediate varied pharmacodynamic effects of Dexmedetomidine. Agonism at alpha 2A receptor appears to promote sedation, hypnosis, analgesia, sympatholysis, neuroprotection[29] and inhibition of insulin secretion[30]. Agonism at the alpha -2B receptor suppresses shivering centrally, promotes analgesia at spinal cord sites and induces vasoconstriction in peripheral arteries. The alpha 2C receptors are associated with modulation of cognition, sensory processing, mood and stimulant-induced locomotor activity and regulation of epinephrine outflow from the adrenal medulla. Inhibition of nor epinephrine release appears to be equally affected by all three alpha-2 receptor subtypes[31].

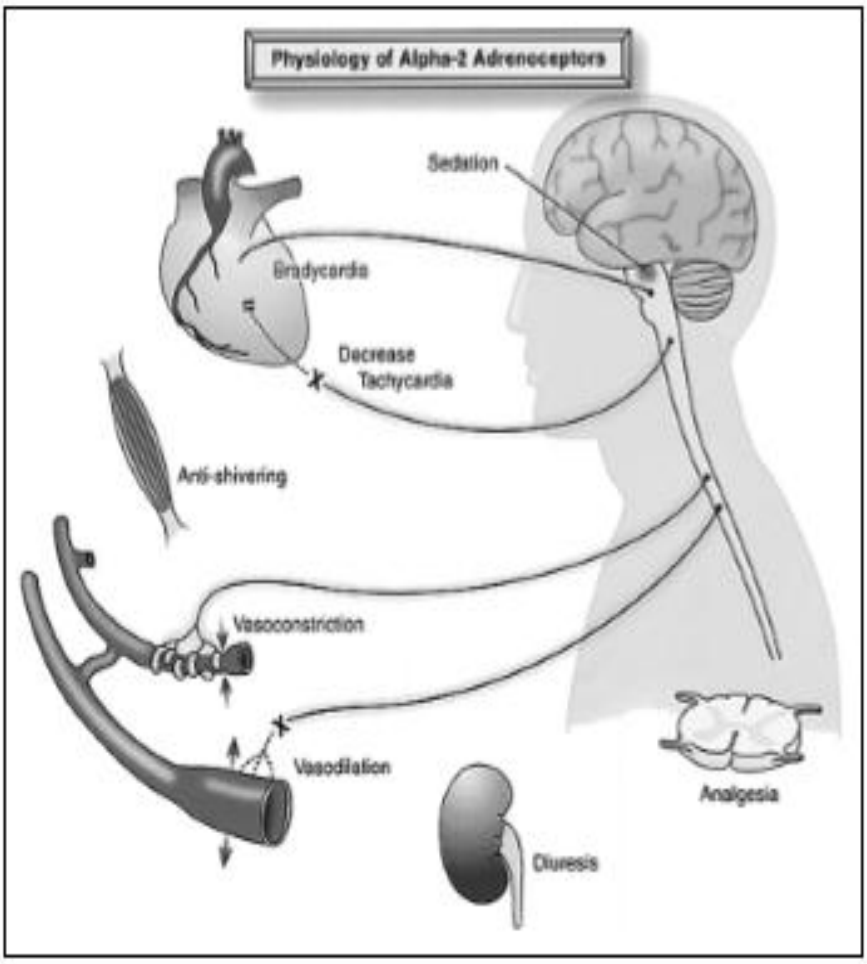


Figure 13: Responses mediated by α-2 adrenergic receptors

The mechanism of action of Dexmedetomidine is unique and differs from currently used sedative drugs. Presynaptic activation of alpha-2A adrenoceptor in the locus ceruleus inhibits the release of nor-epinephrine and results in the sedative and hypnotic effects[32]. Stimulation of alpha-2 adrenoceptors in this area terminates the propagation of pain signals leading to analgesia. Postsynaptic activation of alpha-2 receptors in the CNS results in decrease in sympathetic activity leading to hypotension and bradycardia[33].

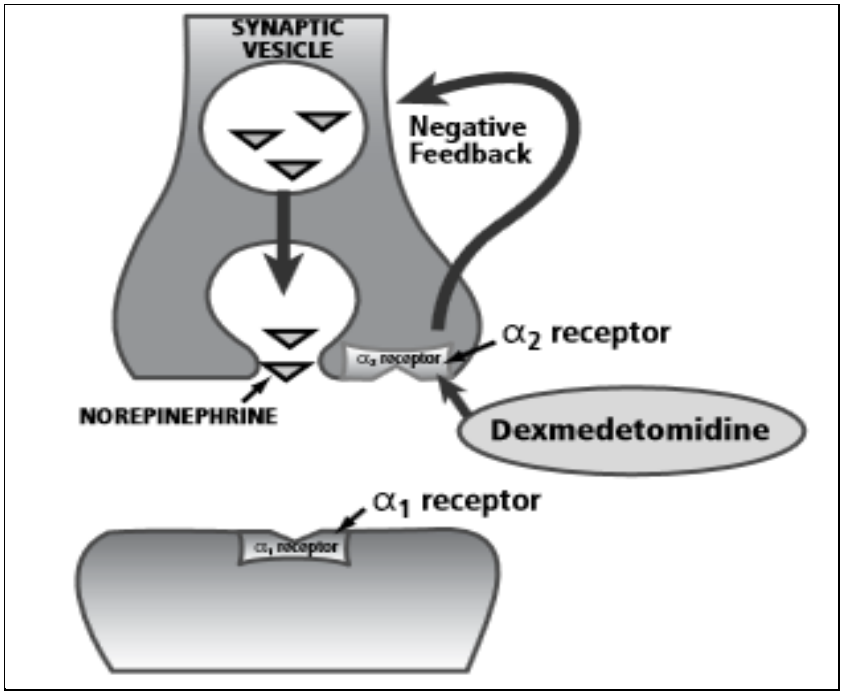


Figure 14: Alpha receptors

At the spinal cord, stimulation of alpha-2 receptors at the substantia gelatinosa of the dorsal horn leads to inhibition of the firing of nociceptive neurons and inhibition of release of substance P. Also the alpha-2 adrenoceptors located at the nerve endings have a possible role in the analgesic mechanism by preventing nor epinephrine release. The spinal mechanism is the principal mechanism for the analgesic action of Dexmedetomidine even though there is a clear evidence for both a supraspinal and peripheral sites of action[34].

PERIPHERAL ACTION:

Alpha-2 receptors activation at blood vessels and on sympathetic terminals, lead to contraction of vascular and other smooth muscles; decreased salivation and decreased bowel motility in the gastrointestinal tract, inhibition of renin release, increased glomerular filtration and increased secretion of sodium and water in the kidney, decreased release of insulin from the pancreas, decreased intraocular

pressure, decreased platelet aggregation and decreased shivering threshold by 2˚C[7].

Pharmacodynamics of dexmedetomidine

Dexmedetomidine has dose dependent alpha 2 adrenoreceptor selectivity, at low to medium doses and on slow infusion, high levels of alpha-2 selectivity is observed, while high doses or rapid infusions of low doses are associated with both alpha-1 and alpha-2 activities[6].

Central nervous system

1. Sedation, anxiolysis, hypnosis and amnesia

Dexmedetomidine provides dose dependent increase in anxiolysis and sedation. Arousability is maintained at deep levels of sedation, with good correlation between the level of sedation and the bispectral EEG (BIS). Dexmedetomidine induced sedation qualitatively resembles normal sleep. Dexmedetomidine induces sleep by activating endogenous non-rapid eye movement pathways. Stimulation of alpha-2A receptors in the nucleus ceruleus inhibits nor adrenergic neurons and disinhibits GABAnergic neurons in the ventrolateral preoptic nucleus (VLPO) [35].

The type of sedation is branded “cooperative or arousable”, to distinguish it from sedation induced by drugs acting on the GABA system, such as midazolam or propofol which produce a clouding of consciousness[36]. Sedation with Dexmedetomidine is dose dependent, however even low doses might be sufficient to produce sedation[37]. Dexmedetomidine may lack amnestic properties but amnesia is achieved with dexmedetomidine only at high plasma level (>1.9 ng/ml) without retrograde amnesia[38].

2. Analgesia

Dexmedetomidine appears to exert analgesic effects at the spinal cord level and at supraspinal sites by acting on locus ceruleus in the brain stem and directly through alpha 2 receptors in the spinal cord. Dexmedetomidine significantly decreases opioid requirement in the post-operative period[39].

Intra-articular administration during knee surgery improves postoperative analgesia, with less sedation than IV route[40]. Suggested mechanisms are activation of alpha-2A receptors, inhibition of the conduction of nerve signals through C and Aδ fibres and the local release of encephalin[41].

Respiratory effects

Dexmedetomidine is able to achieve its sedative, hypnotic and analgesic effects without causing any clinically relevant respiratory depression unlike opioids. The changes in ventilation appeared similar to those observed during natural sleep[38]. It also exhibited a hypercarbic arousal phenomenon, which has been described during normal sleep and is a safety feature[42].

Dexmedetomidine is effective in achieving excellent sedation without respiratory depression during fibreoptic intubation or other difficult airway procedures[43, 44]. Intubating conditions are further enhanced as Dexmedetomidine decreases saliva production and airway secretions[28].

Cardiovascular effects

Dexmedetomidine has no direct effects on the heart. A biphasic cardiovascular response has been described after the application of dexmedetomidine. The administration of a bolus of 1 μg/kg body weight, initially results in a transient increase of the blood pressure and a reflex decrease in heart

rate, especially in young healthy patients. This is due to the peripheral stimulation of alpha 2B adrenoceptors which acts on vascular smooth muscles and this can be avoided by a slow infusion over 10 or more minutes[37]. The initial response lasts for 5-10 minutes and is followed by a decrease in blood pressure of approximately 10%-20% below baseline values; both these effects are caused by the inhibition of the central sympathetic outflow overriding the direct stimulant effects resulting in bradycardia and hypotension[45].

Effect on thermoregulation

Dexmedetomidine is associated with lower rates of shivering. Dexmedetomidine and other alpha-2 agonists suppress shivering, possibly by their activity at alpha-2B receptors in the hypothalamic thermoregulatory center of the brain[35].

Effects on renal function

Renin release is stimulated by beta adrenoreceptor activation, while alpha 2 adrenoreceptors directly inhibit renin release[46]. Alpha-2 agonists exert a diuretic effect by inhibiting the antidiuretic action of arginine vasopressin at the collecting duct, resulting in decreased expression of aquaporin-2 receptors and decreased salt and water absorption[7].

Pharmacokinetics

After intravenous injection, onset of action is after approximately 15 minutes. Peak concentrations are achieved in 1 hr after continuous infusion. It has a rapid distribution half-life ($t_{1/2}\alpha$) of 6 minutes and a terminal elimination half-life ($t_{1/2}\beta$) of between 2 and 2.5 hrs. The drug is highly protein bound (94%) with a 6% free fraction. It has a steady state volume of distribution (Vdss, 1.33 l/kg).

Dexmedetomidine is rapidly distributed and extensively metabolized in the liver. It undergoes conjugation (41%), n-methylation (21%) or hydroxylation followed by conjugation. Dexmedetomidine is 94% protein bound and its concentration ratio between blood and plasma is 0.66. The context sensitive half time ranging from 4 minutes after a 10 minute infusion to 250 minutes after an 8 hr infusion[47].

Dexmedetomidine is also absorbed systematically through transdermal, buccal or intramuscular routes, with a mean bioavailability from the latter 2 routes of 82% and 104% respectively. After intramuscular administration, the time to maximum concentration (T_{max}) in the blood is 1.6 to 1.7 hrs, with an absolute bioavailability of 73%. After transdermal administration, the T_{max} is six hours with an absolute bioavailability of 88%[48].

Perioperative uses of Dexmedetomidine

1. Premedication[7]

Dexmedetomidine has anxiolytic, sedative, analgesic, antisialogogue and sympatholytic properties which render it suitable as a premedication agent. IV doses of 0.33 to 0.67 μg/kg given 15 minutes before surgery, seems efficacious, while minimizing the cardiovascular side effects of hypotension and bradycardia.

a. It reduces thiopental requirements.

b. Reduces the requirements of volatile anaesthetics[39].

c. More effectively attenuates the hemodynamic responses to endotracheal intubation.

d. Decreases plasma catecholamine concentrations[7].

e. Improves perioperative hemodynamic and sympathoadrenal stability.

2. Use of dexmedetomidine for regional anaesthesia

a. Epidural dexmedetomidine at a dose of 100µg decreased the incidence of postoperative shivering[51].

b. Intrathecal dexmedetomidine at a dose of 3µg causes significant prolongation of sensory and motor blockade[52].

c. Addition of 0.5µg/kg body weight of dexmedetomidine to lidocaine for intravenous regional anaesthesia improves the quality of anaesthesia and perioperative analgesia[53].

3. Use in monitored anaesthesia care (MAC):

Dexmedetomidine confers arousable sedation with ease of orientation, anxiolysis, mild analgesia without respiratory depression[27].

4. Dexmedetomidine has also been used as **sole anaesthetic agent** upto doses of 10µg/kg/hr[44].

5. Use of dexmedetomidine in postoperative period:

Infusion can be continued in extubated and spontaneously breathing patients. The ongoing sedation and sympatholytic effects is beneficial in reducing postoperative myocardial ischemic events in high risk patients undergoing non-cardiac surgery[27].

6. Use of dexmedetomidine in pediatric age group[54]

Addition of dexmedetomidine 2µg/kg body weight to bupivacaine for caudal analgesia promotes analgesia after anaesthetic recovery without increasing the incidence of side effects.

7. Use of dexmedetomidine in intensive care unit (ICU) [55]:

It provides adequate sedation with minimal respiratory depression and can be used for weaning patients from ventilator.

Adverse effects

Side effects of dexmedetomidine other than hypotension and bradycardia are hypertension after loading dose, dystonic movements, atelectasis, nausea and vomiting, dry mouth, tachycardia, atrial fibrillation, hemorrhage, acidosis, confusion, agitation and rigors which are rare.

Withdrawal phenomenon is reported after abrupt discontinuation with prolonged administration of dexmedetomidine, leading to development of hypertension, tachycardia, emesis, agitation, dilated pupils, diarrhea, increased muscle tone and tonic clonic seizures[56, 57].

Dosage and administration[49, 50].

Dexmedetomidine is available as 1ml/2ml ampoules containing 100mcg/ml. It is compatible with ringer lactate, 0.9% normal saline, dextrose 5%, mannitol 20%

For attenuation of intubation response→ 0.25-1mcg/kg Iv

For maintenance of anaesthesia→ 0.2-0.7mcg/Kg/hr Iv

For attenuation of extubation response→ 0.5-1mcg/kg Iv

For subarachnoid block→ 3-15mcg added to local anaesthetic

For epidural anaesthesia→1-2mcg/kg added to local anaesthetic

For caudal anaesthesia→ 1-2mcg/kg added to local anaesthetic

For ICU sedation→ loading dose- 0.5-1mcg/kg over 10 min Iv

Maintenance dose- 0.3-0.7mcg/kg.hr

Fiber optic intubation→ loading- 1mcg/kg Iv over 10 min

Maintenance dose- 0.7mcg/kg/hr

Drug interactions

Dexmedetomidine has shown to inhibit CYP2 D6 in vitro, but the clinical significance of this inhibition is not well established. Dexmedetomidine appears to have little potential for interactions with drugs metabolized by the cytochrome p450 system. Co-administration of Dexmedetomidine with sevoflurane, isoflurane, propofol, alfentanil and midazolam may result in enhancement of sedative, hypnotic or anaesthetic effects[58].

REVIEW OF LITERATURE

History of review of literature[1, 59]

Cerebrospinal fluid was discovered by Domenico Cotugno in 1764 and its circulation was described by F. Magendie in 1825.

Alexander wood introduced hollow needle and glass syringe in 1853. Cocaine was first isolated in 1860 from erythroxylon coca, its ananlgesic properties were first described by Schroff in 1862 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 patiens. 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-first used 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.

History of opioids:

Opioids were used for recreation purposes since 5000yrs. N. Racoviceanu-Pitresti was the first to report the use of opioids through intrathecal route in 1890[60]. In 1901, Katawata reported the use of intrathecal morphine for pain control[61].

In 1973, Pert and colleagues provided definite evidence of multiple opioid receptors and named them Mu (morphine), kappa (Ketocyclazocine) and sigma (SKF 10047, N- allylnormetazocine). In 1977, Soloman H and Syndel H D several actions exerted by opioids are due to activation of selective sites on neuronal membrane in brain[62].

REVIEW OF CLINICAL STUDIES:

Harbhej Singh, Katina Thornton, Jay Yang And Adolf H Giesecke in 1995 concluded that addition of Fentanyl 25 mcg to hyperbaric bupivacaine (0.5%) 13.5 mg intrathecally in 43 patients undergoing elective lower extremity or genitourinary surgeries under spinal anaesthesia, fentanyl prolonged the duration of bupivacaine induced sensory block and reduced the requirement of analgesics in the early post-operative period though fentanyl has no effect on the onset of bupivacaine induced motor and sensory block[63].

Mustafa Karakan, Nursan Tahtaci and Sitki Goksu in 1999 concluded that addition of Fentanyl 12.5mcg to hyperbaric bupivacaine (0.5%) 10 mg intrathecally in 80 patients undergoing elective lower abdominal and lower limb surgeries under spinal anaesthesia, showed to have anti nociceptive synergism, and increased bupivacaine induced sensory block without affecting motor block[64].

Khanna M S and Ikwinder KJP Singh in 2002 concluded that addition of preservative free fentanyl 25mcg to hyperbaric bupivacaine (0.5%) 12.5mg intrathecally in 40 patients aged above 60yrs undergoing total hip replacement under spinal anaesthesia, fentanyl prolongs sensory block, improves intra operative analgesia, produces post-operative pain relief, preserves cognitive function, induces pruritus, without altering the characteristic of motor blockade and can produce fall in oxygen saturation when combined with benzodiazepines as result of respiratory depression[65].

B N Biswas et al. in 2002 concluded that addition of Fentanyl 12.5mcg to hyperbaric bupivacaine (0.5%) 10 mg intrathecally in 40 patients undergoing caesarian section under spinal anaesthesia, fentanyl markedly improved

intraoperative anaesthesia and significantly reduced the demand for post-operative analgesics with good maternal and fetal well-being[66].

Uma Srivastava, Adithya Kumar, Gandhi N K, Surekha Saxena in 2004 concluded that addition of Fentanyl 25mcg to hyperbaric bupivacaine (0.5%) 10 mg or plain bupivacaine 10 intrathecally in 60 patients undergoing caesarian section under spinal anaesthesia, produced significant difference between the 2 groups despite difference in baricity suggesting spread of local anaesthetic is not dependent on baricity in patients undergoing caesarian section[67].

Anchalee Techanivate, Pakorn Urusopone, Predee Kiatgungwanglia and Rungrat Kosawiboonpol in 2004 concluded that addition of Fentanyl 10mcg and 20 mcg to hyperbaric bupivacaine (0.5%) 20 mg intrathecally in 60 patients undergoing appendectomy under spinal anaesthesia, fentanyl significantly improved the quality of analgesia, prolonged the duration of action of hyperbaric bupivacaine and delayed the analgesic requirement in the post-operative period[68].

Jaishree Bogra, Namitha Arora and Pratima Srivastava in 2005 concluded that addition of preservative free Fentanyl 12.5mcg to different doses of hyperbaric bupivacaine (0.5%) 8mg, 10mg, 12.5mg intrathecally in 120 parturient undergoing caesarian section under spinal anaesthesia, fentanyl significantly reduced the dose of hyperbaric bupivacaine and therefore its harmful effects[69].

M Seyedhejazi and E Madarek in 2007 concluded that addition of Fentanyl 10mcg to different doses of hyperbaric bupivacaine (0.5%) 8mg and 12.5mg intrathecally in 40 parturients undergoing caesarian section under spinal

anaesthesia, provided good spinal anaesthesia for caesarian section with less hypotension, nausea and vomiting[70].

Kanazi GE et al.[52] in **2006** conducted a study on 60 patients to compare the effects of low dose dexmedetomidine 3mcg or clonidine 30 mcg on the characteristics of intrathecal hyperbaric bupivacaine(0.5%) 12mg in patients posted for transurethral resection of prostrate or bladder tumor under spinal anesthesia. They concluded that the supplementation of bupivacaine spinal block with low dose of intrathecal dexmedetomidine or clonidine produce significantly shorter onset of motor block and a significantly longer sensory and motor block than bupivacaine alone. Dexmedetomidine 3µg and clonidine 30µg have equipotent effect on characteristics of the block without any significant hemodynamic instability and sedation.

Al Ghanem SM et al.[72] in **2009** conducted a double blind controlled study on the effect of adding dexmedetomidine versus fentanyl to intrathecal bupivacaine on spinal block characteristics in gynecological procedures.

They concluded that addition of dexmedetomidine 5mcg to 10 mg isobaric bupivacaine in 66 patients undergoing gynecological procedures under spinal anaesthesia, dexmedetomidine proved to be an attractive alternative as an adjuvant to spinal bupivacaine in surgical procedures especially in those that need quite long time with minimal side effects and excellent quality of spinal analgesia.

Al-Mustafa MM et al.[73] in **2009** conducted a study on 66 patients to study the effects of different doses of dexmedetomidine 5 mcg and 10 mcg added to spinal isobaric bupivacaine 12.5mg for urological procedures. They concluded that dexmedetomidine improved the onset of sensory and motor blockade while

prolonging the duration of sensory and motor blockade when used with bupivacaine in spinal anaesthesia in a dose dependent manner.

Gupta R et al.[74] in **2011** Studied the use of dexmedetomidine 5 mcg as an intrathecal adjuvant for post-operative analgesia with isobaric ropivacaine (0.75%) 22.5mg in 60 patients undergoing surgeries under spinal anaesthesia. They concluded that addition of 5 mcg dexmedetomidine prolonged 2 segment sensory regression time, sensory and motor block and provided prolonged duration of analgesia, there by proving to be an excellent adjuvant in spinal anaesthesia for surgeries requiring long time.

Eid HEA et al.[75] in **2011** studied dose related effect of intrathecal Dexmedetomidine with hyperbaric bupivacaine in a prospective randomized double blind study. 48 patients schedule for anterior cruciate ligament reconstruction were randomized to one of the 3 groups receiving 10 µg Dexmedetomidine in first group (D1), 15 µg Dexmedetomidine in second group (D2) and normal saline in the third group with 3 ml of 0.5% hyperbaric bupivacaine (B) in all the three groups, total volume of drug was 3.5 ml. They concluded that intrathecal dexmedetomidine in doses of 10µg and 15µg significantly prolonged the anesthetic and analgesic effects of spinal hyperbaric bupivacaine in a dose dependent manner.

Gupta R et al.[76] in **2011** conducted a comparative study of intrathecal dexmedetomidine and fentanyl as adjuvants to bupivacaine. 60 patients scheduled for lower abdominal surgeries were randomly allocated to receive either 12.5 mg hyperbaric bupivacaine with 5µg dexmedetomidine (group D) or 25µg fentanyl (group F) intrathecally. They concluded that 5µg dexmedetomidine seems to be an

attractive alternative to 25µg fentanyl as an adjuvant to spinal bupivacaine in the surgical procedures, especially those requiring long time by providing good quality intraoperative analgesia, hemodynamically stable conditions, minimal side effects, and excellent quality of postoperative analgesia.

Shukla D et al.[77] in **2011** compared the effects of intrathecal dexmedetomidine and magnesium sulfate used as adjuvants to bupivacaine. 90 scheduled for lower abdominal and lower limb surgeries were randomly allocated to receive either 15 mg hyperbaric bupivacaine with 10µg (0.1 ml) dexmedetomidine (group D) or 50 mg (0.1 ml) magnesium sulfate (group M) or 0.1 ml saline (group C). They concluded that intrathecal dexmedetomidine supplementation of spinal block seems to be a good alternative to intrathecal magnesium sulfate as it produces earlier onset and prolonged duration of sensory and motor block without associated significant hemodynamic alterations.

S. Fyneface-Ogan et al[78] **in 2012** conducted a study on 90 laboring multiparous women to compare the effects of Single Shot Intrathecal hyperbaric bupivacaine (0.5%) 2.5 mg with Dexmedetomidine 2.5mcg and hyperbaric Bupivacaine(0.5%) 2.5 mg with Fentanyl on Labor Outcome. They concluded that Single shot intrathecal bupivacaine with dexmedetomidine significantly prolonged sensory block in laboring women with normal neonatal outcome.

Rachana Joshi, Jignesh Mori, Kamala H Metha[79] **in 2013** conducted a study on 50 patient to compare efficacy of intrathecal hyperbaric bupivacaine (0.5%) 15mg plain with intrathecal hyperbaric bupivacaine (0.5%) 15mg, dexmedetomidine 5mcg combination on

duration of subarachnoid block and post-operative analgesia. They concluded, 5µg dexmedetomidine is an attractive alternative as adjuvant to spinal bupivacaine in surgical procedures especially in those that need quite long time with minimal side effects and excellent quality of spinal analgesia.

Ji Eun Kim et al[80] in 2013 conducted a study on 54 patients to compare the effects of intrathecal Dexmedetomidine 3 mcg on Low-Dose hyperbaric Bupivacaine (0.5%) Spinal Anesthesia in Elderly Patients Undergoing Transurethral Prostatectomy. They concluded that Dexmedetomidine 3 µg when added to intrathecal bupivacaine 6 mg produced faster onset with prolonged duration of sensory block and postoperative analgesia in elderly patients for transurethral surgery.

S L Solanaki et al[81] in 2013 conducted a study on 90 patients to compare the analgesic effect of intrathecal dexmedetomidine 5 mcg or clonidine 50mcg, with hyperbaric bupivacaine (0.5%) 15mg, in trauma patients undergoing lower limb surgery. They concluded that dexmedetomidine 5 µg added to intrathecal bupivacaine 15 mg produces longer postoperative analgesia than clonidine 50 µg among trauma patients undergoing lower limb surgery.

MATERIAL AND METHODS

MATERIAL AND METHODS:

SOURCE OF DATA:

This study was done on patients admitted to R.L. Jalapa hospital and undergoing elective surgeries under spinal anaesthesia during the period January 2012 to May 2014. Approval from institutional ethics committee was taken.

METHOD OF COLLECTION OF DATA:

Inclusion criteria:

9 Patients of either sex, aged between 20 to 45 years, of physical status ASA Grade I and Grade II undergoing elective lower abdominal and lower limb surgeries under spinal anaesthesia.

Exclusion criteria:

1) Patients with known liver and renal problems.

2) Patients with known cardiac problems.

3) Patients using adrenergic receptor blockers, calcium channel blockers.

4) Patients with weight >120kg or height <150cms.

5) Patients with contraindications for spinal anesthesia.

6) Patients posted for emergency surgeries.

7) Hypersensitivity to local anaesthetics, fentanyl, dexmedetomidine.

Sampling Procedure:

After obtaining informed written consent, 90 patients undergoing lower limb and lower abdominal surgeries under spinal anaesthesia were selected. They were randomly divided into 3 groups of 30 each. Randomization was done using simple sealed envelope technique.

Group **C**: Control group.

Group **D**: Dexmedetomidine group.

Group **F**: Fentanyl group.

All patients were examined a day before surgery. All were kept fasting overnight after 10:00pm and received tab. Ranitidine 150mg orally and tab. Alprazolam 0.5mg orally as premedication at night before surgery and at 6:00am in the morning on the day of surgery. All patients were monitored with electrocardiography, oxygen saturation, noninvasive blood pressure, end-tidal carbon-di-oxide. An intravenous line with 18G cannula was secured and all were preloaded with Ringer lactate 5ml/kg.

Under all aseptic precautions after putting patient in left lateral position, using 23G quincke spinal needle, spinal block was performed at level of L3-L4 through a midline approach and patient put to supine position. Patients in group D received 3ml of 0.5% hyperbaric bupivacaine with 10mcg dexmedetomidine in 0.5ml of normal saline. Patients in group F received 3ml of 0.5% hyperbaric bupivacaine with 25mcg fentanyl in 0.5ml of normal saline. Patients in group C received 3ml of 0.5% hyperbaric bupivacaine with 0.5ml of normal saline.

The time at intrathecal injection was considered as 0 and the following parameters were observed.

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.

5) Quality of analgesia.

6) Two segment sensory regression time.

7) Need for rescue analgesia when patient complains of pain.

8) Incidence of side effects.

Pulse rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, Spo2 and respiratory rate was recorded every 5 min for 15 min and then every 10mins throughout the intra operative period and also at the completion of surgery. Post-operatively monitoring of pulse rate, systolic and diastolic blood pressure, mean arterial pressure, Spo2 was recorded hourly.

DEFINTIONS:

Onset of sensory blockade: is 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.

Duration of sensory blockade: is defined as time taken from the onset of sensory blockade till the two segment regression time.

Duration of motor blockade: is defined as time taken from the onset of motor blockade to the time when the patient develops Bromage 1.

Duration of two segment sensory regression time: is defined as the time taken from the maximum level of sensory block attained till the sensation has regressed by 2 segments.

Duration of effective analgesia: is defined as time taken from the completion of injection of the study drug till the patient complains of pain

Rescue analgesia: is defined as time taken from the completion of injection of the study drug till the patient complains of pain and need for analgesic drugs.

Quality of motor block was assessed using **modified Bromage scale**[52].

Bromage 0 - patient able to move hip, knee and ankle.

Bromage 1 – patient unable to move the hip but is able to move the knee.

Bromage 2 – patient unable to move the hip and knee but is able to move the ankle.

Bromage 3 – patient is unable to move the hip, knee and ankle.

Level of sedation[71]: level of sedation was assessed by sedation scale.

Grade 0- no sedation

Grade 1- mild sedation

Grade 2- moderate sedation

Grade 3- severe sedation.

Quality of analgesia will be assessed by visual analogue scale.

Visual analogue scale for pain[73]:

0	No pain
1-3	mild pain
4-6	moderate pain
7-10	severe 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 mephentermine 6mg increments given IV.

Bradycardia:

Defined as heart rate less than 60/minute and will be treated with injection atropine 0.6mg IV.

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

STATISTICAL ANALYSIS

A sample size of 25patients per group was determined through power analysis (a ¼ 0.05; b ¼ 0.80) to detect an increase of 30 min in the time of a two-segment sensory regression with a standard deviation of 28 min. Considering the drop outs, 30 patients were selected for each group in our study. Results are expressed as the means and standard deviations, medians and ranges, or numbers and percentages. The comparison of normally distributed continuous variables between the groups was performed using one-way analysis of variance (ANOVA) and, if appropriate, followed by the Bonferroni test for post hoc analysis. Nominal categorical data between study groups were compared using the chi-squared test or Fisher's exact test as appropriate. Ordinal categorical variables and non-normal distribution continuous variables were Dexmedetomidine or fentanyl for supplementation of spinal bupivacaine compared using the Mann—Whitney U-test. $P < 0.05$ was considered to be significant.

STATISTICAL METHODS APPLIED

Frequencies

The Frequencies procedure provides statistics and graphical displays that are useful for describing many types of variables. The Frequencies procedure is a good place to start looking at your data.

Descriptive

The Descriptive procedure displays univariate summary statistics for several variables in a single table and calculates standardized values (z scores). Variables can be ordered by the size of their means (in ascending or descending order), alphabetically, or by the order in which you select the variables (the default).

Independent-Samples T Test

The Independent-Samples T Test procedure compares means for two groups of cases. Ideally, for this test, the subjects should be randomly assigned to two groups, so that any difference in response is due to the treatment (or lack of treatment) and not to other factors.

One-Way ANOVA

The One-Way ANOVA procedure produces a one-way analysis of variance for a quantitative dependent variable by a single factor (independent) variable. Analysis of variance is used to test the hypothesis that several means are equal. This technique is an extension of the two-sample t test.

Repeated Measures ANOVA

GLM Repeated Measures analyzes groups of related dependent variables that represent different measurements of the same attribute. This dialog box lets

you define one or more within-subjects factors for use in GLM Repeated Measures. Note that the order in which you specify within-subjects factors is important. Each factor constitutes a level within the previous factor.

All the statistical calculations were done through SPSS 16.0 (2007) for windows.

RESULTS

RESULTS

Table 2: Age distribution in years

Age Distribution		GROUP C	GROUP D	GROUP F
Number of patients in Age group	20-29	7	10	8
	30-39	9	14	11
	40-49	14	6	11
Mean Age		35.4	32.7333	34.7
Standard deviation		8.95	6.84	7.43
Minimum Age		20	20	22
Maximum Age		45	45	45

FIGURE 15: Graph1: Age distribution in years

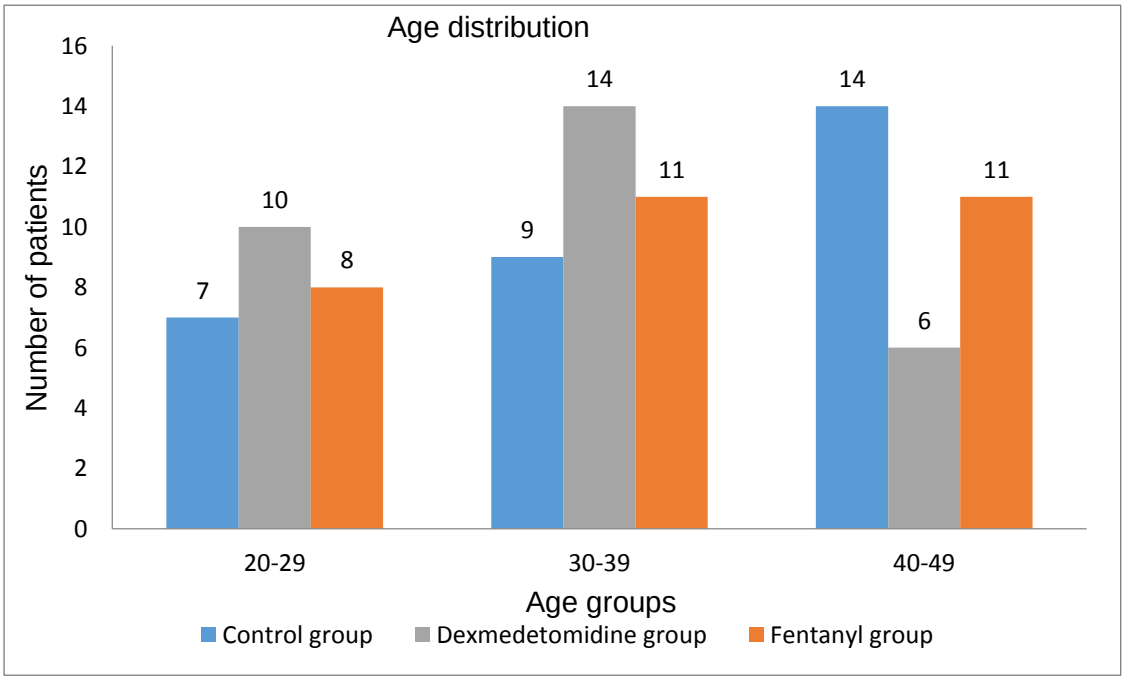


Table 1 shows the age distribution of the patients in all the three groups. The minimum age in group C (control group) and group D (Dexmedetomidine group) is 20 years and the maximum age in group B is 45 years. The minimum age in group F (Fentanyl group) is 22 years and maximum age is 45 years. The mean age in group C (control group) is 35.4 ± 8.95years, group D (Dexmedetomidine group) is 32.73 ± 6.84

yrs and group F (Fentanyl group) is 34.7 ± 7.43 years. There is no significant differenc e in the age of patients between the groups. P-value 0.501(which is more than 0.05 a t 5% significance level) indicates that all the three groups are similar with respect to age distribution.

Table 3: Sex distribution

	GROUP C		GROUP D		GROUP F	
Sex Distribution	**Number of patients**	**% of patients**	**Number of patients**	**% of patients**	**Number of patients**	**% of patients**
Female	9	30.0%	10	33.3%	9	30.0%
Male	21	70.0%	20	66.7%	21	70.0%

FIGURE 16: Graph 2: Sex distribution

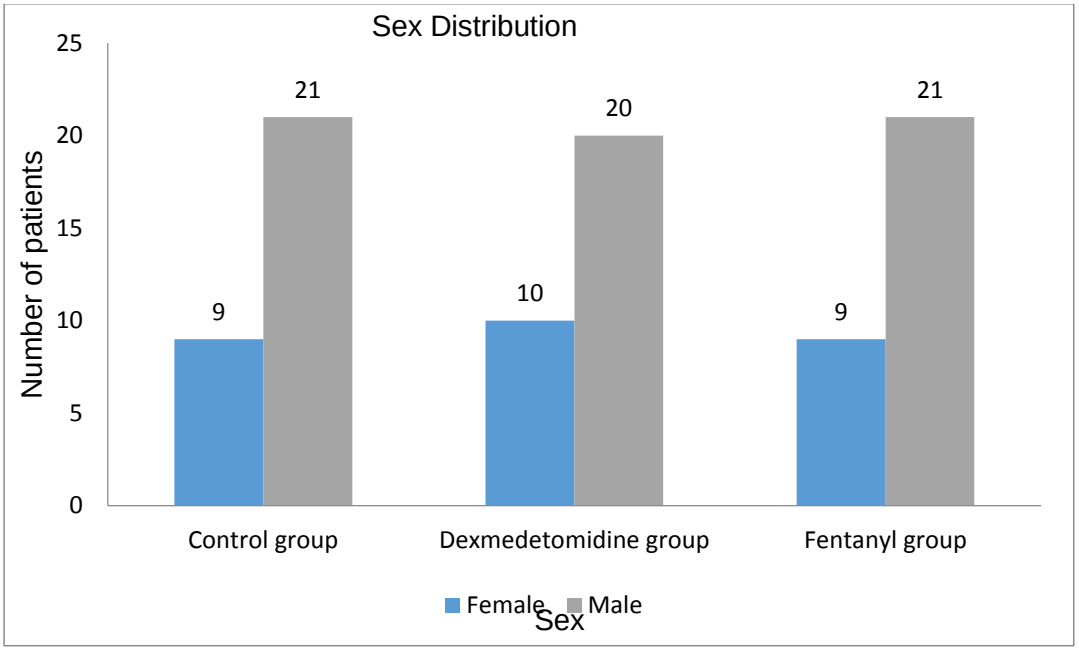


Table 2 shows the sex distribution of the patients in all the three groups. The re is no significant difference in the sex distribution of the patients between the grou ps (P>0.05).

Table 4: Height distribution in centimeters

Height in cms	GROUP C	GROUP D	GROUP F
N	30.0	30.0	30.0
Mean	166.0	168.3	168.0
Standard deviation	5.9	5.7	4.8
Minimum	154.0	160.0	158.0
Maximum	176.0	179.0	178.0

FIGURE 17: Graph 3: Height distribution in centimeters

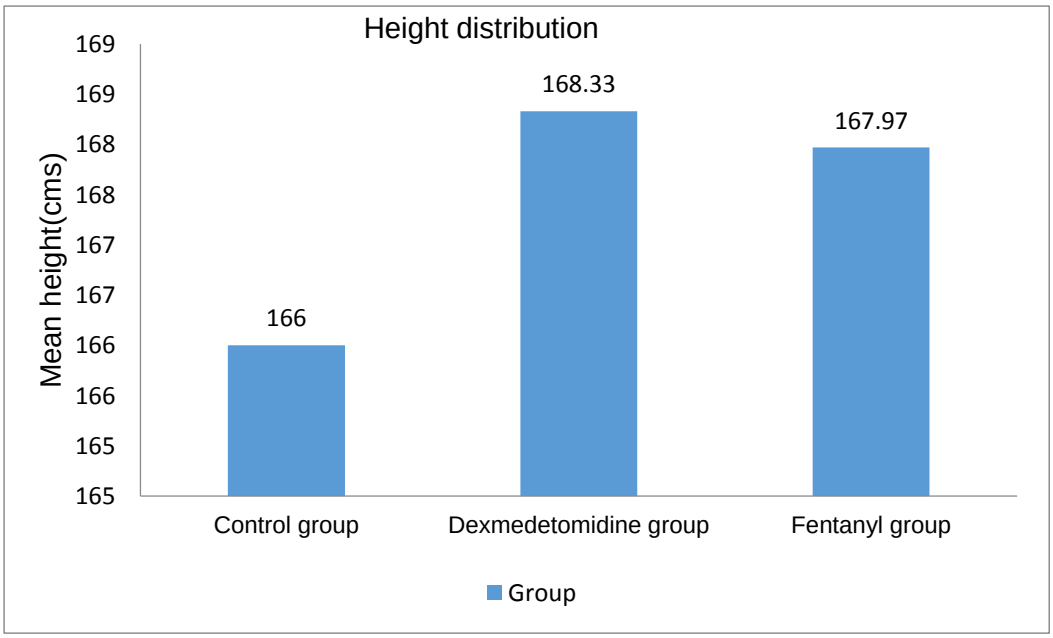


Table 3 shows the height distribution of patients. The mean height in group C (control group) is 166.00± 5.9cm, group D (Dexmedetomidine group) is 168.30± 5.7 cm and group F (Fentanyl group) is 168.0±4.8cm. The minimum height is 154cm in group C (control group), 160cm in group D (Dexmedetomidine group) and 158cm in group F (Fentanyl group). The maximum height is 176 cm in group C (control group) and 179cm in group D (Dexmedetomidine group) and 178 cm in group F (Fentanyl group). P value 0.141(p>0.05) suggests that there is no significant difference in the height of patients between the groups.

Table 5: Body weight distribution in kilograms

Weight Distribution	GROUPS		
	GROUP C	GROUP D	GROUP F
N	30.0	30.0	30.0
Mean	62.2	62.8	65.8
Standard Deviation	8.3	9.4	9.9
Minimum	45.0	50.0	50.0
Maximum	75.0	90.0	90.0

FIGURE 18: Graph 4: Body weight distribution in Kilograms

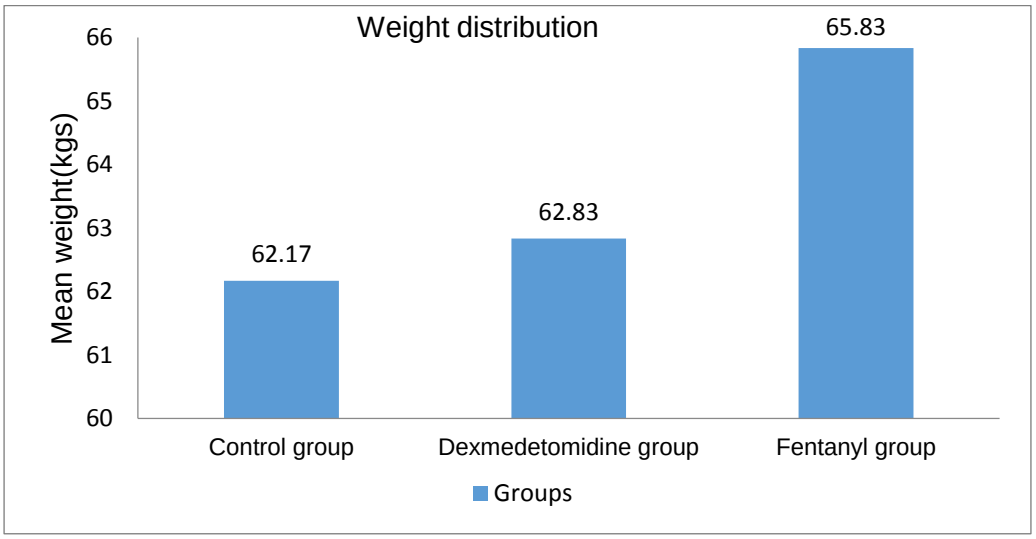
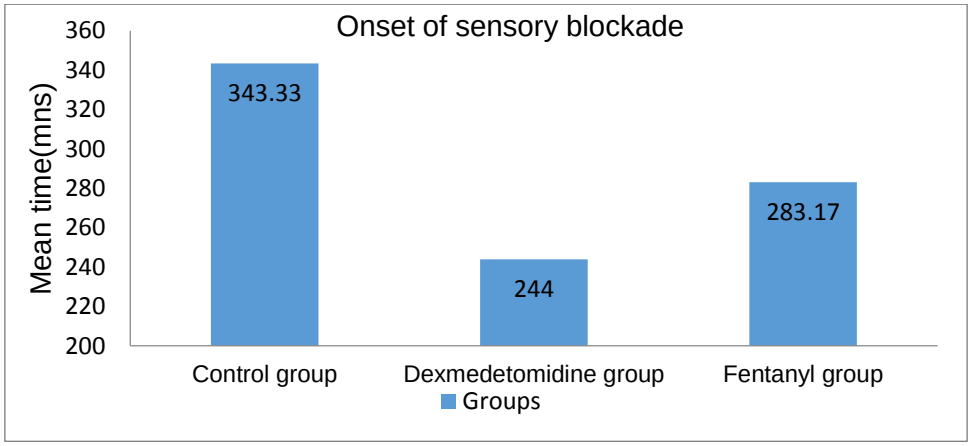


Table 4 shows the body weight distribution of patients. Mean body weight of group C (control group) is 62.2 ± 8.3 kg, group D (Dexmedetomidine group) is 62.8 ± 9.4kg and group F (Fentanyl group) is 65.8±9.9 kg. Minimum body weight in group C (control group) is 45 kgs and 50 kgs in group D (Dexmedetomidine group) and in grou p F (Fentanyl group). Maximum body weight in group C (control group) is 75kgs and 90 kgs in group D (Dexmedetomidine group) and group F (Fentanyl group). P value 0 .205($p>0.05$) indicates there is no significant difference in the body weight of patient s between the groups.

Table 6: Time taken for onset of sensory blockade in seconds

Time taken for Onset of sensory blockade	Groups			P Value: GROUP C Vs GROUP D	P Value: GROUP C Vs GROUP F	P Value: GROUP D Vs GROUP F
	GROUP C	GROUP D	GROUP F			
Mean ±SD	343.33±53.52	244±70.31	283.17±47.60	0	0	0.028
Minimum	20	20	22			
Maximum	45	45	45			

FIGURE 19: Graph 5: Mean time taken for sensory block onset in seconds

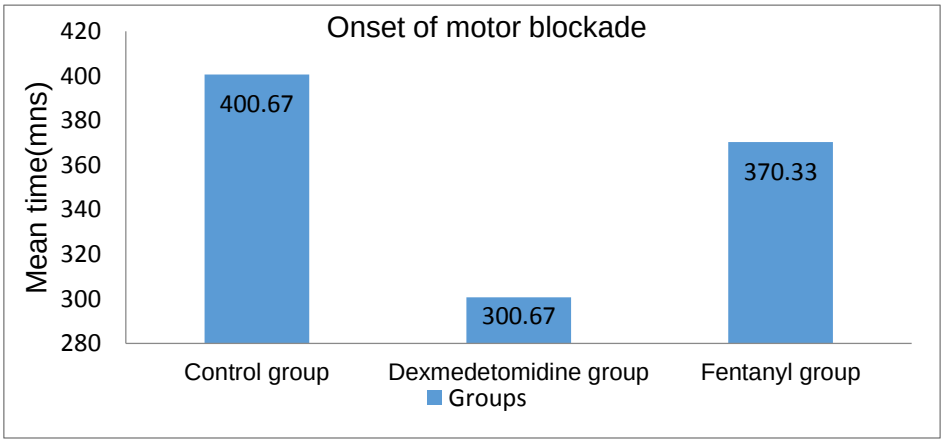


The mean time taken for onset of sensory blockade in group C (control group) is 343.33±53.52 seconds, 244.0±70.31 seconds in group D (Dexmedetomidine group) and 283.17±47.60 seconds in group F (Fentanyl group). All the three groups are statistically different. Group C (control group) is statistically different from group D (Dexmedetomidine group) and F (Fentanyl group) with p-value 0.0, which is less than 0.05 at 5% significance level. Also group D (Dexmedetomidine group) and F (Fentanyl group) are statistically different with p-value 0.028, which is less than 0.05 at 5% significance level.

Table 7: Time taken for onset of motor blockade in seconds

Time taken for Onset of motor blockade	Groups			P Value: GROUP C vs GROUP D	P Value: GROUP C vs GROUP F	P Value: GROUP D vs GROUP F
	GROUP C	GROUP D	GROUP F			
Mean ±SD	400.67±55.64	300.67±61.40	370.33±64.67	0	0.135	0
Minimum	270	180	270			
Maximum	540	420	600			

FIGURE 20: Graph 6: Mean time taken for motor blockade onset in seconds

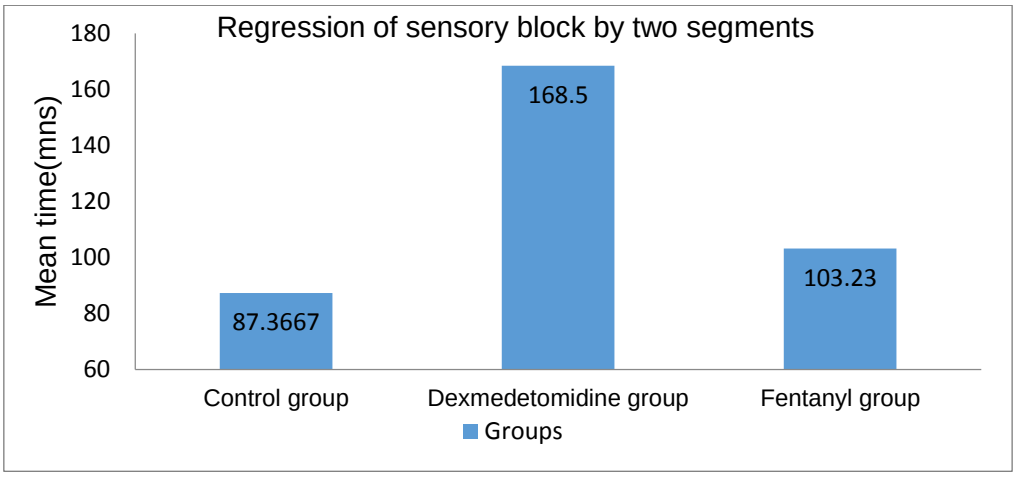


The mean time for onset of motor blockade in group C (control group) is 400.67±55.64 seconds, 300.67±61.40 seconds in group D (Dexmedetomidine group) and 370.33±64.67 seconds in group F (Fentanyl group). Group C (control group) is statistically different from group D (Dexmedetomidine group) with p-value 0.0, which is less than 0.05 at 5% significance level. Group C (control group) is statistically same as group D (Fentanyl group) with p-value 0.135, which higher than 0.05 at 5% significance level. Also group D (Dexmedetomidine group) and group F (Fentanyl group) are statistically different with p-value 0.0, which is less than 0.05 at 5% significance level.

Table 8: Time taken for regression of sensory block by two segments in minutes

Duration of two segment sensory regression in mins	GROUP C	GROUP D	Fentanyl group	P Value: GROUP C vs GROUP D	P Value: GROUP C vs GROUP F	P Value: GROUP D vs GROUP F
Mean ±SD	87.37±5.88	168.5±20.68	103.23±8.82	0.0	0.0	0.0
Minimum	75	130	90			
Maximum	100	210	120			

FIGURE 21: Graph 7: Mean time taken for regression of sensory block by two segments in minutes

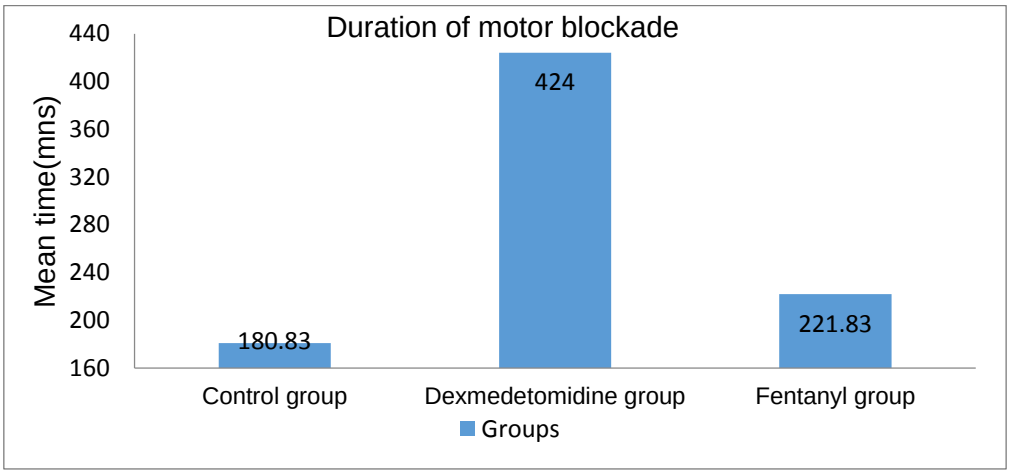


The mean time for regression of sensory block by two segments in group C (control group) is 87.37±5.88 mins, 168.5±20.68 mins in group D (Dexmedetomidine group) and 103.23±8.82 mins in group F (Fentanyl group). All the three groups are statistically different. Group C (control group) is statistically different from group D (Dexmedetomidine group) and group F (Fentanyl group) with p-value 0.0, which less than 0.05 at 5% significance level. Also group D (Dexmedetomidine group) and group F (Fentanyl group) are statistically different with p-value 0.0, which is less than 0.05 at 5% significance level.

Table 9: Duration of motor blockade in minutes.

Duration of motor blockade	Group			P Value: group C Vs Group D	P Value: group C Vs group F	P Value: group D vs Group F
	Group C	Group D	Group F			
Mean ±SD	180.83 ±24.95	424± 36.32	221.83 ±27.14	0	0	0
Minimum	140	380	150			
Maximum	230	540	280			

FIGURE 22: Graph 8: Duration of motor blockade in minutes

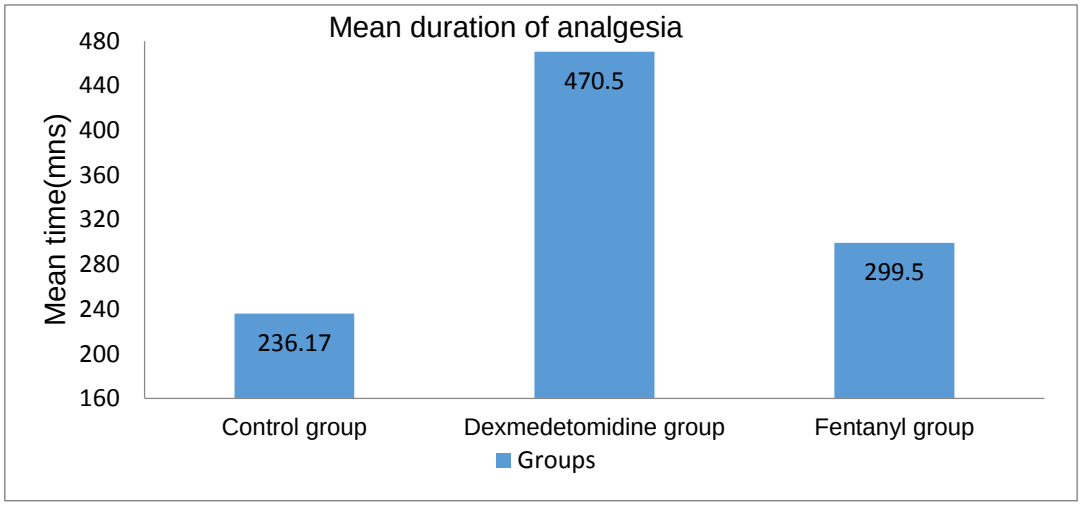


The mean duration of motor blockade in group C (control group) is 180.83±24.95 mins, 424±36.32 mins in group D (Dexmedetomidine group) and 221.83±27.14 mins in group F (Fentanyl group). All the three groups are statistically different. Group C (control group) is statistically different from group D (Dexmedetomidine group) and F (Fentanyl group) with p-value 0.0, which is less than 0.05 at 5% significance level. Also, group D (Dexmedetomidine group) and F (Fentanyl group) are statistically different with p-value 0.0, which is less than 0.05 at 5% significance level.

Table 10: Duration of Analgesia in minutes

Duration of Analgesia	Group			P Value: Group C vs Group D	P Value: Group C vs Group F	P Value: Group D vs Group F
	Group C	Group D	Group F			
Mean ±SD	236.17 ±20.37	470.5 ±59.89	299.5 ±47.98	0	0	0
Minimum	200	410	180			
Maximum	300	720	435			

FIGURE 23: Graph 9: Mean duration of Analgesia in minutes

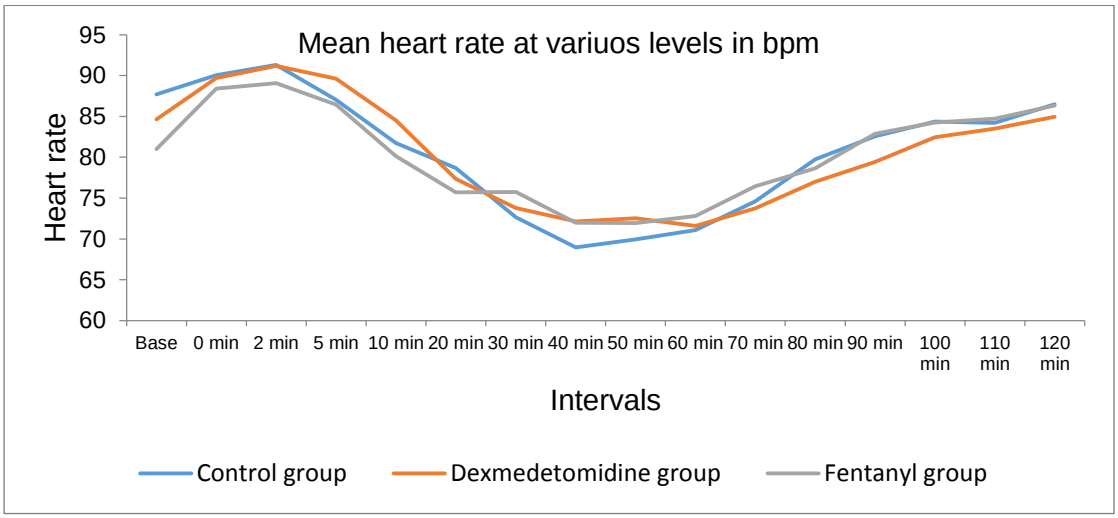


The mean duration of Analgesia in group C (control group) is 236.17±20.37 mins, 470.5±59.89 mins in group D (Dexmedetomidine group) and 299.5±47.98 mins in group F (Fentanyl group). All the three groups are statistically different. Group C (control group) is statistically different from group D (Dexmedetomidine group) and group F (Fentanyl group) with p-value 0.0, which is less than 0.05 at 5% significance level. Also group D (Dexmedetomidine group) and F (Fentanyl group) are statistically different with p-value 0.0, which is less than 0.05 at 5% significance level.

Table 11: Heart rate in bpm at various intervals

Heart rate	Groups			P Value: Control vs	P Value: Control vs	P Value: Dexmedetomidine
	Control group	Dexmedetomidine group	Fentanyl group			
BASAL_HR	87.7±14.22	84.63±10.89	81±8.53	0.556	0.066	0.44
HR_0_MIN	90.07±11.84	89.7±12.69	88.4±9.49	0.977	0.8	0.9
HR_2_MIN	91.3±10.31	91.2±11.78	89.06±9.92	0.99	0.647	0.721
HR_5_MIN	87.03±12.27	89.63±11.73	86.43±10.99	0.721	0.962	0.544
HR_10_MIN	81.73±11.77	84.53±13.15	80.13±11.29	0.688	0.846	0.345
HR_20_MIN	78.7±10.43	77.36±10.19	75.7±11.60	0.861	0.513	0.824
HR_30_MIN	72.66±8.41	73.8±10.18	75.73±12.07	0.922	0.523	0.753
HR_40_MIN	68.97±9.93	72.13±10.20	71.97±12.53	0.528	0.564	0.998
HR_50_MIN	69.93±10.50	72.53±11.58	71.93±11.90	0.6	0.725	0.977
HR_60_MIN	71.1±9.78	71.6±11.35	72.8±11.099	0.979	0.809	0.903
HR_70_MIN	74.6±9.25	73.73±11.48	76.43±10.90	0.984	0.709	0.591
HR_80_MIN	79.73±8.51	77±10.27	78.63±10.67	0.667	0.972	0.796
HR_90_MIN	82.57±8.02	79.43±9.44	82.87±8.14	0.484	0.928	0.273
HR_100_MIN	84.37±7.85	82.43±7.86	84.23±8.71	0.861	0.942	0.662
HR_110_MIN	84.2±7.56	83.5±7.03	84.73±8.49	0.867	0.995	0.812
HR_120_MIN	86.5±8.12	84.97±7.21	86.33±7.10	0.589	0.956	0.758

FIGURE 24: Graph 10: Mean heart rate at various interval in bpm



Basal mean heart rate is 87.7 ± 14.22 bpm in group C (control group). The me an heart rate has decreased by 18.73 bpm compared to Basal mean heart rate at 40th min.

Basal mean heart rate is 84.63 ± 10.89 bpm in group D (Dexmedetomidine gr oup). The mean heart rate has decreased by 13.03 bpm compared to Basal mean hea rt rate at 60th min.

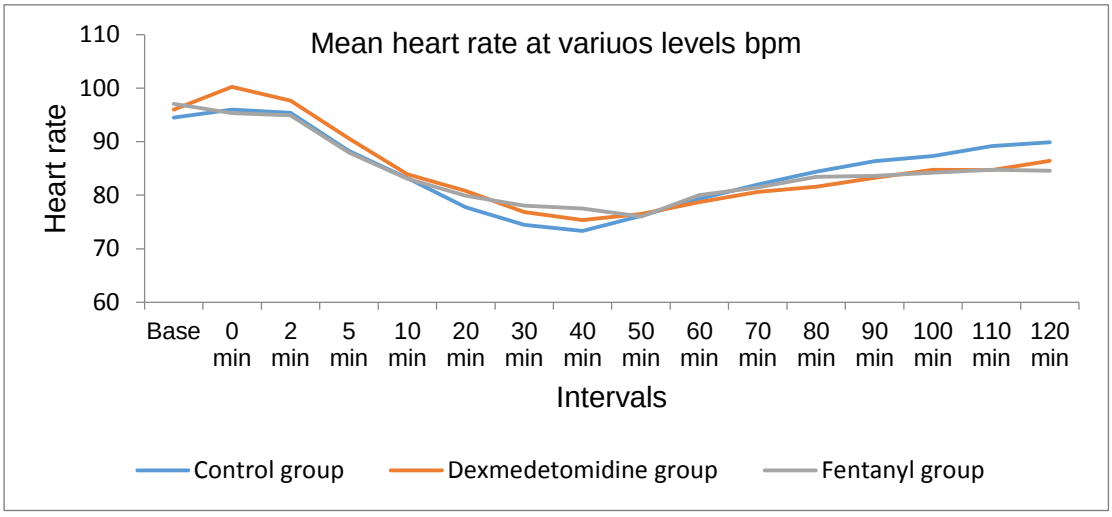
Basal mean heart rate is 81 ± 8.53 bpm in group F (Fentanyl group). The mean heart rate has decreased by 9.03 bpm compared to Basal mean heart rate at 50th min.

The mean heart rate from basal to 120th minute recording is statistically insignificant between the groups.

Table 12: Mean MAP at various intervals in mm Hg

MAP	Groups			P Value: Control vs Dexmedetomidine	P Value: Control vs Fentanyl group	P Value: Dexmedetomidine vs Fentanyl group
	Control group	Dexmedetomidine group	Fentanyl group			
BASAL_MAP	94.47±11.10	96±9.69	97.03±9.90	0.81	0.579	0.92
MAP_0_MIN	96±8.73	100.23±8.46	95.3±9.71	0.189	0.949	0.095
MAP_2_MIN	95.4±9.92	97.63±7.69	94.9±7.96	0.507	0.995	0.44
MAP_5_MIN	88.3±9.10	90.6±8.70	88±8.39	0.387	0.984	0.475
MAP_10_MIN	83.2±9.27	83.93±8.33	83.0667±8.54	0.831	0.978	0.921
MAP_20_MIN	77.73±9.24	80.8±8.74	79.9±9.12	0.254	0.449	0.92
MAP_30_MIN	74.47±9.53	76.87±9.39	78.03±9.97	0.481	0.244	0.886
MAP_40_MIN	73.33±10.22	75.37±8.91	77.5±9.34	0.625	0.184	0.665
MAP_50_MIN	76.13±9.77	76.5±7.97	76.03±8.73	0.985	0.999	0.978
MAP_60_MIN	79.3±7.64	78.7±6.66	80±8.99	0.928	0.964	0.8
MAP_70_MIN	82±6.74	80.6±5.49	81.43±6.31	0.618	0.903	0.864
MAP_80_MIN	84.37±7.19	81.6±6.10	83.43±7.02	0.238	0.814	0.556
MAP_90_MIN	86.37±6.63	83.23±5.04	83.6±6.18	0.112	0.179	0.969
MAP_100_MIN	87.3±6.52	84.77±6.29	84.2±5.91	0.264	0.138	0.934
MAP_110_MIN	89.17±6.07	84.7±6.82	84.77±6.16	0.021	0.024	0.999
MAP_120_MIN	89.9±5.66	86.43±7.4	84.6±5.19	0.081	0.004	0.485

FIGURE 25: Graph 11: Mean MAP at various intervals in mm Hg



Basal mean arterial pressure is 94.47±11.10 mm hg in group C (control group). The mean arterial pressure (MAP) has decreased by 21.14 mm hg compared to bas

al MAP at 40th min.

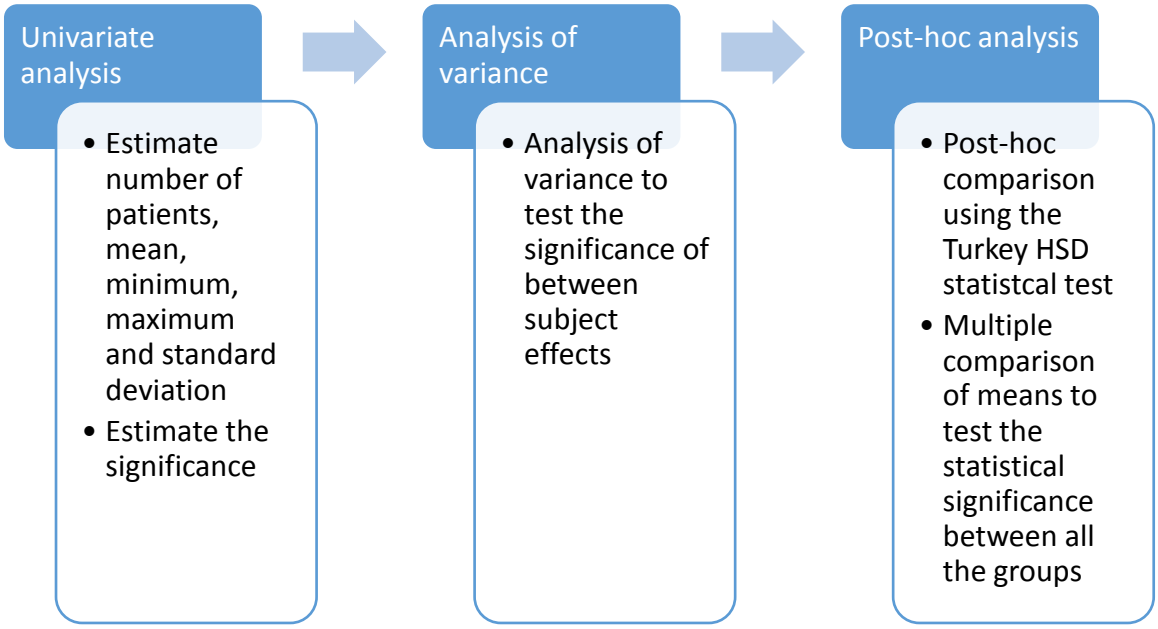
Basal mean arterial pressure is 96 ± 9.69 mm hg in group D (Dexmedetomidine group). The MAP has decreased by 20.63 mm hg compared to Basal MAP at 40th min.

Basal MAP is 97.03±9.90 mm hg in group F (Fentanyl group). The MAP has decreased by 21.00 mm hg compared to Basal MAP at 50th min. The mean MAP from basal to 120th minute recording is statistically insignificant between group c, group D and group F.

The mean MAP of group C (Control group) is statistically different from group D (Dexmedetomidine group) and group F (Fentanyl group) at 110th minute recording with p-value of 0.021 and 0.024 respectively at 5% significance level. But MAP of the group D (Dexmedetomidine group) and group F (Fentanyl group) are statistically insignificant with p-value of 0.999 at 5% significance level. It indicates that Control group MAP is different from Dexmedetomidine group and Fentanyl group MAP. Whereas Dexmedetomidine group and Fentanyl group MAP are statistically same.

The mean MAP at 120th min of group C (Control group) is statistically different from group F (Fentanyl group), whereas it is statistically same as group D (Dexmedetomidine group) MAP with a p-value of 0.004 and 0.081 respectively at 5% significance level. Group D (Dexmedetomidine group) and group F (Fentanyl group) MAP are statistically insignificant with a p-value of 0.485 at 5% significance level. It indicates Control group MAP is statistically different from Fentanyl group MAP and Dexmedetomidine group MAP. Dexmedetomidine group MAP and Fentanyl group are statistically same.

FIGURE 26: Statistical analysis methodology:



Appendix:

Table 13: Surgical procedure

Surgical procedure	Control group	Dexmedetomidine group	Fentanyl group
APPENDICECTOMY		2	2
ARTHRODESIS	1		
CORRECTION OF PENILE FRACTURE	1		
CRIF & IMIL		6	5
CRIF WITH IMIL	2		
CYSTOLITHOTOMY			1
EX FIX REMOVAL			1
FISSURECTOMY	2		
FISTULA REPAIR		1	
FISTULECTOMY	3		
FLAP COVERAGE		1	
HAEMORROIDECTOMY	1		
HERNIOPLASTY		3	4
IMPLANT REMOVAL	6	2	2
INCISION & DRAINAGE	2		
MUSCLE FLAP RECONSTRUCTION			1
ORIF K WIRE			1
ORIF & IMIL		3	
ORIF & LCP PLATING			4
ORIF & LCP PLATONG		1	
ORIF & PROXIMAL TIBIAL PLATE		1	
PROXIMAL TIBIAL LOCKING PLATE		1	
SPLIT SKIN GRAFTING	2		
TAH	2	6	4
TENDON REPAIR K WIRE FIXATION	1		
TRENDELENBERG SURGERY		1	2
TUBOPLASTY			1
URETHRO LITHOTOMY			1
VAGINAL HYSTERECTOMY	4		
VAGINAL HYSTRECTOMY		2	
WOUND DEBRIDEMENT	1		
WOUND DEBRIDEMENT	1		
WOUND DEBRIDEMENT & K WIRE FIXATION	1		
WOUND DEBRIDEMENT WITH K WIRE FIXATION			1

Table 14: Height of sensory blockade

Height of sensory blockade	Control group	Dexmedetomidine group	Fentanyl group
T10	1		
T4		2	
T6	1	20	21
T7		5	3
T8	28	3	6

Table 15: Side effects

Side effects	Control group	Dexmedetomidine group	Fentanyl group
HYPOTENSION AND BRADYCARDIA	1		
ABSENT	12	12	16
BRADYCARDIA	3	2	2
BRADYCARDIA, HYPOTENSION			3
HYPOTENSION	12	6	7
HYPOTENSION , BRADYCARDIA		1	
HYPOTENSION AND BRADYCARDIA	2	1	
HYPOTENSION, BRADYCARDIA		3	
NAUSEA		1	
NAUSEA, BRADYCARDIA			1
NAUSEA, BRADYCARDIA , HYPOTENSION		1	
NAUSEA, HYPOTENSION		1	
NAUSEA, HYPOTENSION, BRADYCARDIA			1
NAUSEA, VOMMITING, BRADYCARDIA		1	
SEDATION		1	

DISCUSSION

DISCUSSION

Subarachnoid block has been most extensively used for lower abdominal and lower limb surgeries because of its simplicity, speed, reliability and minimal exposure to depressant drugs. The aim of good post-operative analgesia is to produce a long lasting, continuous effective analgesia with minimum side effects. Commonly used local anaesthetics for intrathecal anaesthesia are Lignocaine and Bupivacaine in India. Bupivacaine 0.5% heavy single intrathecal injection provides analgesia for 2-2.5hrs, but the post-operative analgesic duration is limited. Other method of prolonging analgesia is using a continuous epidural analgesia, which is technically more difficult and more costly.

Hence, an intrathecal additive to these local anaesthetics forms a reliable and reproducible method of prolonging post-operative analgesia and to prolong the duration of anaesthesia. This technique being simple and less cumbersome has gained a wide acceptance.

A number of adjuvants to local anesthetics for spinal anaesthesia like opioids (fentanyl and buprenorphine), benzodiazepines (midazolam), ketamine and neostigmine have been used. The most common agents used are opioids and they have formed a cornerstone option for the treatment of post-operative pain.[52]

Neuraxial administration of opioids along with local anaesthetics improves quality of intra operative analgesia and also provides post-operative pain relief for longer duration[66]. Highly hydrophilic opioids such as morphine, though provides excellent intra and post-operative analgesia, its use has become limited because of delayed respiratory depression occurring as a result of rostral spread in intrathecal space.

Fentanyl, a highly lipophilic μ-receptor agonist opioid, has rapid onset of action following intrathecal injection. Fentanyl exerts its effect by combining with opioid receptors in the dorsal horn of spinal cord and may have a supraspinal spread and action. It is associated with fewer side effects compared to morphine. It has become a very popular additive to hyperbaric bupivacaine in recent times. However it has associated side effects like pruritus, nausea and vomiting and even a serotonin syndrome related to intrathecal fentanyl has been reported[5].

Spinal opiates prolong the duration of analgesia, but they do have drawbacks of late and unpredictable respiratory depression, pruritus, nausea, vomiting and urinary retention.[75, 76] which requires constant postoperative monitoring and urinary catheterization. Hence opioids are not ideally suited for all patients and for ambulant surgeries.

Hence there is a requirement of an adjuvant to be used along with local anesthetics which can produce prolonged analgesia without the above said side effects of opioids. Intrathecal alpha 2 agonists are found to have antinociceptive action for both somatic and visceral pain.[6] So in this context alpha 2 agonists may be a very useful drug along with the local anesthetic Bupivacaine 0.5% heavy for spinal anaesthesia.[52]

Dexmedetomidine an α-2adrenergic agonist is pharmacologically related to clonidine and is the most recent agent in this group approved by FDA in 1999 for the use in humans as short term medication (<24 hrs) for analgesia and sedation in intense care unit.[7] Dexmedetomidine is a highly selective alpha 2 agonist with 8times more affinity for alpha 2 receptors than clonidine.[52] The ratio of alpha 1:alpha 2 receptor affinity for dexmedetomidine is 1:1620 and for

clonidine is 1:220.[7,52] is commonly used for premedication and as an adjunct to general anaesthesia. It reduces opioid and inhalational anaesthetic requirements.[7]

While clonidine has been used as an adjuvant to local anaesthetic agents for intrathecal purposes with successful results, there are only a few studies available for dexmedetomidine as adjuvant to local anesthetic agents for intrathecal purpose. Dexmedetomidine has been recently introduced in India and hence there is a need to compare its effectiveness as a spinal adjuvant to bupivacaine.

Hence, we have undertaken this study to evaluate and compare the effect of adding dexmedetomidine or fentanyl as adjuvants to hyperbaric bupivacaine with a control group.

Ninety patients of ASA Grade-I and Grade-II posted for elective lower abdominal and lower limb surgeries were selected randomly into 3 groups (n=30). Randomization was done using simple sealed envelope technique. It was found that a sample size of 25 patients per group was required to detect an increase of 30 min in the time of a two-segment sensory regression with a standard deviation of 28 min. considering the drop outs, 30 patients were selected for each group in our study.

Demographic data: demographic data comparing age, sex, height, weight shows no statistical difference among the groups.

Hypothesis done before the study: it was hypothesized that both fentanyl and dexmedetomidine will produce a prolonged duration of postoperative analgesia compared to the control. There will be no difference regarding the duration of analgesia between fentanyl and dexmedetomidine as equipotent doses are used.

Dosages of drugs selected

Fentanyl

Various authors have used different doses of fentanyl for intrathecal blockade. Harbhej singh et al[63] in 1995, Biswas et al[66] in 2002, Khanna M S et al[65] in 2002, Gupta R et al[75] in 2011 have chosen 25 mcg fentanyl as an additive to intrathecal hyperbaric bupivacaine in their studies. Hence in our study we have chosen 25mcg fentanyl as an additive to hyperbaric bupivacaine.

Dexmedetomidine

Small doses of intrathecal dexmedetomidine (3µg) used in combination with bupivacaine in humans have been shown to shorten the onset of motor block and prolong the duration of motor and sensory block with hemodynamic stability and lack of sedation[52]. Al-Ghanem et al[71] studied the effect of addition of 5 µg dexmedetomidine or 25 µg fentanyl intrathecal to 10 mg isobaric bupivacaine in vaginal hysterectomy and concluded that 5 µg dexmedetomidine produces more prolonged motor and sensory block as compared with 25 µg fentanyl. Kanazi et al[52] found in their study that the supplementation of bupivacaine (12 mg) spinal block with a low-dose dexmedetomidine (3 mcg) produces a significantly shorter onset of motor block and a significantly longer sensory and motor block than bupivacaine alone. The results of Al-Mustafa et al[72] and Al-Ghanem et al[71] used higher doses of dexmedetoidine (5 mcg and 10 mcg), and found that its effect is dose-dependent and that the onset of sensory block to reach T10 dermatome was shorter with the use of dexmedetomidine.

Various authors have used different doses of dexmedetomidine for intrathecal blockade starting from 3 µg to 15µg along with local anesthetics.

Table 16: Depicting the various studies, dosages and the effects of Intrathecal Dexmedetomidine

Authors	Year	Dose of Dexmedetomidine used	Onset of sensory block in Dexmedetomidine group	Max sensory level attained in Dexmedetomidine group	Duration of analgesia in Dexmedetomidine group	Quality of motor block attained in Dexmedetomidine group	Duration of motor blockade in Dexmedetomidine group	Side effects
Kanazi GEet al.[52]	2006	3µg	8.6±3.7 mins	T6	303±75min	Bromage grade 3	250±76 min	Hypotension 1/16 patients
Al-Ghanem SM et al.[71]	2009	5µg	7.5±7.4mins	T6	274±73min	Bromage grade 3	240±60 min	Mild-moderate Hypotension 4/38 patients
Al-Mustafa MM et al.[72]	2009	5µg 10µg	6.3±2.7 mins 4.7±2 mins	-----	277.1±23min 338.9±44.8 mins	Bromage grade 3	246.4±25.7 min 302.9±36.7 min	Bradycardia 1/21 patients Hypotension 1/21 patients
Gupta R et al.[73]	2011	5µg	4.8±1.2 mins	T5	478.4±20.9 min	Bromage grade 3	------	Bradycardia 2/16 patients Hypotension 2/16 patients
Gupta R et al.[75]	2011	5µg	11.6±1.8 mins	T5	251.77±30.69 min	Bromage grade 3	421±21 min	No deleterious side effects
Eid HEA et al.[74]	2011	10µg 15µg	---	T5 T7	320±65.8min 336±58 mins	Bromage grade 3	280±46 min 336±58 min	Hypotension 3/15 patients Hypotension 2/16 patients
Shukla D et al.[76]	2011	10µg	2.27±1.09 mins	----	352±45 mins	Bromage grade 3	331±35 min	No deleterious side effects

[The spaces which have left blank (------) are the parameters not studied by the authors]

Kalso E et al[81] showed that 1:10 dose ratio between intrathecal dexmedetomidine and clonidine produces a similar effect in animal models. Not many studies are there to study the effects of intrathecal 10mcg dexmedetomidine and 25 mcg fentanyl on 15 mg hyperbaric bupivacaine. Hence in our study we selected 10 mcg dexmedetomidine and 25mcg fentanyl as adjuvants to hyperbaric bupivacaine.

Selection of route of administration

Availability in the parenteral form of α-2adrenergic agonists have made it possible to study their effect along with local anaesthetics. While clonidine has been studied extensively there are only a few studies available for intrathecal use of dexmedetomidine.

The rationale behind intrathecal administration of α_2-adrenergic agonists is to achieve a high drug concentration in the vicinity of α_2-adrenoreceptor in the spinal cord and it works by blocking the conduction of C and A delta fibers, increases potassium conductance and intensifies the conduction block of local anesthetics.[6]

Al-Mustafa MM et al.[72] in their study have used intravenous dexmedetomidine and found that it prolonged isobaric bupivacaine spinal anaesthesia. However the dose required was 1µg/kg dexmedetomidine bolus and an infusion of 0.5µg/kg/hr. whereas when dexmedetomidine has been used intrathecally by various authors the total dose is used from 3 µg to 15 µg. so intrathecal route is more specific and a low doses can be used. Hence in our study we have selected intrathecal route as the route of administration.

Analysis of data between the groups:

Sensory block characteristics

Onset of sensory blockade

In our study the mean time taken for onset of sensory block is 5.43±0.53 mins in the control group, 4.43±0.47mins in the fentanyl group and 4.04±1.10mins in the dexmedetomidine group. There is a statistically highly significant decrease in the onset of sensory blockade in dexmedetomidine group and in the fentanyl group compared to the control group.

In a study conducted by Al-Mustafa MM et al.[72] authors observed the onset of analgesia to be 9.5±3mins in control group and 6.3±2.7 mins and 4.7±2 mins in dexmedetomidine group (5 µg and 10 µg respectively) and in this study there was a significant reduction in the onset time of sensory block which concurs with our study.

In a study conducted by Kanazi GE et al.[52] authors observed the onset of analgesia to be 9.7±4.2 mins in control group, 7.6±4.4 mins in clonidine group and 8.76± 3.7 mins in dexmedetomidine group, which is more than the value in our study and there is no significant reduction in the onset time of sensory blockade. This could be due to the less doses of clonidine and dexmedetomidine used.

In a study conducted by Al Ghanem et al[71] and Gupta R et al[75] authors observed to have no significant difference in the onset of sensory block between the 2 groups Dexmedetomidine 5mcg and fentanyl 25mcg probably due to lesser dose of dexmedetomidine used.

Maximum level of sensory blockade achieved

In our study the maximum level of sensory blockade achieved is T4. Two out of 30 patients in dexmedetomidine group had T4 level of sensory blockade and 20 patients had achieved a block until T6. In fentanyl group 21 patients had achieved a block level of T6, and non of the had a block more T6 level. In control group the maximum level of sensory blockade was till T6 level in 1 of 30 patients. There is a statistical significant difference in the maximum level of sensory blockade in the dexmedetomidine group and fentanyl group compared to the control group.

In studies conducted by Kanazi GE et al[52], Al-Ghanem SM et al[71], Gupta R et al,[73] Gupta R et al.[75] and Eid HEA et al.[74] there was no statistically significant difference in the maximum level of sensory blockade which concurs with our study.

The time taken for regression of sensory block by two segments

The time taken for regression of sensory block by two segments in the present study is 87.37±5.88 mins in the control group, 103.23±9 mins in the fentanyl group and 168.5±20.68 mins in dexmedetomidine group. There is a statistically significant increase in the mean time taken for regression of sensory block by two segments in fentanyl and dexmedetomidine group compared to the control group.

In a study conducted by Gupta et al.[73] authors observed the time taken for regression of sensory block by two segments to be 70±20.3 mins in fentanyl group, and 120±22.2 mins in dexmedetomidine group, where they found a

significant prolongation of two segment regression which compares with our study.

In a study conducted by Vidhi Mahendu et al[82] authors observed that time taken for 2 segment sensory regression was 147±21 min in dexmedetomidine group, 117±22min in clonidine group, 119±23 min in fentanyl group and 102±17 in control group which were statistically significant.

Duration of effective post-operative analgesia

The mean duration of analgesia in our study is 236.17±20.37 mins in control group, 299.5±48 mins in fentanyl group and 470.5±59 mins in dexmedetomidine group. There is a statistically highly significant increase in the duration of analgesia in dexmedetomidine and fentanyl group compared to the control group.

In studies conducted by Gupta R et al[73], Gupta R et al[75], and Eid HEA et al.[74] authors observed a statistically significant increase in the mean duration of analgesia in dexmedetomidine group which concurs with our study.

Motor block characteristics

Onset of motor blockade

In our study the mean time for onset of motor block is 6.40±0.55 mins in control group, 6.10±1.04 mins in fentanyl group and 5±1.01 mins in dexmedetomidine group. There is a statistically highly significant decrease in the mean time for onset of motor blockade in the dexmedetomidine group compared to fentanyl group compared to the control group.

In studies conducted by Kanazi GE et al[52], Al-Mustafa MM et al[72], Gupta R et al.[73] and Shukla D et al.[76] in the dexmedetomidine group authors observed a significant decrease in the mean time for onset of motor blockade which concurs with our study.

Duration of motor blockade

In our study the mean duration of motor blockade was 181±25 mins in control group, 222±27.14 mins in fentanyl group and 424.35±36.32 mins in dexmedetomidine group. There is a statistically significant increase in the duration of motor blockade in dexmedetomidine group and fentanyl group compared to the control group.

This compares with study conducted by Kanazi GE et al.[44] where the mean duration of motor blockade is 163±47 mins in control group, 216±35 mins in clonidine group and 250±76 mins in dexmedetomidine group which is less than the value in our study. This could be due to the less doses of clonidine and dexmedetomidine used.

Our study concurs with studies conducted by Al-Mustafa MM et al,[72] Al-Ghanem SM et al[71], Gupta R et al,[73] Gupta R et al,[75] Eid HEA et al.[74] and Shukla D et al.[76], authors observed a significant increase in the duration of motor blockade in dexmedetomidine group compared to fentanyl group which was more than control group.

HEMODYNAMIC EFFECTS

MEAN ARTERIAL BLOOD PRESSURE: In the control group we observed a maximum fall in mean MAP of 21.14 mmHg from mean basal MAP at 40th min,

in the fentanyl group it was 21 mmHg at 50th min and in the dexmedetomidine group it was 20.63 mmHg at 40th min.

There was statistically no significant difference in any of the three groups regarding fall in MAP. However it was found that there was a delay in maximum fall in MAP in the fentanyl group compared to the dexmedetomidine group and control group.

Fifteen patients in control group, eleven patients in fentanyl group and thirteen patients in dexmedetomidine group developed hypotension and were easily managed with intravenous fluids and vasopressor.

In a study conducted by Al-Ghanem SM et al.[71] authors observed that the hypotension (fall in MAP of>30% of preinduction value) was mild to moderate in both dexmedetomidine and fentanyl group. 4/38 patients in dexmedetomidine group and 9/38 patient in fentanyl group had hypotension but it did not reach a significant difference.

Hemodynamic disturbances resulting from intrathecal Alpha 2 agonists depends upon other factors like segmental site of injection, patient position, preloading and baricity of local anaesthetic employed.[6]

HEART RATE

In the control group we observed a maximum decrease in the mean heart rate of 19 bpm from basal value at 40th min, in the fentanyl group it was 10 bpm at 50th min and in the dexmedetomidine group it was 13 bpm at 60th min.

There was no statistically significant difference in any of the three groups regarding decrease in the mean heart rate. However it was found that there was a delay in maximum decrease in the mean heart rate in the dexmedetomidne group compared to the fentanyl group and the control group.

Nine patients in dexmedetomidine group, seven patients in fentanyl group and five patient in control group had bradycardia which is statistically not significant.

Bradycardia was easily reversed with 0.6mg intravenous atropine in all the patients.

Our study is consistent with the studies done by Kanazi GE et al[52], Al-Ghanem SM et al[71], and Al-Mustafa MM et al[72], who observed that there was no significant difference in mean value of heart rate throughout the intraoperative and postoperative period.

CONCLUSION

CONCLUSION

From the present study it can be concluded that intrathecal dexmedetomidine in the dose of 10μg in 3 ml 0.5% heavy bupivacaine in patients undergoing elective lower abdominal and lower limb surgeries,

- Decreases the onset time for sensory blockade
- Decreases the onset time for motor blockade
- Produces prolonged postoperative analgesia
- Produces prolonged sensory blockade
- Produces prolonged motor blockade
- Produces sedation in which patients were asleep and easily arousability
- Produces hemodynamic changes which could be easily managed.

It was not associated with side effects like cardiovascular change in rate and rhythm, respiratory depression and hence can be an attractive alternative for opioids for prolonging spinal analgesia.

Dexmedetomidine when used intrathecally along with bupivacaine significantly prolongs the duration of sensory, motor blockade and duration of effective post op analgesia and as there was no clinically significant difference between fentanyl and dexmedetomidine on spinal block characteristics, use of dexmedetomidine as adjuvant to hyperbaric bupivacaine in spinal anaesthesia is an attractive alternative especially in those surgeries requiring long duration.

SUMMARY

SUMMARY

The present study entitled "A COMPARATIVE STUDY OF INTRATHECAL DEXMEDETOMIDINE 10mcg AND FENTANYL 25mcg AS ADJUVANTS TO 0.5% HYPERBARIC BUPIVACAINE IN SPINAL ANAESTHESIA WITH A CONTROL GROUP" was undertaken to evaluate the efficacy and the safety of dexmedetomidine or fentanyl as adjuvant to intrathecal hyperbaric 0.5% bupivacaine.

Ninety patients were randomly divided into three groups, each group consisting of thirty patients (n=30):

Group C (control group): received 15 mg of 0.5% hyperbaric bupivacaine with 0.5 ml normal saline.

Group F (fentanyl group): received 15 mg of 0.5% hyperbaric bupivacaine with 25 µg fentanyl.

Group D (dexmedetomidine group): received 15 mg of 0.5% hyperbaric bupivacaine with 10µg dexmedetomidine.

All patients of age group between 20 to 45 years of either sex, belonging to ASA class I and II posted for elective lower abdominal and lower limb surgeries under spinal anaesthesia were included in the study.

Patients who had contraindication for spinal anaesthesia, pregnant women, patients posted for emergency surgery, patients whose weight more than 120 kg, patients whose height less than 150cm were excluded from the study.

The onset, maximum level and duration of sensory blockade, motor blockade and hemodynamic parameters were studied

Table 17: Results obtained in our study

Spinal block characteristics	Group F	Group C	Group D
Time taken for onset of sensory blockade	4.43±0.47 mins	5.43±0.53 mins	4.04±1.1 mins
The time taken for regression of sensory block by two segments	103.23±9 mins	87.37±6 mins	168.5±21mins
Duration of effective analgesia	299±48 mins	236.17±20.37mins	470±59 mins
Onset of motor blockade	6.10±1.04 mins	6.40±0.55 mins	5±1.01 mins
Duration of motor blockade	222.±27.14 mins	181±25 mins	424.35±36.32mins

It is found from our study that in dexmedetomidine group and fentanyl group there is an early onset of both sensory and motor blockade compared to control group and duration of sensory, motor blockade and duration of analgesia is significantly prolonged in the dexmedetomidine group and fentanyl group compared to the control group.

Hemodynamics were preserved both intraoperatively and postoperatively. However there was a small percentage of patients who developed significant fall in blood pressure and bradycardia which were easily managed without any untoward effect. Thirteen patients in dexmedetomidine group and eleven patients in fentanyl group and fifteen patients in control group developed hypotension requiring treatment. Nine patients in dexmedetomidine group, seven patients in fentanyl group and five patient in control group developed bradycardia requiring treatment.

No patient had any respiratory depression, or shivering in either of the groups. Four patients in dexmedetomidine group and two patients in fentanyl group had nausea and vomiting.

In the present study the efficacy of intrathecal dexmedetomidine and fentanyl were compared and we noticed that intrathecal dexmedetomidine was better than fentanyl with regards to onset and duration of both sensory and motor blockade as well as duration of analgesia. Hence dexmedetomidine is a better neuraxial adjuvant compared to fentanyl for providing early onset of sensory and motor blockade, and prolonged duration of sensory, motor block and post-operative analgesia.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Brown DL. Spinal, epidural and caudal anesthesia. 7th ed. Chapter 43. Miller's Anesthesia, Miller RD, ed.Philadelphia: Elsevier Churchill livingstone; 2010:1653-60.
2. Corbey MP, Bach AB. Transient radicular irritation (TRI) after spinal anaesthesia in day-care surgery. Acta Anaesthesiol Scand 1998; 42: 425–429.
3. Colin VJ. Spinal anesthesia – principles. 3rd edition. In: Principles of anesthesiology, Philadelphia: Lea & Febiger; 1993.1452-1497.
4. Saxena A K, Arava S K. current concepts in neuraxial administration of opioids and non-opioids: An overview and future prespectives. Indian J Anaesth. 2004; 48:13-24.
5. Morgan M. The rational use of intrathecal and extradural opioids. Br J Aanesth. 1989; 63: 165-188.
6. Ozkardesler S, Gurpinar T. Akan M, Kora et al. A possible perianaesthetic serotonin syndrome related to intrathecal fentanyl. J Clin Anaesth. 2008; 20: 143-145.
7. Eisenach James C, De Kock Marc, Klimscha, Walter. Alpha sub 2- adrenergic agonist for regional anesthesia. A clinical review of clonidine. Anesthesiology: 1996; 85:655-674.
8. Ralph Getler, Clieghton H Brown, Mitchel H, Silvius N. Dexmedetomidine:a novel sedative analgesic agent. Baylor University Medical Centre Proceedings. 2001; 14(1).
9. Bernards CM Epidural and spinal anaesthesia.6th ed. Chapter 37. Clinical Anaesthesia, Barash PG, Cullin.BF, Stoelting R K,, eds. Philadelphia: Lippincott Williams & Wilkins;2009.pp.928-37.

10. Lee J A, Atkinson R S, Walt M S. Text book of Anaesthesia. Anatomy, chapter 2. Sir Robert Macilnosh's lumbar puncture and spinal analgesia; Intradural and extradural, 4th edition Edinburg 2001; Churchill livingstone: 37-38.
11. Colin VJ. Spinal analgesia – physiological effects. 3rd edition. In: Principles of anesthesia: General and regional anaesthesia. Philadelphia: Lea & Febiger; 1993.1499-1516.
12. Drake et al: Gray's anatomy for students. Anatomy of vertebral column.
13. Ganong W F. review of medical physiology. 23rd edition New York: Mc Graw-Hill company. Chapter 34, circulation through special regions. 2010: 571.
14. Vincent J Collins. Principals of Anaesthesiology General and regional Anaesthesia. 3rd edition. Lee and Febiger. 1993: 1233-1281.
15. Morgan G E Jr, Mikhail M S, Murray MJ. Pain management. 4th edition. In:Clinical Anaesthesiology, eds. Newyork: Tata McGraw-Hill;2009.pp.361-368.
16. Christoph Stein, Andreas Kopf. Anaesthesia and treatment of chronic pain. Chapter 58. Millers Anaesthesia. 7th edition. 2010.
17. Wang J K, Nauss L A, Thomas J E. Pain relief by intrathecally applied morphine in man. Anaesthesiology 1979; 50: 149-151.
18. Adrea M Trescot, Sukdeb Datla, marion Lee, Hans Hansen. Pain physician. 2008; 11: 133-153.
19. Z P Khan, C N Ferguson, R M Jones. Alpha 2 and imidazole receptor agonist. Anaesthesia. 1999; 54: 146-165
20. Colin VJ. Spinal anesthesia – principles. 3rd edition. In: Principles of anesthesiology, Philadelphia: Lea & Febiger; 1993.1445-1497.

21. Stoelting R K, Hillier S C. Local anaesthetics. 4th ed. Chapter 7. In:Pharmacology and physiology in anesthetic practice, eds. Philadelphia: Lippincott Williams & Wilkins; 2006. pp. 179-99.
22. Dejong R H. basic sciences of regional anaesthesia. In regional anaesthesia and analgesia. 1st edition. David c Brown. W B Saunders Company. 1996: 132-137.
23. Bernard J. Regional anaesthesia in children. In Anaesthesia. ed by Ronald D Miller. 5th edition. Churchill Livingstone. New York; 1: 1564-1565.
24. Robert K stoelting. Opioid agonists and antagonists. Chapter 3. In: Pharmacology and physiology in anaesthetic practice. Philadelphia. Lippincott Raven publishers; 1999: 77-112.
25. Gourlay G K, Murphy T M Plummer et al pharmacokinetics of fentanyl in lumbar epidural and intravenous administration. Pain. 1989; 39:253-259.
26. Margert W, Alastair W. opioid agonist and antagonist. Chapter 7, in . Drugs and anaesthesia pharmacology for anesthesiologist. Williams and wilkins publishers, London. 2nd edition; 129-178.
27. Abramav D, Nogid B, Nogid A. Drug forecast. Pain J. 2005; 30(3): 158.
28. Scheinin H, Aantaa R, Anttila M, Hakola P, Helminen A, Karhuvaara S. Reversal of the sedative and sympatholytic effects of dexmedetomidine with specific alpha-2 receptor antagonist atipamazole; pharmacodynamic and kinetic study in healthy volunteers. Anaesthesiology. 1998; 89: 574-84.
29. Ma D, Hossain M, Raja Kumara Swamy N. Dexmedetomidine produces its neuroprotective effect via the alpha-2 receptor subtype. Eu J Pharmacol. 2004; 502: 87-97.

30. Fagerholm V, Scheinin M, Haaparanta M. Alpha -2 adrenoceptor antagonism increases insulin secretion and synergistically augments the insulinotropic effect of glibenclamide in mice. Br J Pharmacol. 2008; 154: 1287-96.
31. Moura E, Afonso J, Hein L. Alpha-2 adrenoceptor subtypes involved in the regulation of catecholamine release from the adrenal medulla of mice. Br J Pharmacol. 2006; 149(8):1049-58.
32. Jones MEP, Maze M. Can we characterize the central nervous system actions of alpha-2 adrenergic agonists? Br J Anaesth. 2001; 86(1): 1-3.
33. Derbyshire DR, Chmielewski A, Fell D, Vaters M, Achola K, Smith G. Plasma catecholamine response to tracheal intubation. Br J Anaesth. 1983; 55: 855-9.
34. Jaakola ML, Salonen M, Lentinen R, Scheinin H. The analgesic action of dexmedetomidine – a novel alpha-2 adrenoceptor agonist in healthy volunteer. Pain. 1991: 46: 281-5.
35. Panzer O, Moitra V, Roberet N Sladen. Pharmacology of sedative-analgesic agents – Dexmedetomidine, remifentanil, ketamine, volatile anaestheitcs and the role of Mu antagonists. Critical Clin. 2009; 25: 451-69.
36. Aho M, Erkola O, Kallio A, Scheinin H, Korttila K. Comparison of dexmedetomidine and midazolam sedation and antagonism of dexmedetomidine with atipamazole. J Clin Anaesth. 1993; 5: 194-203.
37. Hall JE, Jurich TD, Barney JA, Arian SR, Ebert TJ. Sedative amnestic, and analgesic properties of small dose of dexmedetomidine infusions. Anaesth Analg. 2000; 90: 699-705.

38. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anaesthesiology. 2009; 93: 382-94.
39. Arian SR, Ruchlow RM, Uhrich TD, Ebert TJ. Efficacy of dexmedetomidine versus morphine for post-operative analgesia after major in-patient surgery. Anaesth Analg 2004; 98: 153-8.
40. Al-Metwalli RR, Mowafi HA, Ismail SA, Siddiqui AK, Al-Ghamdi, Shafi MA, et al. Effect of intraarticular dexmedetomidine on postoperative analgesia after arthroscopic knee surgery. Br J Anaesth 2008; 101: 395-9.
41. Yoshitomi T, Kohjitani A, Maeda S, Higuchi H, Shimada M, Miyawaki T. Dexmedetomidine enhances the local naesthetic action of lidocaine via an alpha-2A adrenoceptor. Anaesth Analg 2008; 107; 96-101.
42. Bellevile JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans I sedation, ventilation and metabolic rate. Anaesthesiology. 1992; 77: 1134-42.
43. Venn RM, Hell J, Grounds RM. Respiratory effects of dexmedetomidine in the surgical subject requiring intensive care. Crit Care Med. 2000; 4: 302-8.
44. Ramsay MA, Luterman DL. Dexmedetomidine as a total intravenous anaesthetic agent. Anaesthesiology. 2004; 101: 787-90.
45. Jalonen J, Hynyne M, Kuitunen A, Heikkila H, Perttilla J, Salmenpema M, et al. Dexmedetomidine as an anaesthetic adjunct in coronary artery bypass grafting. Anaesthesiology. 1997; 86: 331-45.

46. Pettinger W A, Umenura S, Smyth D D, Jeffries W B. renal alpha 2 adrenoreceptors and the adenylate cyclase-cAMP system. Biochemical and physiological interaction. American J Physiol. 1987; 251(2): 199-208.
47. Venn RM, Karol MD, Grounds RM. Pharmacokinetics of dexmedetomidine infusions for sedation of postoperative patients requiring intensive care. Br J Anaesth. 2002; 88: 669-75.
48. .Anttila M, Penttila J, Helminen A, Vuorilento L, Scheinin H. Bioavailability of dexmedetomidine after extravascular doses in healthy subjects. Br J Clin Pharmacol. 2003; 56(6): 691-93.
49. Sudheesh K, Harsoor S S. dexmedetomidine in anaesthesia practice, A wonder drug. Indian journal of anaesthesia. 2011; 55:323-324.
50. Greva A. dexmedetomidine; New Avenues. J Anaesthesia clinical pharmacol. 2011; 27: 297-302.
51. Maarouf M. Evaluation of effect of dexmedetomidine in reducing shivering following epidural anaesthesia. ASA annual meeting Abstract AA-49.
52. Kanazi GE, Aonad MT, Jabbour Khonry SI, AJ-Jazzar MD, Alameddine MM, AL-Yaman R, et al. Effect of small dose dexmedetomidine or clonidine on the characteristics of bupivacaine – spinal block. Acta Anaesthesiol Scand. 2005; 50: 222-7.
53. Memis D, Turan A, Karamanlioglu B, Pamukai Z, Kurt I. Adding dexmedetomidine to lidocaine for intravenous regional anaesthesia. Anaesth Analg. 2004; 98(3): 835-40.

54. El-Hennawy AM, Abd-Elwahab. Addition of clonidine or dexmedetomidine to bupivacaine prolongs caudal analgesia in children. Br J Anaesth. 2009; 103; 268-74.
55. Siobal SM, Kullet HR, Kivett AV, Tang FJ. Use of dexmedetomidine to facilitate extubation in surgical intensive care unit patients who failed previous weaning attempts following prolonged mechanical ventilational;a pilot study. Respir Care. 2006; 57: 492-6.
56. Weber MD, Thammasitboon S, Rosen DA. Acute discontinuation syndrome from dexmedetomidine after protracted use in pediatric patient. Pediatric Anaesth. 2008; 18: 87-8.
57. Darnell C, Steiner J, Seff, Szmuk, Peter, Sheerun, et al. Withdrawal from multiple sedative agent therapy in an infant; Is dexmedetomidine the cause or the cure? Pediatric Crit Care Med. 2010; 11: e1-e3.
58. Precedex (Dexmedetomidine) Package Insert. Abott Park II; Abott Laboratories; 2004.
59. Wulf, Hinnerk F W. The centennial of spinal anaesthesia. 1998; 89(2): 500-506.
60. Brill S, Gurman M, Fisher A. A history of administration of local anaesthetics and opioids.
61. Maduska A L, Hajghassemali M. A double blind comparison of butrophanol and meperidine in labour: Maternal pain relief and effect on the new born. Canadian anaesthetist society J. 1978; 25: 398-404.
62. Pert C B, Synder S H. Opiate receptor: Demonstration in new born tissue. Science. 1973; 179: 1011-1014.

63. Singh H, Yang J, Thornton K, Giesecke A H. Intrathecal fentanyl prolongs sensory bupivacaine spinal block, Can J Anaesth: 1995; 42(11): 987-997.
64. Karakan M, Tahtaci N, Goksu S. Synergistic effect of intrathecal bupivacaine and fentanyl in spinal anaesthesia. Gazi Medical J. 1999; 10:100-105.
65. Khanna M S, Singh IKJP. Comparative evaluation of bupivacaine plain versus bupivacaine with fentanyl in spinal anaesthesia in geriatric patients. Indian J Anaesth. 2002; 46(3): 199-203.
66. Biswas B.N, A. Rudra , B. K. Bose, S. Nath, S. Chakrabarty. Intrathecal Fentanyl with Hyperbaric Bupivacaine improves analgesia during Caesarean delivery and in early post-operative period. Indian J Anaesthesiology 2002; 46: 469-472.
67. Srivastava U, Kumar A, Saxena S, Gandhi N K, Dutta D, Chandra P et al. Hyperbaric bupivacaine combined with fentanyl for spinal anaesthesia during caesarean delivery. Indain J Anaesth. 2004; 48(1): 44-46.
68. Techanivate A, Urusopone p, Kiatgungwanglia P, Kosawiboonpol R. Intrathecal fentanyl in spinal anaesthesia for appendicectomy. J Med Assoc Thai. 2004; 87(5): 525-530.
69. Bogra J, Arora N, Srivastava P. Synergistic effect of intrathecal fentanyl and bupivacaine in spinal anaesthesia for caesarian section. BMC Anaesthesiology. 2005; 5: 1-6.
70. Syedhejazi M, Madarek E. The effect of small dose bupivacaine fentanyl in spinal anaesthesia on hemodynamics, nausea and vomiting in caesarean section. Pak J Med Sci. 2007; 23(5): 747-750.
71. Al-Ghanem SM, Massad IM, Al-Mustafa MM, Al-Zaben KR, Qudaisat IY, Qatawneh AM, Abu-Ali HM. Effect of Adding Dexmedetomidine versus Fentanyl

to Intrathecal Bupivacaine on Spinal Block Characteristics in Gynecological Procedures: A Double blind Controlled Study. American Journal of Applied Sciences 2009; 6(5): 882-887.

72. Al-Mustafa MM, Abu-Halaweb SA, Aloweidi AS, Mursbidi MM, Ammari BA, Awawad ZM, et al. Effect of Dexmedetomidine added to spinal Bupivacaine for Urological procedures. Saudi Med J. 2009; 30(3): 365-370.
73. Gupta R, Bogra J, Verma R, Kohli M, Kushwaha JK, Kumar S. Dexmedetomidine as an intrathecal adjuvant for postoperative analgesia. Indian J Anaesth 2011; 55(4): 347-351.
74. Eid HEA, Shafie MA, Youssef H. Dose-Related Prolongation of Hyperbaric Bupivacaine Spinal Anesthesia by Dexmedetomidine. Ain Shams Journal of Anesthesiology. 2011 July; 4(2): 83-95.
75. Gupta R, Verma R, Bogra J, Kohli M, Raman R, Kushwaha JK. A Comparative study of intrathecal Dexmedetomidine and Fentanyl as adjuvants to Bupivacaine. J Anaesthesiol Clin Pharmacol 2011; 87: 835-841.
76. Shukla D, Verma A, Agarwal A, Pandey HD, Tyagi C. Comparative study of intrathecal dexmedetomidine with intrathecal magnesium sulfate used as adjuvants to bupivacaine. J Anaesth Clin Pharmacol 2011; 27: 495-499.
77. S Fyneface-ogan, Gogo Job, Enyindah. Comparative study of single shot intrathecal bupivacaine with dexmedetomidine and bupivacaine with fentanyl on labour analgesia. International Scholarly Research Network Anesthesiology 2012; 08: 816984

78. Rachana Joshi, Jignesh Mori, Kamla H. Effect of intrathecal dexmedetomidine bupivacaine combination on duration of sub arachnoid block and post-operative analgesia. International journal of scientific research 2013; 2: 288-290.
79. Ji Eun Kim, Na Young kim, Hye Sun Lee, Hae Kaun Kil. Effects of intrathecal dexmedetomidine on low dose bupivacaine spinal anaesthesia in elderly patients undergoing transurethral prostatectomy. Biol Pharm Bull. 2013; 36(6): 959-965.
80. Solanki S L, Bharti N, Batra YK, Jain A, Kumar P, Nikhar SA. The analgesic effect of intrathecal dexmedetomidine or clonidine, with bupivacaine, in trauma patients undergoing lower limb surgery: a randomized, double-blind study. Anaesth Intensive Care. 2013; 4: 51-56.
81. Kalso E, Poyhia R, Rosenberg P. Spinal antinociception by dexmedetomidine, a highly selective α2-adrenergic agonist. Pharmacol Toxicol. 1991;68:140–3,
82. Vidhi Mahendru, Anurag Tewari, Sunil Katyal, Anju Grewal et al. A comparative study of intrathecal dexmedetomidine, clonidine, and fentanyl as adjuvants to hyperbaric bupivacaine for lower limb surgeries: A double blind controlled study. JOACP. 2013; 29: 496-502.

PROFORMA

PROFORMA

A COMPARATIVE STUDY OF INTRATHECAL DEXMEDETOMIDINE 10mcg AND INTRATHECAL FENTANYL 25mcg AS ADJUVANTS TO 0.5% HYPERBARIC BUPIVACAINE IN SPINAL ANAESTHESIA WITH A CONTROL GROUP

INVESTIGATOR- Dr. HARISH B G **GUIDE-** Dr. SOMASEKHARAM.P

NAME: AGE: SEX: WEIGHT: HOSPITAL NO:

DEPT: ASA GRADING: HEIGHT:

GROUP:

DIAGNOSIS AND OPERATION:

PREANAESTHETIC EVALUATION-

GENERAL PHYSICAL EXAMINATION:

PALLOR: CLUBBING: ICTERUS: OEDEMA:

LYMPHADENOPATHY: BP: PR: RR:

SYSTEMIC EXAMINATION- CVS: RS:

INVESTIGATIONS:

Hb%- BT/CT - BLOOD UREA- SERUM CREATININE-

RBS- Na+: K+: ECG- CHEST X RAY:

PROTOCOL: At 10:00pm-Tab Rantac 150 mg + Tab ALPRAZOLAM 0.5mg.

At 6:00AM-Tab Rantac-150mg+ Tab ALPRAZOLAM-0.5mg.

Preloading (5ml/kg):

Type of spinal needle used:

Lumbar puncture at: position of patient:

Objectives:

1. Time of injection: 0 min
2. Time of onset of sensory blockade(level upto T10 segment): _____ min
3. Time of onset of motor blockade(Bromage score 3): _____ min
4. Height of sensory blockade achieved:_____
5. Time of two segment sensory regression :_____min
6. Duration of motor blockade(Bromage score 0) : _____min
7. Time of initiation of rescue analgesia : _____min

	PRE SPINAL	Post spinal												
		5 MIN	10 MIN	15 MIN	20 MIN	30 MIN	60 MIN	90 min	120 MIN	180 min	240 min	300 min	360 min	420 min
HEART RATE In bpm														
SYSTOLIC BP mm of Hg														
DIASTOLIC BP In mm of Hg														
MAP in mm of Hg														
SPO2 in %														

Visual analogue scale:

Side effects:

1. Nausea : YES NO
2. Vomiting: YES NO
3. Pruritus YES NO
4. Respiratory depression: YES NO
5. Hypotension: YES NO
6. Bradycardia: YES NO
7. Urinary retention: YES NO
8. Sedation YES NO

Visual Analogue Scale: for pain

0 No pain
1-3 mild pain
4-6 moderate pain
7-10 severe pain

MASTER CHART

KEY TO MASTER CHART

HT	→ Height in centimeters
WT	→ Weight in kilograms
ONSB	→ onset of sensory block in seconds
ONMB	→ Onset of motor block in seconds
BHR	→ Basal mean heart rate in beats per minute
BMAP	→ Basal mean arterial pressure in mm of Hg
TTSR	→ Time to two segment sensory regression
DMB	→ Duration of motor blockade
IRA	→ Initiation of rescue analgesia
SE	→ Side effects
N	→ Nausea
B	→ Bradycardia
H	→ Hypotension
VH	→ Vaginal Hysterectomy
TAH	→ Total abdominal hysterectomy
IR	→ Implant removal
CRIF	→ Closed reduction internal fixation
IMIL	→ Intramedullary interlocking
ORIF	→ Open reduction internal fixation
PTP	→ Proximal tibial plating
LCP	→ Lateral condylar plating
SSG	→ Split skin grafting

CONTROL GROUP

										HEART RATE																MEAN ARTERIAL PRESSURE																			
SL.NO	IP.NO	AGE	SEX	HT	WT	SURGERY	ONSB	ONMB	HSB	BHR	HR 0 MIN	2 MIN	5 MIN	10 MIN	20 MIN	30 MIN	40 MIN	50 MIN	60 MIN	70 MIN	80 MIN	90 MIN	100 MIN	110 MIN	120 MIN	BMAP	MAP 0 MIN	2 MIN	5 MIN	10 MIN	20 MIN	30 MIN	40 MIN	50 MIN	60 MIN	70 MIN	80 MIN	90 MIN	100 MIN	110 MIN	120 MIN	TTSR	DMB	TRA	SE
1	941157	45	F	165	70	FISSURECTOMY	280	305	T8	74	79	77	76	71	73	67	68		64	76	78	90	98	76	74	103	99	105	106	96	92	86	82	78	78	82	80	84	82	78	80	90	230	260	A
2	899849	30	M	168	70	IR	420	540	T8	108	88	82	72	68	65	63	58	64	70	74	76	78	84	88	89	102	104	102	86	85	80	76	68	66	81	76	81	92	80	84	84	86	220	250	H
3	926115	20	M	170	60	SSG	360	375	T8	105	108	92	92	84	80	68	69	74	78	80	86	84	90	91	96	90	100	104	89	74	66	68	60	72	74	78	86	80	84	81	83	85	200	230	H
4	902645	20	M	164	60	IR	360	420	T10	112	108	102	97	98	88	90	96	98	88	90	96	98	88	92	96	106	102	100	97	95	94	87	84	86	88	82	88	92	98	94	96	80	210	265	A
5	921461	45	M	172	70	TENDON REPAIR K WIRE FIXATION	420	480	T8	104	108	110	88	81	76	70	67	68	70	70	78	90	92	88	86	97	100	102	92	86	80	78	82	84	82	86	81	88	92	96	91	88	185	240	A
6	922155	32	M	170	70	FISTULECTOMY	300	360	T8	95	98	96	90	83	91	78	73	76	73	72	80	74	80	86	88	114	108	110	103	98	94	89	88	82	88	92	90	96	98	99	93	90	190	240	A
7	922064	45	M	160	55	FISTULECTOMY	240	300	T8	112	108	106	100	96	104	89	78	68	70	78	78	80	90	84	86	100	104	102	93	88	68	64	68	70	74	78	80	82	80	86	90	88	180	250	H
8	922062	35	F	155	60	HAEMORROIDECTOMY	300	360	T8	82	88	86	80	78	70	62	56	64	64	70	78	74	80	78	86	96	99	98	83	76	70	73	74	78	82	80	84	88	84	89	90	80	185	210	B
9	937036	23	M	168	70	IMPLANT REMOVAL	360	480	T8	74	66	66	68	64	63	58	54	62	70	74	80	84	83	82	83	83	88	86	84	78	77	73	73	74	80	81	86	92	88	94	96	88	210	235	B
10	973433	40	M	174	75	CORRECTION OF PENILE FRACTURE	180	270	T8	93	94	98	94	95	87	82	80	88	86	90	84	83	85	90	88	110	108	112	92	88	84	89	90	87	84	82	84	86	83	90	91	85	190	220	A
11	979737	30	F	162	60	FISTULECTOMY	315	390	T8	108	110	104	121	113	87	80	84	80	84	86	88	84	82	90	92	117	114	110	98	96	81	77	70	68	64	70	78	80	82	86	82	90	210	300	H
12	975519	38	M	162	55	ARTHRODESIS	410	450	T8	89	88	98	73	75	73	74	74	80	66	70	74	78	84	90	90	93	96	90	95	94	99	97	94	106	90	92	97	91	94	98	92	80	200	240	A
13	927864	40	M	165	60	IR	290	360	T8	72	78	82	70	69	68	64	62	66	70	73	74	78	78	82	84	78	80	82	83	76	70	68	64	82	87	88	78	76	82	84	88	88	190	245	H
14	966202	26	M	164	55	IR	300	360	T8	64	83	89	88	84	96	70	60	65	68	74	88	100	90	92	98	89	90	92	80	77	72	64	66	70	77	81	88	78	84	88	90	95	180	230	H
15	988938	45	M	167	60	WD	315	370	T8	88	90	92	96	84	80	78	74	76	78	80	86	92	96	96	94	96	98	94	86	83	76	70	61	65	73	77	83	82	88	86	90	88	170	240	H
16	979473	45	M	172	70	CRIF WITH IMIL	345	390	T8	108	104	110	107	102	86	83	78	80	90	86	84	88	90	94	96	80	92	88	84	82	76	73	68	77	83	91	94	92	96	98	100	95	190	230	A
17	982450	20	M	175	70	WD	330	390	T8	75	82	86	88	78	75	76	67	63	60	66	68	74	80	74	76	90	92	96	94	82	77	70	62	63	68	72	70	77	82	84	88	85	200	260	H
18	931387	23	M	168	65	IR	360	390	T8	90	94	96	93	84	82	80	78	76	74	80	82	84	90	94	96	103	105	101	97	86	72	64	66	68	74	78	74	80	82	86	88	95	210	240	H
19	981395	21	M	164	65	SSG	360	405	T8	84	88	90	86	80	76	74	70	68	72	72	74	80	82	83	90	88	90	92	83	80	76	74	79	81	83	91	96	98	90	94	92	90	180	220	A
20	984281	40	M	176	70	CRIF WITH IMIL	370	420	T8	90	94	98	92	88	80	76		78	80	84	96	90	94	83	88	90	92	94	90	87	83	78	73	75	76	78	84	87	81	86	88	80	160	220	A
21	986708	34	M	170	65	FISSURECTOMY	360	405	T8	84	88	92	82	78	72	70	68	60	68	70	74	80	82	90	83	88	92	94	86	82	77	73	81	86	81	82	84	86	82	84	88	85	160	260	A
22	864529	45	M	168	65	I & D	375	420	T8	88	90	96	90	88	86	77	72	76	74	75	80	84	86	88	92	96	98	99	98	84	78	70	61	64	68	71	75	80	84	86	88	90	170	220	H
23	957600	36	F	162	55	VH	370	430	T8	80	88	84	74	68	66	64	62	58	56	64	72	78	73	77	82	78	80	82	70	68	63	61	60	64	70	74	75	80	82	86	84	95	170	230	H, B
24	981705	38	M	170	70	I & D	380	420	T8	88	90	94	96	88	84	70	68	64	70	74	88	90	86	84	88	96	98	97	86	81	66	60	66	70	70	80	84	88	93	86	89	100	150	210	H
25	1011787	45	F	155	45	VH	380	420	T8	66	70	78	64	63	68	70	54	56	58	60	64	68	74	78	82	106	104	98	96	97	88	83	80	76	80	86	92	94	98	103	105	90	160	240	B
26	1006340	32	F	158	45	TAH	340	410	T8	60	64	73	74	68	60	58	54	50	48	48	68	74	62	64	58	83	88	86	72	63	68	64	72	77	83	88	84	78	80	82	79	80	150	200	H, B
27	1002030	42	F	166	60	VH	310	380	T8	88	90	94	84	80	74	68	64	70	72	78	83	90	96	84	82	103	91	81	76	83	86	88	92	96	98	95	99	100	102	94	91	75	140	240	A
28	1010059	40	F	154	45	VH	390	420	T6	80	88	90	92	76	72	74	60	54	58	62	64	66	78	80	84	83	88	86	91	87	72	64	62	70	72	76	76	82	90	96	98	85	140	220	H,B
29	1006497	45	F	162	55	TAH	410	480	T8	88	90	92	94	94	88	83	74	67	70	74	76	78	74	70	78	103	102	109	90	83	80	73	71	75	86	91	92	92	86	87	89	95	155	230	A
30	483	42	M	174	70	WD	370	420	T8	82	88	86	90	74	91	64	78	79	84	88	95	86	84	78	90	73	78	70	69	61	67	80	83	74	85	82	88	90	92	90	94	80	140	210	H

FENTANYL GROUP

SL.NO	IP.NO	AGE	SEX	HT	WT	SURGERY	ONSB	ONMB	HSB	BHR	HEART RATE HR O MIN	2 MIN	5 MIN	10 MIN	20 MIN	30 MIN	40 MIN	50 MIN	60 MIN	70 MIN	80 MIN	90 MIN	100 MIN	110 MIN	120 MIN	BMAP	MEAN ARTERIAL PRESSURE MAP O MIN	2 MIN	5 MIN	10 MIN	20 MIN	30 MIN	40 MIN	50 MIN	60 MIN	70 MIN	80 MIN	90 MIN	100 MIN	110 MIN	120 MIN	TTSR	DMB	IRA	SE
1	928469	35	F	162	55	TRENDELENBERG SURGERY	300	360	T6	76	79	80	73	66	57	64	57	59	56	60	70	84	88	90	92	80	84	86	85	79	74	70	67	66	74	77	84	82	80	85	81	94	240	280	N, H, B
2	928473	40	M	178	80	CRIF & IMIL	300	480	T8	80	89	85	77	63	62	55	52	61	54	63	68	70	72	74	80	107	104	100	98	95	96	93	93	90	87	84	86	82	86	84	81	100	210	340	B
3	904673	40	M	176	80	MUSCLE FLAP RECONSTRUCTION	285	315	T6	82	88	85	74	67	68	64	64	75	70	80	78	88	90	94	96	107	105	103	88	80	70	66	65	64	61	70	78	74	76	74	70	90	210	360	H
4	931148	43	M	168	60	HERNIOPLASTY	290	360	T6	74	76	78	70	70	64	64	60	72	78	79	82	84	86	98	90	100	102	98	80	71	66	62	68	74	79	80	77	73	75	79	84	96	220	350	H
5	931022	34	M	168	55	HERNIOPLASTY	330	360	T8	84	88	90	92	83	76	80	76	71	76	76	80	80	85	90	89	89	92	96	93	88	84	88	86	83	87	86	93	96	84	88	94	104	280	330	A
6	942314	32	M	168	65	CRIF & IMIL	180	270	T6	102	98	99	94	90	94	96	94	87	87	92	87	89	89	90	90	110	106	103	99	78	73	68	66	63	70	73	71	75	78	80	81	108	240	310	H
7	936757	28	M	168	60	CRIF & IMIL	240	390	T6	98	100	105	100	95	93	92	93	83	85	90	93	92	92	93	89	92	96	89	86	87	89	86	89	83	89	87	80	83	84	83	86	110	250	330	A
8	933613	25	M	170	75	ORIF K WIRE	240	360	T6	92	88	82	80	76	74	74	72	72	80	85	80	82	88	81	86	86	89	82	81	79	76	73	74	73	83	83	75	80	94	76	79	90	230	310	A
9	935907	32	F	168	60	APPENDICECTOMY	300	340	T6	78	74	90	95	60	52	71	64	65	70	70	72	80	90	78	89	89	75	80	79	70	85	81	81	73	83	82	86	88	86	82	84	98	245	325	N, B
10	922131	30	M	176	80	IR	240	300	T7	84	92	88	83	80	79	77	71	77	80	89	90	94	100	98	96	109	106	100	98	88	86	89	82	70	76	82	98	94	91	95	97	100	200	435	A
11	936757	28	M	165	55	CRIF & IMIL	285	360	T6	90	90	88	84	84	78	90	94	88	84	80	84	84	86	81	90	83	73	72	72	67	62	60	70	73	78	75	79	73	77	82	81	102	220	310	H
12	933326	40	M	174	80	ORIF & LCP PLATING	230	330	T6	72	76	75	79	64	66	60	67	66	70	74	78	84	80	86	82	116	100	98	80	78	76	74	76	83	81	80	86	87	83	89	85	108	225	330	A
13	931674	45	M	170	65	CRIF & IMIL	315	375	T8	72	80	73	70	66	63	58	56	54	52	54	58	68	60	66	68	96	92	94	84	79	87	85	89	90	98	89	84	83	84	80	78	100	220	335	B
14	934620	45	M	172	70	WD	270	330	T6	76	80	86	80	76	70	74	78	68	70	74	78	90	94	90	85	86	89	90	77	66	63	71	66	70	72	81	87	87	92	89	86	120	210	280	H
15	918442	28	M	174	70	IR	190	330	T8	76	87	86	83	89	80	73	66	70	72	78	84	90	94	90	92	105	100	98	89	88	90	86	90	89	92	99	92	94	96	100	90	90	150	180	A
16	917578	45	F	162	55	ORIF & LCP PLATING	210	300	T6	68	84	89	96	86	85	84	79	68	67	78	76	78	82	88	90	94	72	99	73	95	84	88	84	81	90	83	91	88	89	90	91	95	160	240	A
17	918774	22	M	168	70	ORIF & LCP PLATING	240	480	T6	96	107	108	112	96	93	97	90	86	88	84	90	98	94	96	94	107	100	96	91	88	91	91	86	87	94	89	96	90	89	86	82	98	190	260	A
18	921148	45	M	164	65	ORIF & LCP PLATING	240	375	T6	90	86	80	82	90	69	74	62	63	70	88	96	90	88	87	84	110	104	98	92	91	87	88	90	92	96	90	88	84	82	84	81	98	190	220	A
19	946780	23	M	165	65	APPENDICECTOMY	300	330	T7	74	100	114	90	77	79	80	88	104	90	94	96	98	99	100	101	98	96	95	94	94	86	84	88	80	78	76	84	86	80	88	90	100	210	330	A
20	900429	35	F	164	60	TAH	345	390	T8	76	76	84	96	90	80	72	68	72	74	76	80	88	84	80	83	100	107	112	106	100	94	86	79	71	78	80	84	86	88	80	83	104	220	300	A
21	930975	38	M	168	70	HERNIOPLASTY	360	405	T8	74	90	94	98	96	86	83	81	76	74	78	76	81	84	83	80	96	98	94	88	86	91	89	83	80	86	82	83	86	88	81	86	104	225	320	A
22	976871	24	M	170	75	HERNIOPLASTY	330	400	T6	78	93	89	73	70	66	60	54	53	61	66	68	72	78	81	70	95	96	90	88	87	77	69	82	66	70	74	72	79	80	83	84	94	210	300	B,H
23	933196	30	M	164	60	CYSTOLITHOTOMY	330	390	T6	73	87	88	89	78	62	60	56	54	59	61	67	75	79	83	86	93	98	91	90	81	74	78	64	69	71	75	78	82	80	86	82	104	230	280	B,H
24	859291	24	F	158	50	TUBOPLASTY	330	390	T6	80	86	88	90	86	84	83	79	78	93	88	86	84	80	78	83	88	92	96	90	88	82	70	78	72	75	80	81	78	76	79	83	110	240	310	A
25	902042	36	M	168	70	URETHRO LITHOTOMY	300	330	T6	74	78	76	70	68	65	67	62	57	55	56	52	68	70	72	76	88	90	95	98	78	70	63	65	70	71	76	74	79	80	83	84	120	250	280	B,H
26	940032	45	M	174	90	EX FIX REMOVAL	255	300	T6	84	114	110	108	98	96	99	89	93	82	88	92	79	76	83	88	114	110	108	96	84	76	70	66	62	70	78	83	84	80	78	83	110	260	280	H
27	957457	40	F	165	65	TRENDELENBERG SURGERY	290	350	T6	74	96	92	90	78	79	83	68	72	77	78	76	83	86	79	85	93	98	100	97	86	76	74	75	76	83	91	94	86	90	94	88	100	230	280	A
28	955907	35	F	164	60	TAH	360	420	T6	90	98	90	95	94	85	82	75	76	78	80	84	85	79	83	88	94	98	95	90	84	77	82	78	85	82	86	76	77	80	83	85	115	210	240	A
29	1003340	42	F	166	60	TAH	310	390	T7	80	84	90	86	88	84	80	74	70	68	64	70	74	78	70	86	103	98	97	80	87	84	89	80	77	73	80	85	92	95	98	89	115	230	250	A
30	1006470	32	F	162	50	TAH	300	600	T6	83	88	90	84	80	82	76	70	68	64	70	68	74	76	80	82	83	89	92	78	70	71	68	65	69	73	75	78	80	83	84	90	120	250	290	H

DEXMEDETOMIDINE GROUP

											HEART RATE														MEAN ARTERIAL PRESSURE																		
SL.NO	IP. NO	AGE	SEX	HT	WT	SURGERY	ONSB	ONMB	HSB	BHR	HR 0 MIN	2 MIN	5 MIN	10 MIN	20 MIN	30 MIN	40 MIN	50 MIN	60 MIN	70 MIN	80 MIN	90 MIN	100 MIN	110 MIN	120 MIN	BMAP	MAP 0 MIN	2 MIN	5 MIN	10 MIN	20 MIN	30 MIN	40 MIN	50 MIN	60 MIN	70 MIN	80 MIN	90 MIN	100 MIN	110 MIN	120 MIN	TTSR	DMB	IRA	SE
1	933682	38	F	164	60	TAH	220	245	T6	78	108	106	101	109	72	77	76	74	81	84	86	82	80	76	74	107	103	102	87	80	84	80	78	76	82	84	86	80	81	78	70	200	460	520	N, H, B
2	947680	25	M	176	70	ORIF & PTP	210	230	T6	90	95	93	80	74	76	78	80	83	73	73	78	68	74	78	76	74	110	107	103	92	82	74	70	68	64	72	74	76	79	80	83	150	510	530	H
3	919294	35	M	170	65	CRIF & IMIL	170	180	T7	110	118	108	92	93	90	88	85	82	78	74	76	79	85	83	82	110	113	107	105	101	99	96	93	94	88	83	80	78	84	90	93	180	540	560	A
4	941240	45	F	160	50	VH	5	240	T6	82	80	88	84	83	80	84	74	75	78	74	82	84	86	88	90	88	86	96	84	81	73	71	83	81	86	88	94	92	86	88	90	160	490	530	H
5	928554	24	M	168	60	CRIF & IMIL	255	300	T8	76	72	71	70	70	56	52	58	76	62	66	76	78	84	88	85	94	97	92	89	91	83	86	83	83	80	84	81	88	90	94	93	130	460	520	B
6	911532	30	M	165	55	FLAP COVERAGE	180	240	T7	82	88	77	103	108	83	83	77	66	68	72	78	90	92	88	94	100	106	102	91	75	70	72	65	63	78	79	75	81	87	83	89	210	410	430	H
7	915895	39	M	174	70	IMPLANT REMOVAL	270	300	T6	80	88	89	85	86	87	76	80	70	64	67	78	80	84	86	83	92	96	93	99	92	91	76	74	78	77	80	84	83	91	93	99	130	420	480	A
8	921470	23	M	178	70	CRIF & IMIL	180	240	T7	98	104	118	98	96	81	69	74	84	90	98	94	96	98	90	100	106	108	85	88	78	70	68	65	70	69	70	78	87	87	80	89	200	400	460	H
9	927864	40	M	168	60	ORIF & IMIL	240	315	T6	84	82	88	80	76	74	70	61	62	66	60	66	68	79	72	74	88	92	90	80	78	87	84	78	93	86	86	90	84	82	88	90	140	440	720	S
10	979676	27	M	179	75	CRIF & IMIL	255	330	T4	118	120	118	128	90	84	89	85	80	88	84	80	86	88	98	88	105	108	102	104	81	75	72	75	78	74	76	84	86	90	94	96	170	410	445	A
11	952488	33	M	164	60	APPENDICECTOMY	270	315	T6	78	77	80	82	60	64	66	50	110	107	110	108	110	104	100	98	81	85	88	81	73	71	68	64	70	73	78	81	78	77	78	78	170	410	440	H,B
12	969720	30	F	168	55	FISTULA REPAIR	300	315	T6	90	92	88	93	65	56	55	59	68	78	81	89	84	88	90	92	83	88	86	72	72	72	65	68	70	72	78	74	82	76	70	74	150	430	480	H, B
13	953318	27	M	178	80	HERNIOPLASTY	310	360	T8	82	88	76	67	66	62	56	64	69	70	74	68	75	78	82	84	101	106	105	96	97	97	98	97	83	84	86	86	86	94	95	93	170	425	460	B
14	976858	30	M	170	65	CRIF & IMIL	240	305	T6	78	85	88	76	85	83	68	72	56	53	61	68	78	84	88	96	110	108	113	98	84	88	79	79	72	90	89	84	88	94	90	96	160	400	430	H, B
15	947270	27	M	164	60	HERNIOPLASTY	300	360	T6	88	96	94	99	106	90	85	78	72	66	72	74	74	76	80	80	91	95	94	91	87	85	85	85	80	80	85	83	84	88	85	90	160	420	450	A
16	951805	35	F	168	65	TAH	270	315	T6	90	98	94	93	100	78	70	56	54	58	78	83	84	88	90	83	94	98	95	92	82	74	60	68	65	79	74	78	76	82	84	81	180	400	460	H, B
17	944294	37	F	162	50	VH	270	340	T6	74	78	86	82	99	82	84	78	74	75	70	68	72	74	76	88	100	104	108	98	84	82	78	77	81	85	86	79	85	83	85	88	180	430	480	A
18	923470	40	M	168	60	HERNIOPLASTY	300	340	T7	70	64	69	77	61	71	62	63	62	62	64	64	70	71	71	73	94	92	84	83	75	78	77	74	72	74	74	76	77	77	76	83	170	410	450	A
19	952652	38	M	166	60	PTP	280	345	T6	68	73	78	79	76	60	66	70	78	74	73	72	70	78	84	85	89	94	96	84	87	81	78	74	76	78	77	80	83	79	76	80	170	410	460	A
20	979568	24	M	168	65	IMPLANT REMOVAL	360	420	T8	88	89	96	99	85	88	82	84	80	82	82	90	90	94	90	90	113	118	104	102	96	87	87	84	84	86	86	93	94	93	96	92	180	430	450	A
21	983583	33	M	178	90	APPENDICECTOMY	360	390	T7	98	99	100	96	94	85	80	77	74	73	70	68	76	77	74	79	98	100	95	96	94	79	72	68	69	70	77	78	80	84	86	82	140	380	430	H
22	976512	20	M	165	60	CRIF & IMIL	315	375	T6	86	101	104	98	90	87	88	84	85	80	81	78	74	77	79	75	103	108	100	85	78	84	88	82	78	79	83	85	79	84	86	88	160	400	430	A
23	934244	25	M	162	50	ORIF & IMIL	305	400	T4	86	88	96	94	91	87	81	86	84	78	77	72	80	83	87	89	108	107	105	103	100	98	90	78	76	77	79	83	84	81	85	88	170	400	440	A
24	976858	30	M	178	80	ORIF & IMIL	270	345	T6	86	88	90	94	87	82	77	74	63	58	52	60	78	77	81	84	81	89	86	73	70	67	66	69	73	74	78	74	79	76	80	84	180	405	440	N, H, B
25	941330	36	F	165	65	TRENDELENBERG SURGERY	220	270	T6	70	89	88	90	72	65	62	60	62	68	79	82	84	86	88	90	91	94	97	89	80	79	78	79	92	92	93	94	90	89	91	93	145	440	480	N
26	844839	35	F	164	60	TAH	220	260	T6	82	88	94	96	87	86	80	81	80	68	78	88	90	88	83	82	91	96	94	87	83	74	67	66	69	73	74	70	77	75	73	82	210	410	440	N, H
27	954620	45	F	164	55	TAH	150	190	T6	78	85	88	86	81	78	66	59	53	58	62	66	70	74	78	84	90	94	96	84	78	72	67	61	70	74	77	80	81	79	77	73	180	400	440	H,B
28	1001513	42	F	162	50	TAH	195	240	T6	84	88	92	86	81	78	76	81	70	63	60	68	69	74	80	86	95	99	98	90	79	70	67	64	70	73	77	75	79	83	84	80	165	390	410	H
29	1006578	40	F	164	60	TAH	210	260	T6	89	96	94	93	84	86	70	74	68	64	70	72	74	78	80	76	103	108	101	94	83	86	76	73	77	80	83	86	89	96	90	96	170	390	420	A
30	1262	29	M	170	60	ORIF & LCP	190	255	T6	76	74	85	88	81	70	74	64	62	65	66	78	70	74	77	89	100	105	108	90	87	86	81	87	84	84	82	83	91	96	86	80	175	400	430	A