"A COMPARATIVE STUDY OF EPIDURAL BUPRENORPHINE AND TRAMADOL FOR POSTOPERATIVE ANALGESIA IN LOWER ABDOMINAL AND LOWER LIMB SURGERIES"

Submitted by

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In partial fulfillment of the requirements for the degree of

MD

In

ANAESTHESIOLOGY

Under the guidance of

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LIST OF ABBREVIATIONS

ASA	**American Society of Anaesthesiologists**
BP	**Blood Pressure**
COPD	**Chronic Obstructive Pulmonary Disease**
CSF	**Cerebrospinal Fluid**
cms	**Centimeters**
GABA	**Gamma Amino Butyric Acid**
I.M.	**Intramuscular**
I.V.	**Intravenous**
kg	**Kilogram**
L.A.	**Local Anaesthetic**
min	**Minutes**
mg	**Milligram**
ml	**Milliliter**
mm	**Millimeter**
MAO	**Mono Amino Oxidase**
NIBP	**Non Invasive Blood Pressure**
NSAIDS	**Non Steroidal Anti Inflammatory Drugs**
PAG	**Periaqueductal Gyrus**
PONV	**Post Operative Nausea & Vomiting**
VAS	**Visual Analog Scale**
VRS	**Verbal Response Score**
yrs	**Years**

ABSTRACT

Introduction:

Pain relief is essential for patients undergoing surgeries to avoid post operative harmful Physiological & Psychological consequences.

Use of newer Opioids like Buprenorphine & Tramadol through epidural route has proved to be an ideal method to provide post-operative analgesia.

Buprenorphine is a semi-synthetic thebaine derivative 25 times more potent than morphine. Tramadol is a synthetic analogue of codeine 1/10 times more potent than morphine.

Aims:

To compare the degree and duration of post-operative analgesia and side-effects with epidural Buprenorphine & Tramadol in patients undergoing lower abdominal and lower limb surgeries.

Methodology:

Hundred and five patients are allocated alternatively into 2 groups of 52 (Group-T) and 53 (Group-B). No analgesic given during pre-medication. All patients were given spinal anaesthesia and epidural catheter was introduced for providing post-operative analgesia. In the post operative period, at VAS > 4 patients were administered 150µg Buprenorphine or 50mg Tramadol diluted to 10ml in NS through epidural catheter.

Results:

The mean time of onset of analgesia in group B 16.49 ± 3.38 (SD)min, in group T 13.33 ± 2.02 (SD)min, duration of action of analgesia in group B 656.6 ± 97.3 (SD)min, in group T 369.4 ± 25.2 (SD)min, quality of analgesia in group B 3.66 ± 0.478 (SD)min, in group T 3.26 ± 0.528 (SD)min, which are statistically significant.

Conclusion:

In our study Buprenorphine provided excellent analgesia, when given epidurally its quality of analgesia and duration of action was better and longer than Tramadol.

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INTRODUCTION

Life is short, and the art is long, the right time an instant and treatment precarious and crisis grevious. It is necessary for the physician not only to provide the treatment needed, but to provide for the patient himself and for those beside him.

Hippocrate 460-370BC

Effective pain control is essential for optimal care of surgical patients undergoing surgeries, as they suffer from considerable pain in the postoperative period. Inadequate relief of postoperative pain may result in harmful physiological and psychological consequences that lead to significant morbidity, which may delay recovery.

Implementation of anaesthesiology based acute pain services by epidural route has allowed patients undergoing potentially painful surgical procedures to have a more comfortable postoperative recovery than was previously possible using parenteral opioid analgesia techniques. The ideal epidural analgesic technique for major surgery would provide effective pain relief with minimal side effects and high levels of patient satisfaction.

With discovery of newer opioids like buprenorphine, tramadol and fentanyl, a new era in pain relief has commenced. Buprenorphine is a semi-synthetic thebaine derivative which is more potent than morphine. Tramadol is a synthetic 4-phenyl piperdine analog of codeine. It is a centrally acting analgesic with low affinity for opioid receptors.

The advantage with these newer drugs is that their potency is comparable to that of morphine, produce lesser respiratory depression, are easily available, have larger margin of safety and a lesser incidence of nausea, vomiting, urine retention, pruritis compared to morphine.

Hence it is feasible that the present study will be conducted to assess the safety and efficacy of postoperative analgesia with epidural buprenorphine compared with epidural tramadol.

OBJECTIVE OF THE STUDY

The objective of the study is,

To assess and compare the degree and duration of postoperative analgesia and side effects with epidural buprenorphine and epidural tramadol in patients undergoing lower abdominal and lower limb surgeries.

REVIEW OF LITERATURE

ANATOMICAL ASPECTS OF VERTERBRAL COLUMN[1,2]

The vertebral column of human body with its 33 vertebrae forms the axial skeleton. These bones are identifiable by the palpating finger and an exploring needle and it is essential to be familiar with the feel of intervertebral ligaments as they yield to the advancing needle.

The adult vertebral column has 33 vertebrae with 31 pairs of spinal nerves traversing the intervertebral formina.

Region	Vertebrae	Pairs of Spinal Nerves
Cervical	7	8
Thoracic	12	12
Lumbar	5	5
Sacral	5	5
Coccygeal	4	1

The adult spine has 4 curvatures. Cervical and lumbar zones are convex forwards (postural, secondary curves) and thoracic and sacral are concave forwards (actual, primary curves). These curves have a significant influence on the spread of local anaesthetic in subarachnoid and epidural spaces.

The highest and lowest points in these curvatures with the subjects supine on horizontal surface are found to be at the level of L3 and T5 respectively.

Vertebrae:

A typical vertebra is composed of the following parts:

1) **Body-** weight bearing and separated from adjoining vertebral bodies by the intervertebral disc.
2) **Vertebral arch –** composed of pedicles and laminae which surround and protect the spinal cord and its coverings.
3) **Transverse process –** give attachment to ligaments.
4) **Spinous process –** gives attachments to ligaments and to muscles.
5) **Superior and inferior articular processes**.

Articulation of these vertebrae is by way of ligaments. Certain gaps are present between any two vertebrae. These are: Laterally, intervertebral formina between pedicles, transmitting spinal nerve roots and posteriorly interlaminar foramina which is the space through which LP needle or epidural needle is passed.

Spinous process of the cervical, the first two thoracic and the last lumbar vertebrae are all practically horizontal and are therefore opposite the bodies of their respective vertebrae. The other spinous processes are inclined downwards, their tips being opposite the bodies of the vertebrae next below; exception, the tip of the first lumbar is opposite the intervertebral disc.

Topographic line of Tuffier:

Line across the back between iliac crests (intercristal plane), passes over spine of L4 in upright position and L4-5 space in lateral position.

A typical lumbar vertebrae:

These are five in number, have large and massive kidney shaped bodies. They are distinguished from thoracic by having no articular facets for the ribs on the vertebral bodies and from cervical vertebrae by having no foramen in the transverse process. The pedicles are directed backwards and laterally. The laminae are thick and sloping and spinal canal is triangular.

Lumbar spines are hatchet shaped and project backwards nearly horizontally. The interlaminar gap is increased by forward flexion of spine, which makes lumbar puncture possible.

Intervertebral disc:

These are principal connecting links between vertebral bodies, and account for nearly 25% of the length of the spine. In the cervical and lumbar regions they are some what wedge shaped and this contributes to the characteristic curves of the column. Each disc adheres above and below to the hyaline articular cartilage which covers facet of adjacent vertebral body and in front and behind each is attached to anterior and posterior longitudinal ligaments. This disc is made up of peripheral fibrous tissue and fibro cartilage, arranged in concentric rings termed “annular fibrosus” and a central core of soft pulpy elastic tissue “nucleus pulposus” which represents the remnant of embyronal notochord.

Ligaments

The vertebral column is bounded together by several ligaments, which give it stability and elasticity.

1) Supraspinous Ligament.
2) Interspinous Ligament.
3) Ligamentum flavum.
4) Longitudinal Ligament.

Supraspinous Ligament:

It is a continuation of the ligamnentum nuchae, and joins together the tips of the spinous processes from the C7 vertebra to the sacrum. It increases in thickness from above downwards and is thickest and widest in the lumbar region.

Interspinous Ligaments:

They connect adjacent spinous processes. 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. They fuse with the supraspinous ligament posteriorly and with the ligamentum flavum anteriorly. In the lumbar region they are wide and dense.

Ligamentum Flavum:

It is composed entirely of yellow elastic fibres. The fibers are perpendicular in direction, they extend from the anterior-inferior surface of the upper lamina down ward to the anterior superior surface of lower lamina. Laterally it blends with the

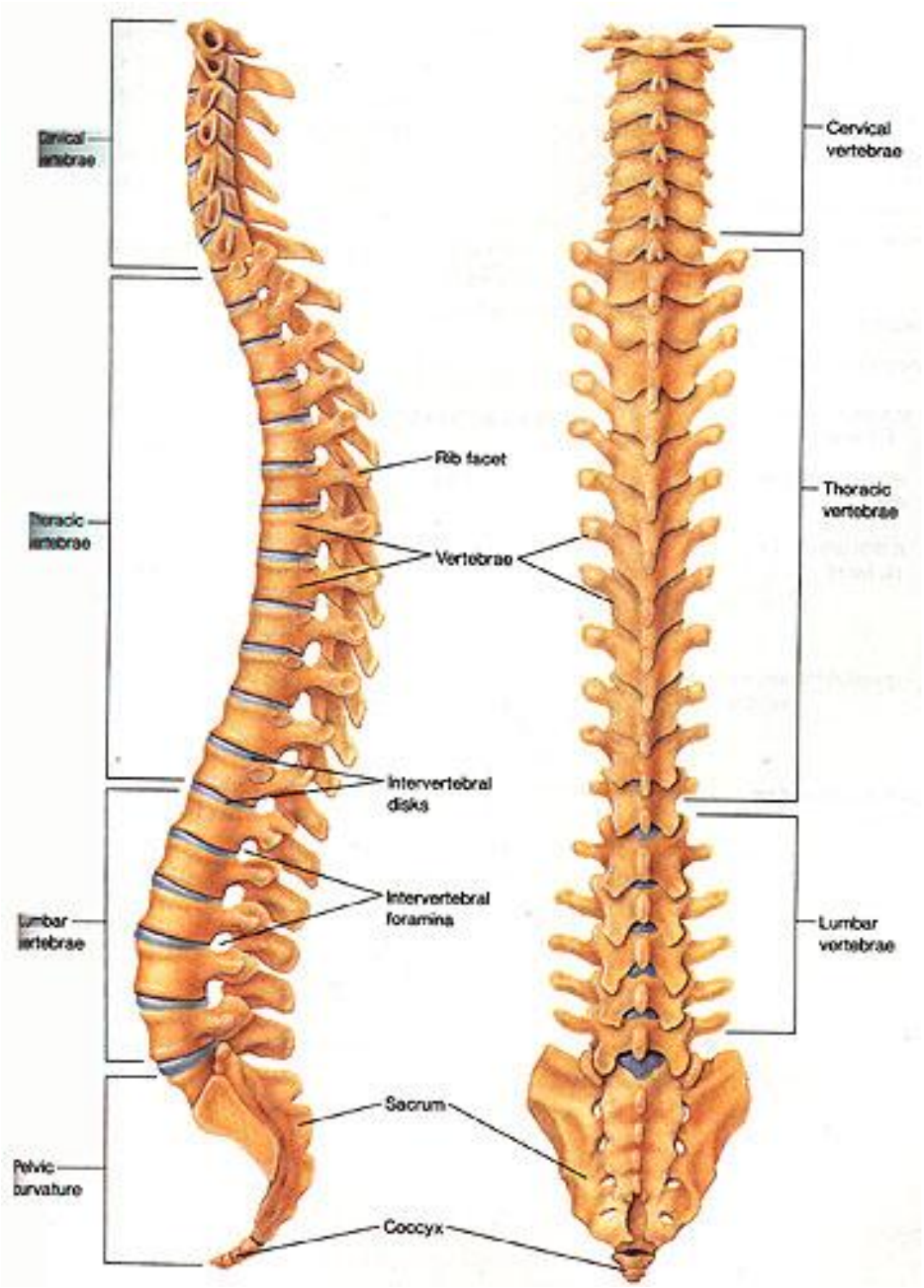
capsule of the facet joint and medially with the interspinous ligament, or with its fellow on the opposite side. It is thinnest in cervical region and thickest in the lumbar region. It measures 3-5mm thick and 16-20 mm wide.

Anterior Longitudinal Ligament:

It runs along the front of the vertebral bodies from C2 to upper sacrum becoming progressively wider from above downwards. It is adherent to anterior aspect of each intervertebral disc and adjustment margins of vertebral bodies.

Posterior Longitudinal Ligament:

It extends along the posterior surface of vertebral bodies. It corresponds in its attachments to those of the anterior longitudinal ligament.



Lateral Aspect **Dorsal Aspect**

Fig: 1 VERTEBRAL COLUMN

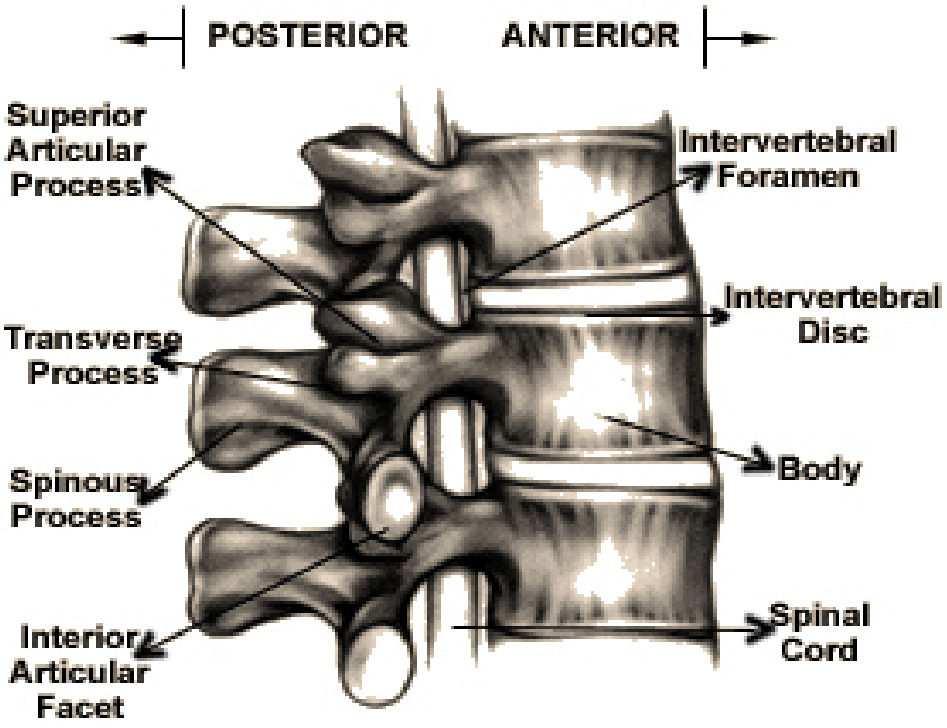


Fig: 2 LATERAL VIEW LUMBAR VERTEBRAE

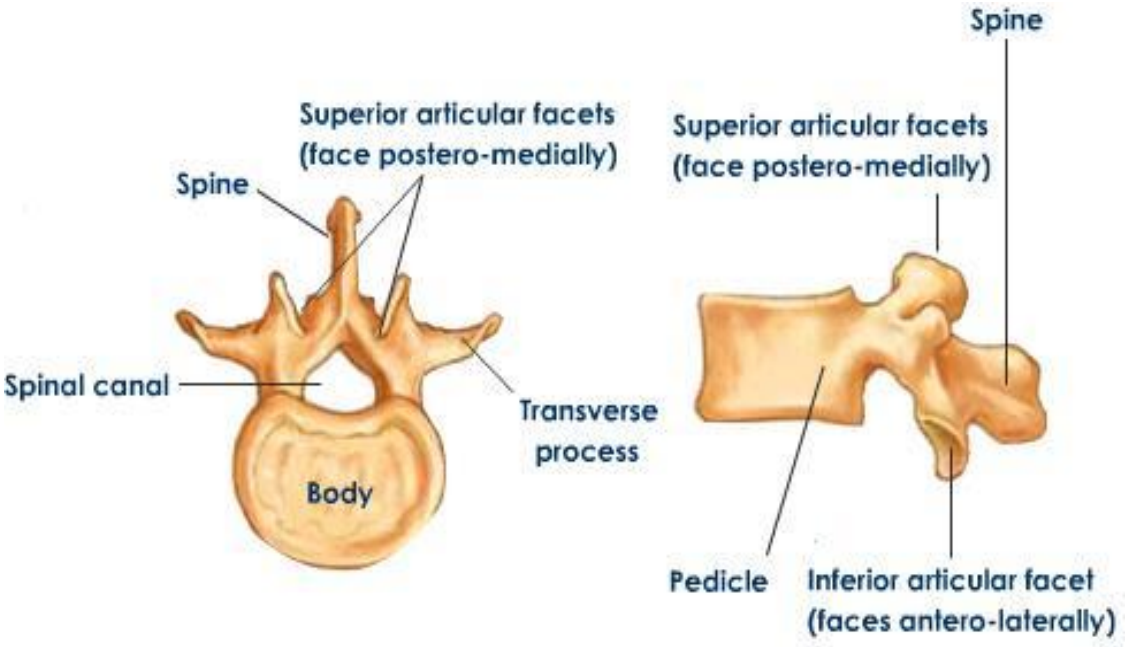


Fig: 3 LUMBAR VERTEBRAE

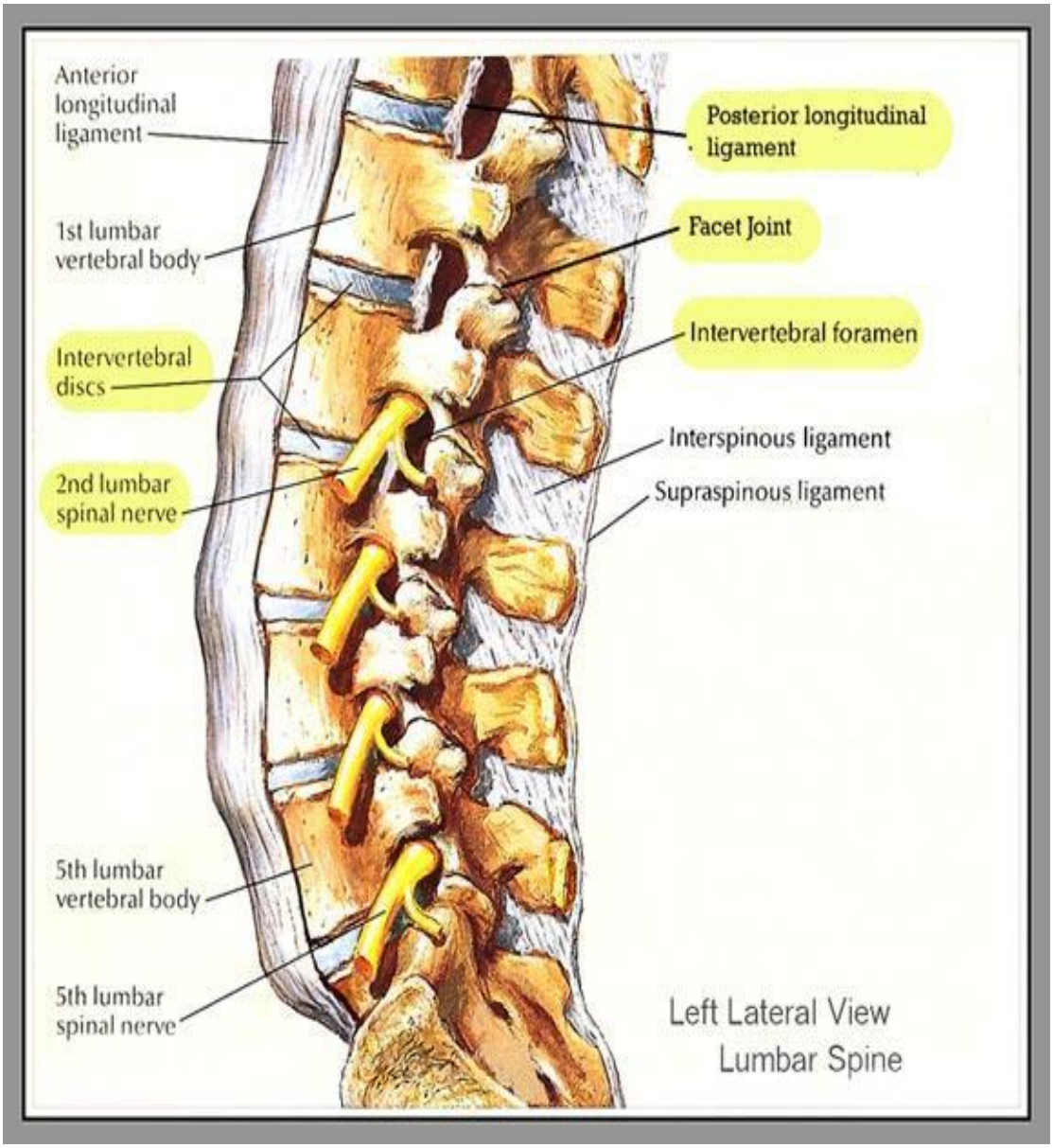


Fig: 4 LATERAL VIEW OF LUMBAR VERTEBRAL LIGAMENTS

Contents of Vertebral Canal

1) Spinal cord and roots of spinal nerves.
2) Spinal meninges and cerebrospinal fluid.
3) Spinal vessels, fat and areolar tissue.
4) Spaces – Epidural Space.
   – Subdural Space.
   – Subarachnoid Space.

Spinal Cord:

The spinal cord, a direct continuation of the medulla oblongata, begins at the upper border of the atlas and ends at the lower border of L_1 in adults and L_3 in the new born. It is 42 – 45 cm in length. It has an elongated cylindrical shape but is somewhat flattened anteroposteriorly especially in lumbar region. It is not uniform in diameter but bears a cervical and lumbar enlargement which corresponds to the origins of brachial and lumbosacral plexuses.

Below, it ends in conus medullaris from the apex of which filum terminale descends as far as the coccyx. The spinal cord is enveloped by 3 membranes: dura, arachnoid, and piamater. Below L1 Vertebra, the canal is occupied by a leash of lumbar, sacral and coccygeal nerve roots forming the cauda equine.

Structure of the Cord:

Spinal cord presents an anterior median fissure and a shallow posterior median sulcus from which, a glial posterior median septum extends about half way into the substance of the cord.

On either side of posterior sulcus lie the posterolateral sulci along which can be seen the emerging line of posterior nerve roots. The anterior nerve roots in contrast emerge by a number of tufts.

In transverse section, the cord comprises of a central canal, 'H' shaped zone of grey mater (nerve cells) and an outer zone of white mater (nerve fibres). Central canal continuous downwards from 4^{th} ventriceles as a narrow tube lined with ciliated ependymal cells and containing cerebrospinal fluid.

The cross limb of the 'H' of grey mater is termed transverse commissure. Each lateral limb consists of short, broad anterior column containing large motor cells and a thinner pointed posterior column, which is capped by the substantia gelatinosa, a component of Rexed's Laminae. These columns are referred to as the anterior and posterior horns. In the thoracic and uppermost lumbar segments lies the lateral grey column. The more important tracts in white mater are:

Descending Tracts	**Ascending Tracts**
1. The Lateral cerebrospinal (or) crossed motor/ pyramidal tract.	1. Posterior columns with medial fasciculus gracilis of Goll (fine touch) and lateral fasciculus cuneatus of Burdach (Proprioception)
2. The anterior cerebrospinal (or) uncrossed motor/ direct pyramidal tract.	2. Spinothalamic tracts (pain and temperature)
	3, Anterior and posterior spinocerebellar tracts.

Blood Supply of Cord:

The main arterial supply of the cord is derived from spinal arteries and to this, a reinforcement by way of radicular arteries exists.

Anterior Spinal Artery:

A branch of terminal part of each vertebral artery lying in the anterior median fissure and supplies a major portion of the anterior 2/3rd of the cord.

Posterior Spinal Artery:

There are 2 pairs, i.e. 4 longitudinal vessels. One lies on front of the attachment of dorsal nerve root and the other, a larger artery behind the attachment. They arise behind the base of brain either directly from vertebral artery or posterior inferior cerebellar artery. (the largest branch of each vertebral artery). These supply posterior 1/3rd of cord, posterior grey columns and white columns on either side.

Reinforcement:

The above arteries are reinforced by spinal branches of verterbral, ascending cervical, posterior intercostals, spinal lumbar, and several lateral arteries. These form anterior and posterior radicular arteries, reinforceing the main supply. Often one of the anterior radicular arteries is of considerable size and termed arteria radicularis magna, usually arising in the lower thoracic or upper lumbar region (artery of Adamkiewicz).

Meninges:

Duramater-

Spinal Duramater represents only the inner or meningeal layer of cerebral duramater, the outer or endosteal layer being represented by the periosteum lining the vertebral canal, which is separated from spinal dura by the extra dural space.

Dura sac extends usually to the level of S_2 vertebra, but it can end up as high as L5 or extend upto S_3.

It is attached at the following points to its bony surroundings: above to the edge of foramen magnum and to the posterior aspects of the bodies of C2 and C3 vertebrae, anteriorly to posterior longitudinal ligament, laterally it blends with epineurium of spinal nerves, inferiorly by filum terminale to the coccyx. Posteriorly, however, the dural sac is completely free.

Arachnoid Mater:

It is a thin transparent sheath closely applied to the dura. It surrounds cranial and spinal nerves as far as their point of exit from skull and vertebral canal.

Piamater:

This closely invests the cord and is separated from arachnoid by subarachnoid space filled with CSF. It send delicate septa into its substance. From each lateral surface of pia, a fibrous band called denticulate ligament projects into the subarachnoid space. Piamater ends as a prolongation of the filum terminale, which pierces the distal end of the dural sac and is attached to periosteum of the coccyx.

Denticulate Ligament:

The denticulate ligaments are folds of the piamater that extend laterally along the lines of attachments of the anterior and posterior roots and fuse with the arachnoid and duramater. Structurally they act as struts to hold the spinal cord suspended within the subdural space. The mechanical property of these ligaments is one of elasticity and is under a stress strain modulus of 3-5gm.

Spinal Nerves

These are 31 pairs in number:

a) 8 cervical
b) 12 thoracic
c) 5 lumbar
d) 5 saccral
e) 1 coccygeal

Anterior root is efferent and motor sympathetic preganglionic axons arise from cells in the intermediolateral horn of spinal cord from T_1 to L_2.

Posterior root is larger than anterior. All the afferent impulses from whole body, including viscera pass into the posterior roots. Each posterior root has a ganglion and conveys fibers of 1) pain 2)touch 3)temperature 4)deep or muscle sensation from bones, joints, tendons. 5) afferent from the viscera and 6)vasodilator fibers.

The anterior and posterior roots each with its covering of pia-arachnoid and dura cross the extra dural space and unite in the inter vertebral foramina to form the main spinal nerve trunks, which soon divide into anterior and posterior primary divisions – mixed nerves.

EPIDURAL SPACE[3,4,5]

Definition:

It is a potential, elliptical space surrounding the dural sac and extends from foramen magnum to coccyx and communication laterally with the paravertebral space through intervertebral foramina. It is a part of vertebral canal lying between spina dura mater and periosteal lining of the vertebral canal.

Boundaries of the Epidural Space:

Superiorly: At the foramen magnum where the periosteal layer of the spinal vertebral canal fuses with dural layer.

Inferiorly: The sacrococcygeal membrane.

Anterior: Posterior longitudinal ligament covering the posterior aspect of vertebral bodies and the intervertebral disc.

Posterior: Anterior surface of the vertebral laminae and the ligamentum flavum.

Lateral: Interverbral foramina and pedicles of vertebrae.

Shape of the epidural space:

The shape of the epidural space in cross section is determined by the shape of the vertebral canal and the dural sac. The vertebral canal is nearly circular in the cervical and upper thoracic regions and triangular in the lumbar segments. For this reason the midline approach is most commonly advocated for entering lumbar epidural space. It is more extensive and easily distensible posteriorly. While anteriorly the dura adheres to the periosteum of the vertebral bodies.

Depth of the epidural:

The structures and tissue planes that are to be penetrated to reach the epidural space in a midline sagittal plane are as follows:

1. Skin and Subcutaneous Tissue.
2. Supraspinous Ligament.
3. Interspinous Ligament.
4. Ligamentum flavum.

The ligamentum flavum is an important landmark for technical identification of epidural space during induction of epidural analgesia. The first 3 tissues offer little resistance to the advancing needle but when the ligmentum flavum is reached, the resistance increases. As the needle passes through this tissue there is a sudden disappearance of resistance. In performing epidural analgesia, it is essentinal that this point is to be recognized, as little further advancement results in subarachnoid penetration.

The distance of the epidural space from skin in the midline has been extensively studied by Guterrietz.

The overall median distance in normal adult females is 4.7cm at L_3-L_4 level. In 60% of patients it is within 5cm. In about 10% patients the depth is more than 6cm. In only 5% of patients it is more than 7cm. On the other hand a loss of resistance at a depth of less than 3cm probably does not identify the epidural space.

The width of epidural space and thickness of dura vary with the level of vertebral canal.

Level	Epidural Space Width (mm)	Thickness of Dura (mm)
1. Cervical	1.0 – 1.5	2.0 – 1.5
2. Upper thoracic	2.5 – 3.0	1.0
3. Lower thoracic	4.0 – 5.0	1.0
4. Lumbar	5.0 – 6.0	0.66 – 0.33

Anatomically the connective tissue is present in significant amounts ventrally, forming strong connections between duramater and anterior longitudinal ligament in vertebral canal. A distinct midline fold of connective tissue, extending in a longitudinal direction in the midline, entitled the plica mediana dorsalis of the duramater, connects the dura to the ligamentum flavum in the midline. These midline bands divide the epidural space into right and left sides and narrow the epidural space in the midline. The existence of dorosomedial connections between dura and ligamentum flavum is of help in explaining some of the results occurring during the performance of clinical epidural anaesthesia.

Contents of the Epidural Space:

1. Dural Space:

It extends from the foramen magnum to the lower border of second sacral vertebra. The dural tube hugs the anterior wall of the spinal canal, so that the epidural space is narrow anteriorly and wider porsteriorly.

2. Spinal Nerve Roots:

Along with their dural cuffs, they traverse the epidural space on their way to their respective interverbral foramina. In the cervical region these travel almost horizontally, but lower down they become more inclined owing to the discrepancy between the length of the spinal cord and the spinal canal, and the lower lumbar and sacral roots are almost vertical.

The roots vary greatly in size and thickness. The thoracic roots are thin, while the cervical and lumbosacral roots subserving the limbs are thick. The great differences in size and neural populations within the roots are interrelated. The very large diameter and high neural population of the dorsal and ventral roots of the first sacral segment are associated with great resistance to epidural blockade. Prolonged latency and poor analgesia of S1 segment are due to poor penetration of local anaesthetic and it deserve a special mention as they have an important role in the mechanism of the action of epidural anaesthesia. In the region of the "dural cuff" the arachnoid villi and granulations invaginate the epidural veins and drain the CSF from the subarachnoid space, into the blood stream. Those villi, which are not in contact with the vessels, drain the CSF into the epidural fat, from where it is drained by lymphatics

3. Epidural Vessels:

The branches of the subclavian, aortic and iliac arteries cross the epidural space and enter the subarachnoid space in the region of the dural cuffs. These branches provide blood supply as far as the spinal roots. Apart from the cervical region, the entire blood supply to the spinal cord passes through the peridural space. The epidural veins are arranged in the form of longitudinal plexuses on either side of

the midline. They do not posses valves. These connect with intervertebral foramina and communicate with the vertebral, ascending cervical, deep cervical, intercostals, illolumbar and lateral sacral veins. As the epidural veins have no valves they afford a connection between the pelvic veins below and the intracranial veins above. The epidural veins become distended during coughing and straining and also when the inferior vena cava is obstructed by large abdominal tumors or in late pregnancy. This distension of epidural veins diminishes the effective volume of the epidural space. Under these circumstances the requirement of the local anaesthetic is markedly decreased, as a small volume of drug tends to spread over a wide area in the epidural space.

4. Fat:

The contents of the spinal canal lie cushioned in a pocket of semifluid, lobulated fat. Solutions injected into the epidural space, track up and down between the fatty areolar tissue. The epidural fat constitutes an important pharmacological space and depot for injected local anaesthetics and drugs and it is one of the three competitors for its share of the drug. The other two competitors being, nervous tissue of spinal roots and cord and blood vessels within the spinal canal. Drugs with high lipid solubility and lipoprotein binding characteristics will tend to enter the fat phase and remain there for a period of time, depending on their pharmacodynamics and on the briskness of the local blood flow competing for uptake. The compliance of the epidural fat varies from person to person and with age. In children and young adults it offers very little resistance.

5. Lymphatics

Surrounding and draining the dural sac, lymphatics run anteriorly from each intervertebral foramen and empty into the longitudinal channels in front of the vertebral column. It is largely present in the dural cuff region

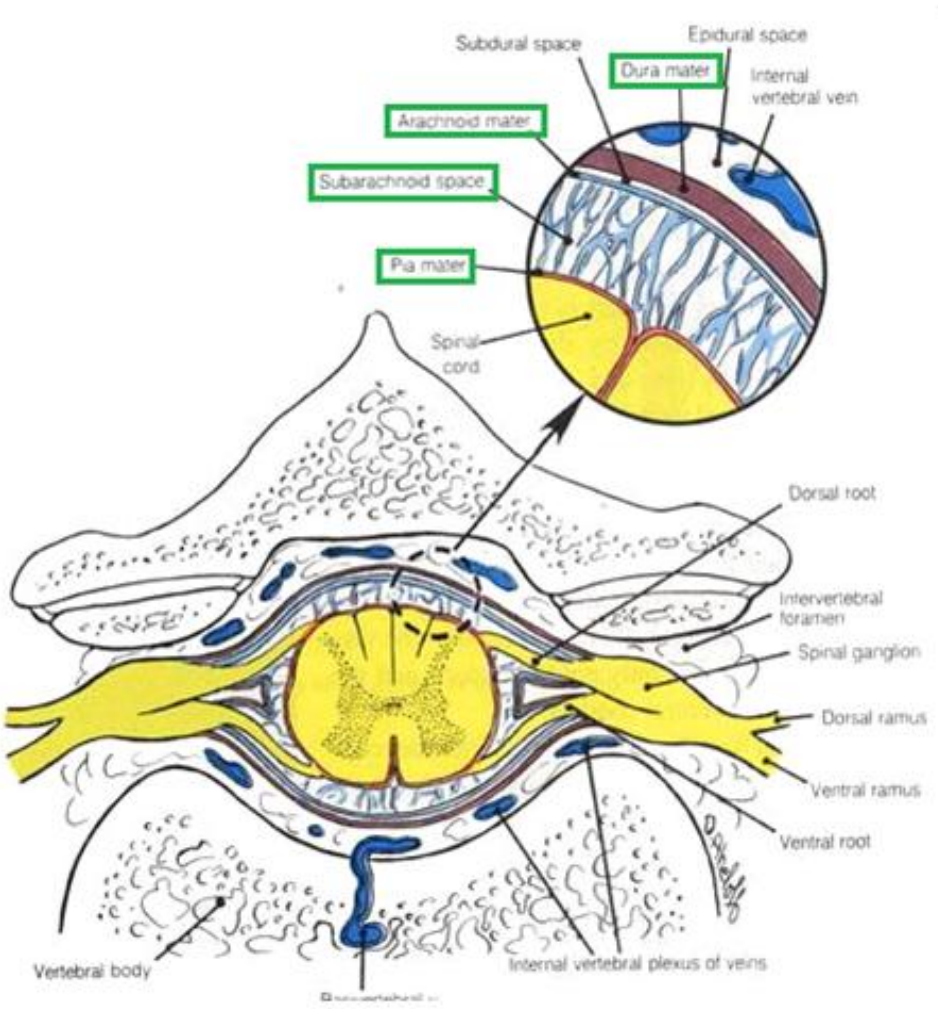


Fig: 5 EPIDURAL SPACE CROSS SECTION

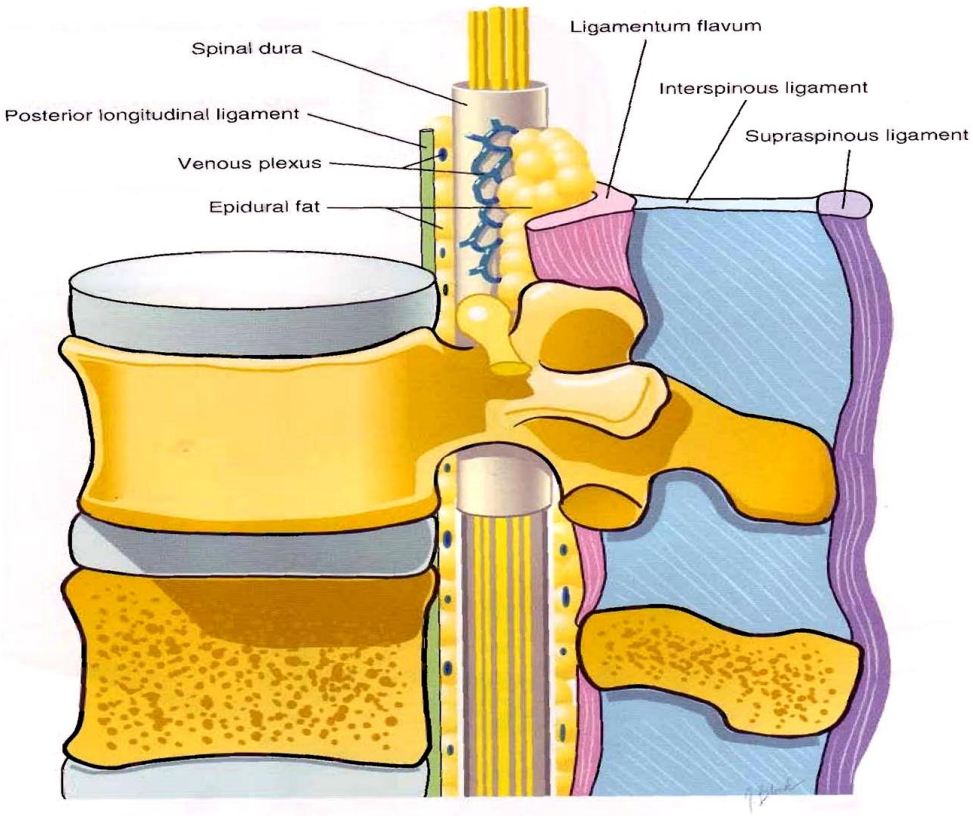


Fig: 6 RELATION AND CONTENTS OF LUMBAR EPIDURAL SPACE

Detection of epidural Space:

a) *Negative pressure techniques*

1. Hanging drop technique of Guterrietz
2. Capillary tube method of Odom
3. Manometer method

b) *Loss of resistance techniques*

1. Syringe technique
2. Spring loaded syringe
3. Macintosh balloon technique
4. Brookes device
5. Vertical tube of dawkins

c) *Others*

1. Ultrasonic localisation
2. The oxford epidural space indicator

Recent techniques

- Use of auditory amplification of the sound made by the epidural needle as it transverses the interspinous ligament and ligamentum flavum
- Doppler guidance
- Pressure transducer guided method

In our study we have used the syringe technique for loss of resistance with air when ligamentum flavum is penetrated.

Accurate location of the epidural space is commonly determined by the loss of resistance technique using a new 10ml glass syringe. The quality of functioning of the syringe is key to success. As the epidural needle with attached air filled syringe is advanced through the ligamentum flavum, while applying gentle finger pressure, on the plunger of the syringe, there is resistance to movement of the plunger. On entering the epidural space, there is a sudden loss of resistance sensed by the operator and easy movement of the plunger.

Intrinsic resistance of the plunger moving into the syringe barrel must be minimal.

Lubrication of syringes was accomplished either by dipping the plunger into saline and wetting the interior of the syringe barrel or by a technique of dry polishing.

Of all the techniques, the loss of resistance technique using syringe has gained popularity.

Epidural pressure

Originally the extradural space was described by Heldt and Molonely. Negative pressure is said to exist in extra dural space. This, so called negative pressure is greatest at point of firm attachments. It is greatest in throiac region (1-3cm H_2o), less in lumbar region (1cm H_2O) and least in sacral region (0.5cm H_2O).This difference in pressures make hanging drop technique at thoracic region and loss of resistance technique at lumbar region the preferable methods of identifying the epidural space. There are 2 theories explaining this negative pressure.

1) *Cone theory*

Considers that indentation of dura by the epidural needle creates a large epidural space as an artefact. Telford and Holloway demonstrated that epidural space is always a positive pressure space.

2) *Transmission theory*

This theory considers that negative pressure in epidural space is caused by transmission of the intrapleural negative pressure through the intervertebral formina into epidural space. Clinically negative pressure in epidural space decreases or is absent in patients who are tense and straining and marked flexion of spinal column while decreased subarachnoid pressure will increase epidural pressure.

Spread of injected solution in epidural space

Local anaesthetic or other agent injected into the epidural space may potentially spread as follows : superior and inferior spread is mainly in posterior portion of the epidural space between dura and ligamentum flavum.

a) *Superiorly* the spread is to magnum. There is possibility of diffusion across dura at base of brain to cerebral CSF with possibility of blockade of cranial nerves, vasomotor and respiratory centers, and other vital centers.

b) *Inferiorly* to sacral hiatus, caudal canal and through anterior sacral foramina.

c) *Laterally* through intervertebral foramina to paravertebral space, to produce paravertebral neural blockade. There is rapid access to CSF at "dura cuff" region to produce spinal nerve root blockade and also subsequent access to spinal cord.

d) *Anteriorly* is the thin epidural space between dura and posterior longitudinal ligament. There is also access for injected solution to CSF by slow diffusion across spinal dura, subdural space, and arachnoid membrane into the subarachnoid space. Vascular absorption by way of epidural veins may convey drug directly to brain and epidural fat also takes up the drug.

***Factors** influencing extent of epidural anaesthesia*

1. Volume of the solution – varies with age, height, pregnancy, atherosclerosis. Spread increases with age escape from the epidural space is less due to intervertebral foramina being more fixed and epidural vessels less penetrable spread is greater in pregnant females.

In arteriosclerosis and occlusive arterial disease the spread is also greater than normal

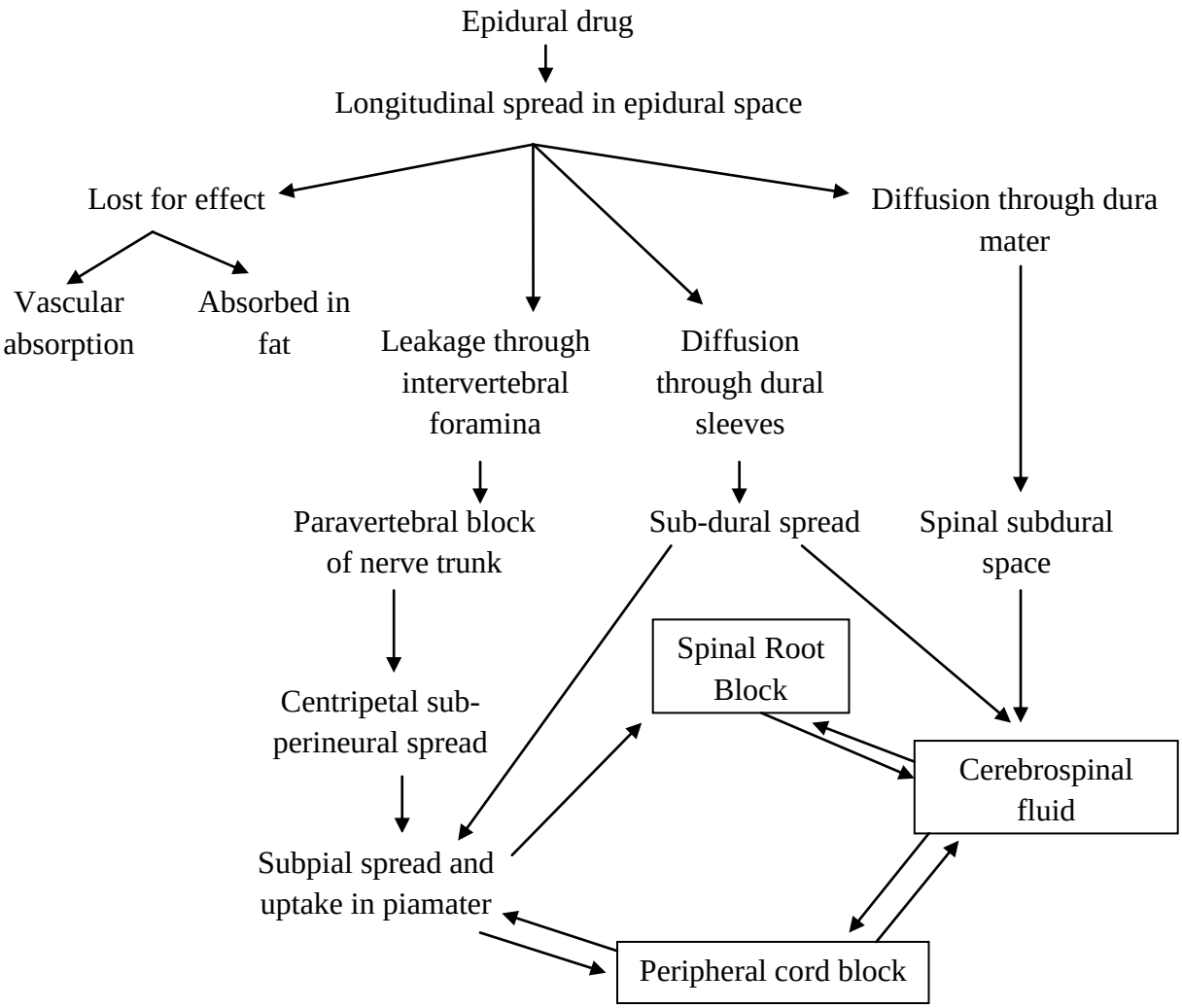
Spread is decreased in dehydration shock and cachexia.

A greater dose is required in taller individuals.

Extent of anaesthesia is greater with more concentrated solution.

2. Selection of appropriate inter space
3. Speed of injection
4. Position of the patient
5. Effect of gravity
6. Effect of specific gravity of the agent

Summarized as – dispersion = $\frac{\text{Volume x force x time}}{\text{Resistance of tissue}}$ + gravity



ANATOMICAL AND PHYSIOLOGICAL ASPECTS OF PAIN PERCEPTION [6,7,8]

To deal intelligently with problems of pain, it requires great deal of familiarity with the anatomy of sensory pathways and sensory supply of body segments.

Definition:

The international association for the study of pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or describe in terms of such damage".

This definition recognize the interplay between the objective, physiologic sensory aspects of pain and its subjective, emotional and psychological components.

Clinical Classification of Pain:

1) Peripheral Pain

a) Superficial pain

b) Deep pain

i) Somatic

ii) Visceral

d) Referred pain

e) Trigger mechanism

2) Central pain

3) Psychogenic pain

Acute Pain:

Acute pain can be defined as that which is caused by noxious stimulation due to injury, a disease process, or abnormal function of muscle or viscera. This type of pain is typically associated with a neuroendocrine stress response that is proportional to intensity.

Chronic Pain:

Chronic pain is defined as that which persists beyond the usual course of an acute disease or after a reasonable time for healing to occur, this period varies between 1 to 6 months in most definitions. Patients with chronic pain often have an attenuated or absent neuroendorcine stress response, and have prominent sleep and affective disturbances.

Somatic Pain:

Superficial pain is in general, well localized. Cutaneous sensation, including that of pin prick, can be related to the spinal segment concerned. The cutaneous area supplied by a single posterior nerve root is termed dermatome. Knowledge of this is important in determining the nerve root that is necessary to block when treating superficial pain. Deep pain impulses from joints, muscles, tendons and fascia arise in a network of fine fibres similar to those in the skin and travel by the same nerve pathways. The deep tissue supplied by a single posterior nerve root is termed a sclerotome, which is not necessarily related to the overlapping dermatome. Deep pain usually has a dull aching character and it may be accompanied by an unpleasant sickening sensation due to an autonomic response. It is poorly localized and tends to spread to other areas.

Visceral Pain:

This is transmitted mainly in the fibers which accompany sympathetic nerves, and so pass via the white rami communicates to the posterior root ganglia where the cell bodies are situated. Not all visceral pain impulses travel with sympathetic nerves. Impulses from the pelvic organs are transmitted through parasympathetic pelvic nerves to the cord. Visceral pain is diffuse, less easily localized and often referred as dull aching.

Referred Pain:

Deep pain, whether visceral or somatic is referred to the dermatomes having the same or adjacent segmental innervations as the painful focus itself. The neurophysiological basis may be due to convergence of several cutaneous and visceral afferent fibres on the same secondary neuron at some point in the pain pathway or due to facilitation theory. The inference is that the perception of a structure by the cortex is a fundamental requisite for referred pain.

Psychogenic pain:

A psychological basis for pain can be inferred when no satisfactorily organic cause for it can be found. It is usually preceded by a phase of exhaustion.

Theories of pain

1) The specificity (sensory) theory :

The specificity theory, postulated by vonfrey, proposes the pain as well as the other sensory modalities like touch, warmth and cold, each has a distinctive end organ in the skin and that each stimulus specific end organ is connected by its own pathways to the brain.

2) The intensive (summation) theory :

A second theory, of which Goldsceider was an early protagonist, held that any stimulus, if sufficiently intense, could produce pain. According to this theory there are no distinctive pain receptors and the sensation of pain is the result of summation of impulses excited by thermal stimuli or pressure applied to the skin originally called intensive theory: it later came to be known as summation theory or pattern theory. The 'gate control theory' is a variation of the pattern concept.

Pain theories in the twentieth century:

1) ***Peripheral pattern theory*** by Sinclair and weddell in 1950's stated that all fibre endings (apart from those that innervate hair cells) are alike, so that the pattern of pain is produced by intense stimulation of nonspecific receptors.

2) ***Central summation theory*** by Livingston in 1943 suggested that the intense stimulation resulting from nerve and tissue damage activates fibres that project to internuncial neuron pools in the spinal cord which inturn project to brain mechanisms that underlie pain perception.

3) Strong proposed the fourth theory of pain and believed that pain can be separated in to two components: the perception of pain and the reaction to pain.

4) ***Sensory interaction theory*** in 1959 by Noordenbos who believes that large fibres inhibit and small fibres excite central transmission neuron, which project to a multisynaptic system that leads to the brain.

5) ***Gate control theory :*** the term 'gate control' is now applied to the rapidly acting mechanisms which accept and control the passage of impulses from the afferent

fibre to cells which may then trigger the various effector systems and evoke sensation (melzack and wall 1965, wall 1978).

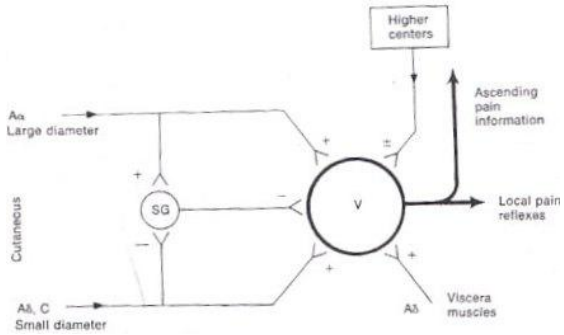


Fig. 7: GATE CONTROL THEORY OF PAIN

Melzack and wall (1965) observed in decerebrated and spinal cats, that peripheral stimulation of large myelinated fibres produced a negative dorsal root potential and that stimulation of c – fibres caused a positive dorsal root potential. They postulated that these potentials, which were reflections of presynaptic inhibition or excitation, modulated the activity of secondary transmitting neurons (T – cells) in the dorsal horn, and that this modulation was mediated through an inhibitory interneuron (1 cell) placed between the T cell in lamina V of the dorsal horn and the still unidentified inhibitory cells, in lamine II and III. The essence of this theory is that the large diameter fibres excite the I cells, which is turn cause a presynaptic inhibition of T cells. Conversely the small pain afferent fibres inhibit the I cells leaving the T cells in an excitatory state.

Melzack and wall emphasized that the transmission of pain impulses from the dorsal horn must also be under the control of a descending system of fibres from the brain stem, thalamus and limbic lobes. In their view, the descending control mechanism was sensitive to environmental factors and also utilized information from large primary afferents.

6) Pshychologic/ Behavioral theories:

'Psychogenic' pain is as real as pain due to 'somatogenic' disorders. It mentions the role of learning, personality, culture and cognition and of psychologic, emotional, and motivational factors, and of environmental influences on pain behaviour.

Physiological Aspects of pain

The 4 systems involved are

1. Peripheral system
2. Medullary dorsal horn
3. Ascending system
4. Supra spinal system

Pain receptor and peripheral afferent pathways:

Basic understanding of physiology associated with pain sensation and appreciation help provide a rational approach to management. Most acute pain originates when specific nerve endings are stimulated. Nerve endings consists largely of two types: Mechanoceptors and polymodal nociceptors. The mechanoceptors are mainly present in the skin and respond to strong pressure, pin prick or heat and the signal is transmitted through small myelinated A fibers. They warn of potential damage and are associated with withdrawal reflexes. The polymodal nociceptors are the nerve endings of unmyelinated C fibres. They are widely distributed throughout most tissues and respond to tissue damage (mechanical, thermal and chemical insults). The transmission of impulses from the receptors is relatively slow and they are responsible for the dull, prolonged, aching pain after injury.

A-delta fibers are finely myelinated 1-5 µm diameter and have rapid conduction 5-45 m/sec.

C fibers are nonmyelinated, diameter 0.4-1.1 µm and have slow conduction (0.5 – 2m/ sec)

Pain Pathways:

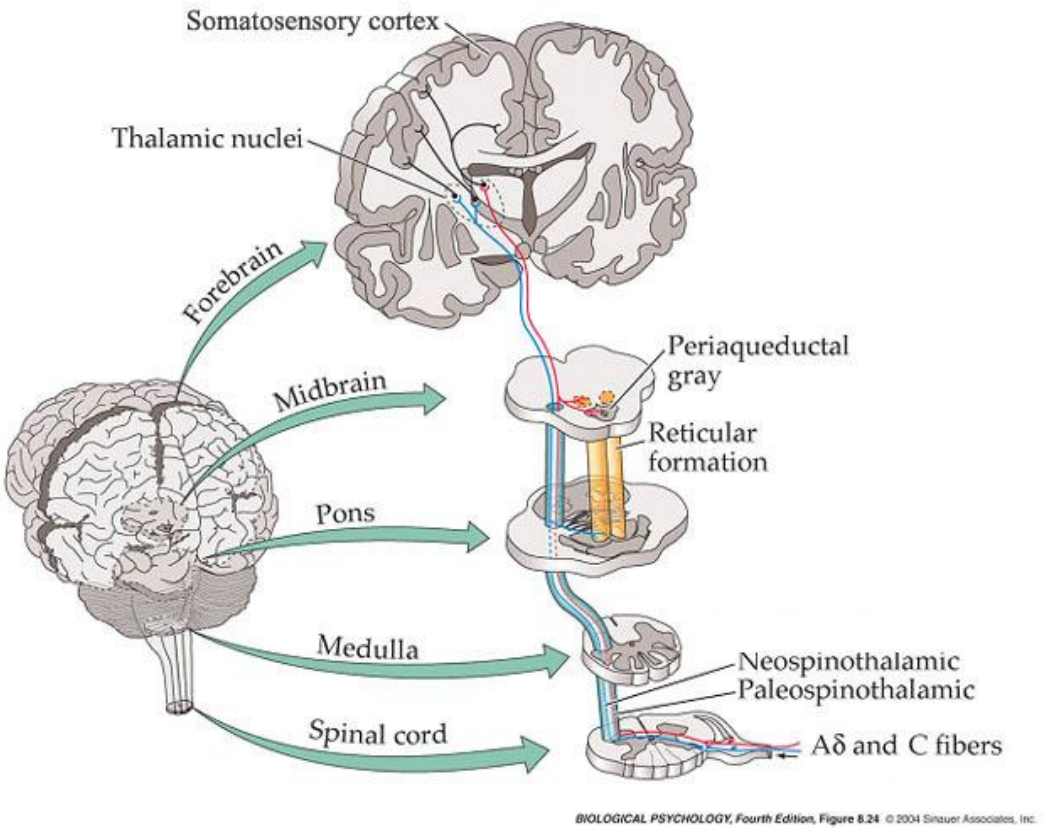


Fig. 8: PAIN PATHWAYS

The cell bodies of the primary pain afferents (i.e. the first order neurons) are located in the dorsal root ganglia. Central extensions of the primary neurons project, via the dorsal root, to the dorsal horn of the spinal cord and in the case of cranial pain afferents, to the nucleus of the trigeminal nerve. These A-delta and C fibers occupy

the lateral part of the root entry zone and within the spinal cord form a discrete bundle, the ‘tract of lissauer’. After traversing the lissauer’s tract, they terminate in the dorsal horn of the spinal cord. In the dorsal horn, cell bodies are arranged in series of laminae some of which have classic names, but which are most simply given roman numericals by Rexed i.e. laminae I-IX.

The A-delta fibers terminate in lamina I, also known as the marginal cells layer of waldyer, whereas “C” fibers terminate in the lamina II also known as ‘substantia gelatinosa’. Some pain fibers penetrate the dorsal gray matter and terminate in lamina V.

The secondary neurons connect with ventral and lateral horn cells in the same and adjacent spinal segments and subserves somatic and autonomic reflexes. In addition to this the secondary neurons decussate in the anterior spinal commissure to the opposite side and ascend in the anterolateral fasciculus (of which the lateral spinothalamic tract forms a major part) to the brain stem and thalamic structure.

The axon from each dermatome enters the spinal cord one to three segments higher than the level of root entry. Crossing fibers are added to the inner side of the spinothalamic tract, so that the longest fibers from successively rostral segments occupy a progressively deeper position. Thus at the cervical level the fibers in the spinothalamic tract form without inwards are sacral, lumbar, thoracic and cervical.

In addition to the lateral spino-thalamic tract which is fast conduction pathway that projects directly to the thalamus, the anterolateral fasiculus of the spinal cord contains a slowly conducting, medially placed system of fibers, which reaches the thalamus via one or more relays in the reticular core of the brain stem. This latter

group of fibers is referred to as spinoreticulothalamic tract or paleospinothalamic tract. These impulses have a major role in the arousal or motivational aspects of pain sensation due to links with limbic system.

Thalamic Terminus:

Most of the fibers of the lateral spinothalamic tract terminate in the nucleus ventralis posterolateralis. A lesser number of them terminate in the nucleus ventralis posteromedialis, the intralaminar nuclei and the venterobasal complex, which also receive extensive projections from the brain stem reticular nuclei. Some afferent connections are also made with the hypothalamic nuclei.

Thalamo cortical projections:

The nuclei of the posterior thalamic complex send their projections to two main cortical areas, the post central cortex and the upper bank of the sylvian fissure.

Inhibitory pathways:

There are various means by which pain transmission may be inhibited at spinal level as mentioned by gate control theory of Melzack and wall.

a) Large Primary afferent fibres:

Here the gate can be closed by stimulation of non painful sensory mechanoreceptors whose impulses are carried in large myelinated fibers. These send collaterals to synapse with the inhibitory interneurons in the dorsal horn. These in turn inhibit the release of transmitter along the pain pathways.

b) Inhibitory fibers:

Reynolds (1969) found that stimulation of ventrolateral periaqueductal grey mater in the rat produced profound analgesia without altering behaviour or motor activity by inhibiting the neurons of lamina I and V of dorsal horn by action on inhibitory interneurons. Pathway is through nucleus raphae magnus (NRM) via dorsolateral funiculus.

C) Betaendorphins:

Found principally in the hypothalamus, where it is passed via long axons to the ventricle. It is more suited for hormonal role. It can therefore be assumed that after release into CSF, beta endorphins act on opiate receptors in the brain stem and spinal cord (substantia gelatinosa). Beta endorphins possess all the actions of morphine producing analgesia, euphoria, behavioural effects and hyperglycemia. It can act as neuromodulator inhibiting the release of acetylcholine, dopamine and substance P.

D) Opiates:

Opiates are metenkephalin, leuenkephalin which have methionine and leucine in their terminal amino acid. They inhibit pain conduction by activating descending inhibitory pathways or by direct action on opiate receptors in substantia gelatinosa.

Enkephalins when released bind to presynaptic and post synaptic opiate receptors located on nerve terminal of C fibers. This receptor neurotransmitter produces conformational changes in receptor resulting in decreased adenylate cyclase activity and subsequently reduction in rate of neuronal firing by altering sodium conductance and decreased depolarization. Thus enkephalins inhibit the release of substance P in substantia gelatinosa and acetyl choline release in the brain. Thus

inhibitory inter neurons in the dorsal horn that are activated by descending seratoninergic fibers are enkephalinergic.

Neurophysiology

While activity in sensory neurons may be excited in the periphery by thermoreceptor, nonciceptor or mechanoreceptor stimulation, cell bodies in the posterior horn are responsive to different intensities of stimulation. Thus certain cells found principally in lamina IV respond only to low intensity of stimulation such as light touch. These are termed as low threshold or 'Lt' cell. Another type of cells found principally in lamina V, respond over a wide range of stimulus intensities. They are called wide dynamic range or WDR cell. Third type of cells were responsive to stimuli only within the noxious range. Such cells are known as high threshold or HT neurons and are found only in lamina I. Thus volleys of activity provoked by the A delta and C fibre stimulation in the periphery results in increased firing of HT and WDR cell in lamina I and V which is conducted up to anterolateral column principally in the spinothalamic tract.

Neuropharmacology[9]

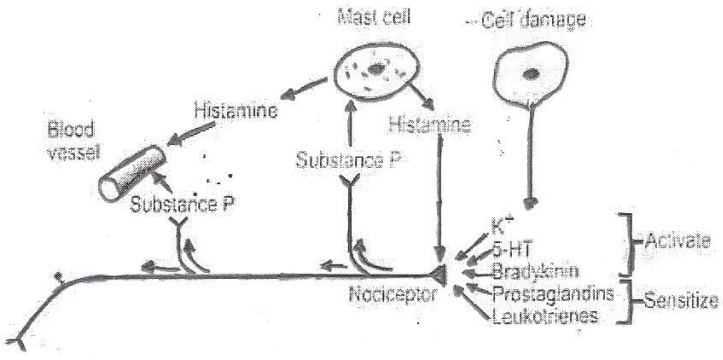


Fig. 9: ORIGIN AND EFFECTS OF PAIN MEDIATORS

Tissue damage results in inflammation that directly affects response of nociceptor to further stimulation. Release of intra cellular contents from damaged cells and inflammatory cells occur. Neurogenic inflammatory response releases substance P, neurokinin A, calcitonine gene related peptide from peripheral terminals of nociceptive afferent fiber. These peptides change the excitability of sensory and sympathetic nerve fibres, vasodilatation, extravasation of plasma proteins and action on inflammatory cells to release chemical mediators. Thus a soop of inflammatory mediator occur like H+,K+, serotonin, bradykinin, substance P, histamine, NO,NGF and products of cyclooxygenase and lipooxygenase pathway or arachidonic acid metabolites (prostaglandins and leukotrienes. These chemicals sensitize high threshold nociceptors which result in peripheral sensitization. Primary hyperalgesia is seen i.e. lower threshold for noxious stimuli provoking enhanced pain response . This feature commonly seen following trauma and surgery. Following sensitization low intensity mechanical stimuli that would not normally cause pain are now perceived as painful i.e. there is increased responsiveness to normal mechanical stimuli in zone of uninjured tissue surrounding the site of injury –secondary hyperalgesia.

Here in contrast to primary hyperalgesia there is no change in threshold to thermal stimuli. These changes occur due to changes in dorsal horn of spinal cord this is central sensitization.

OPIOID RECEPTORS [10,11,12]

Opioid receptors belong to a super family of G protein coupled receptors which posses 7 transmembrane spanning regions.

Martin and co-workers (1979) proposed 3 classes of opiate receptors mu, kappa and sigma. Sigma receptor (prototype agonist N-allyl-normetazocine) that produced mydriasis, tachycardia and delirium are no longer considered to be opioid receptor as they are not reversed by naloxone, exhibit high affinity binding for ketamine and phencyclidine and are stereoselective for dextro rotatory isomers while other opioid receptors are stereoselective for levorotatory isomer. To this classification kosterlize added delta receptor.

Mu, delta and kappa receptors are currently recognized as opioid receptors. The primary effect of opioid receptor activation is reduction in neurotransmission. This occurs largely by presynaptic inhibition of neurotransmitter release, although post synaptic inhibition of evoked activity occurs too.

1. **Mu(μ) receptor (morphine):** morphine is the prototype agonist. Stimulation of this receptor causes supraspinal analgesia, feeling of wellbeing euphoria, respiratory depression and morphine – type physical dependence. Morphine acts as an agonist at these receptors, and beta endorphin is an endogenous ligand. Naloxone is a selective antagonist, further subclasses of mu receptor also exists viz μ_1 (analgesia, euphoria, miosis), μ_2 (respiratory depression, bradycardia, inhibition of gut motility).

2. **Kappa (k) receptors:** ketocyclazocine is the prototype agonist for the kappa receptor. Stimulation of the kappa receptor causes spinal analgesia, sedation and

analgesia, and a cyclozocine- type physical dependence. Morphine also acts as an agonist at this receptor. Diamorphine is an endogenous agonist and naloxone is a selective antagonist. Further subclasses of kappa receptors have been postulated viz k_1,k_2,k_3.

3. **Delta receptor:** some of the in vivo pharmacological effects of the enkephalin and endorphins on the mouse vas deferns are due to another opioid receptor, designated the delta receptor. The enkephalin along D-ala, D-leu enkephalin (DADL) is the prototype agonist. Although the function of the delta receptor in human is not clear, the delta receptor may be responsible for modulation of the activity of mu receptors.

A fifth opiate receptor epsilon (ε) receptor has been described using in vitro binding studies in rat vas deferens preparation. The proposed endogenous agonist is B-endorphin and the selective antagonist naloxone. This receptor is not well characterized at present.

Opiate receptors are found in many areas of the CNS – cerebral and limbic cortex, hypothalamus, medial thalamus, midbrain (PAG), extra pyramidal area (caudate, putamen and striatum) and sympathetic preganglionic neurons. They are localized in the substantia gelatinosa of the caudal spinal trigeminal nucleus. In the spinal cord opiate receptors can be demonstrated throughout the gray matter with highest density in the substantia gelatinosa. They are situated in pre and post synaptic sites of the small afferent terminals of the dorsal horn. The ‘C’ fiber terminals possess the opiate receptors but not the A fibers. The distribution of opiate receptors in the CNS does not parallel the distribution of endogernous opiates. Gray matter has more receptors than white matter.

The intracellular biochemical events of opioid receptor occupancy are now reasonably established. Opioid receptor are essentially presynaptic and activate Gi-proteins leading to inhibition by increased K^+ conductance and hyperpolarization of cell membrane. They also inhibit adenylate cyclase and calcium channels.

Opioid Receptor Actions		**Agonist**
μ1 –	Supraspinal analgesia	Morphine
	Euphoria	Phenylpiperidin
	Miosis	Meptazinol
	Pruritus	
	Nausea/ Vomiting/ constipation	
μ2 –	Respiratory Depression	Morphine
	Vomiting	Phenylpiperidin
	Bradycardia	
K –	Spinal analgesia	Ketocyclazocine
	Sedation, diuresis	Dynorphin
	Miosis	Butorphanol
		Nalbuphine
δ –	Analgesia, Moodchange	
	Nausea/ Vomiting	
	Hallucination – psychomotor change	
Σ –	Analgesia	
	Dysphoria	

EPIDURAL OPIOIDS [13]

Administration of Epidural opioids produces effective analgesia, because they are deposited near the site where they will exert their effect. Opioids receptors are found in the substantia gelantinosa (Rexed's laminae II-III of the spinal cord), the specific binding site for epidural opioids.

Epidurally administered opioids can (1)penetrate the dura, enter the cerebrospinal fluid (CSF), and bind to receptors along the neuroaxis; (2) remain in the epidural fat; and (3) exit the epidural space as a result of vascular uptake by the radicular arteries and epidural venous plexus. The physical chemical properties of opioids, namely, molecular weight, size, pK_a, receptor-binding affinity, and lipid solubility, govern their distribution when administred epidurally. The passage of epidurally administered opioids into the CSF seems to be determined primarily by the lipid solubility of the drug. The more lipid soluble the opioid is, the more rapid its absorption into the CSF will be, and the more rapid the penetration into the spinal cord, the shorter the time for the onset of its effect will be. Although studies in both children and adults after epidural administration of opioids show an analgesic plasma concentration of opioid, the time course of analgesia in relation to the CSF versus plasma pharmacokinetic profile suggests that CSF is the pharmacologically significant compartment. Once the epidurally administered opioid reaches the CSF, uptake of the drug into the spinal cord also seems to be a function of lipid solubility. Relatively hydrophilic opioids such as morphine are prone to retention in the CSF and passive rostral migration through the CSF, whereas more lipophilic opioids such as meperidine and fentanyl are prone to rapid diffusion into the lipid-rich areas of the

spinal cord or the vascular plexus supplying the spinal cord, but they exhibit little CSF migration.

The migration of opioids in the CSF has been believed to be the major determinant of side effects from spinal axis opioids. Once in the subarachnoid space, opioids are believed to migrate rostrally through the slow-passive and fast-active CSF currents to reach the fourth ventricle or lateral ventricles, where opioids can act on cells in the respiratory centres of the brain stem. Mechanisms for nausea and vomiting also are believed to result from the rostral spread of opioid in the CSF and the opioid's subsequent effect on the chemoreceptor trigger zone located in the caudal end of the fourth ventricle.

Advantages of epidural opioids:

1. There is neither sympathetic blockade nor motor blockade.
2. Success in alleviating pain is reasonably predictable.
3. Duration of pain relief is longer than that of other parenteral routes.
4. Limited systemic opioid effects.

Complications of epidural opioids:

1. Pruritus
2. Nausea and vomiting
3. Urinary retention
4. Constipation
5. Sedation and drowsiness
6. Antitussive activity

7. Spasm of sphincter of oddi
8. Tolerance and addiction
9. Respiratory depression – delayed respiratory depression with less lipid soluble opioids since a large reservoir of the drugs remain in the CSF and gets distributed to higher centers. Intrathecal placement increases this risk.
10. Hypotension and bradycardia.

Effect of Narcotic Lipophilicity on Analgesia:

Effect		**Liphophilicity**	
		Low	**High**
Spinal cord receptor uptake	→	Low	High
(Onset of analgesia)		Slow	Rapid
Duration of action	→	Long	Short
C.S.F. concentration	→	High	Low
Rostral spread of narcotic	→	Extensive	Limited

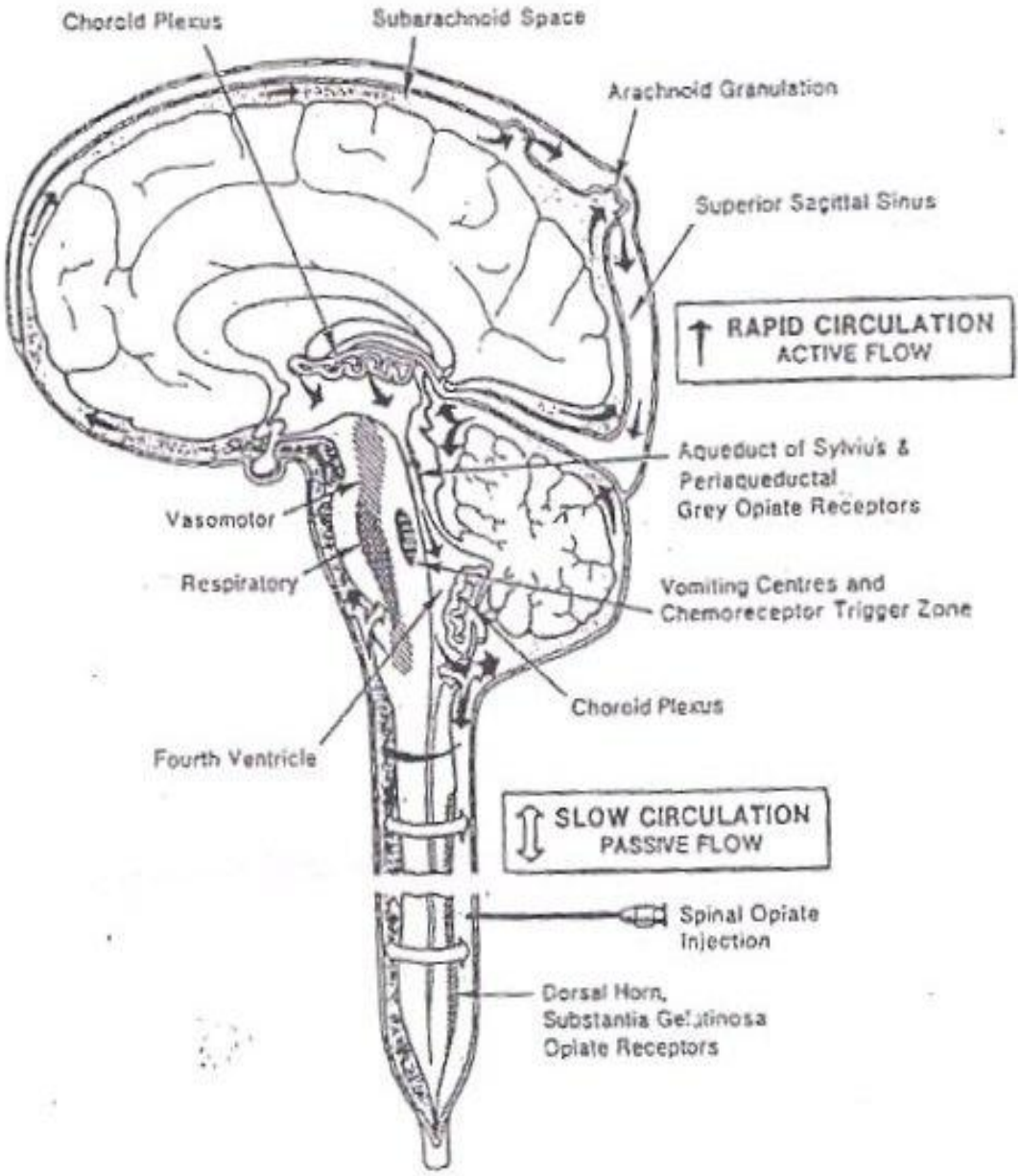


Fig. 10: MODEL OF CSF FLOW AND SPREAD OF OPIOID IN CSF

METHODS OF PAIN RELIEF [4,7]

The incidence of postoperative pain varies with the individual patient. The state of pain following a surgical procedure is a combination of pain as a specific sensation due to nociceptive response to tissue damage and pain as a suffering. Uncontrolled pain in the postoperative period can have detrimental physiological effects.

i) Pain can greatly impede the return of normal pulmonary function splinting, inability to cough., bronchospasm – all lead to atelectasis and hypoxemia especially in upper abdominal and thoracic surgeries.

ii) Pain promotes immobility and hence the development of deep vein thrombosis.

iii) Alteration in the stress response to surgery, increased catecholamine release, increased oxygen demand and increased cardiac work.

iv) Increased catabolic response to surgical trauma and impaired immune mechanisms and delayed wound healing.

Following any surgery, the pain following the tissue damage is rather self limiting i.e., persists at the most for the first twenty four hours; subsides in four days time. The postoperative pain is dull in nature aggravated by mobility, relieved by rest to that part. The acute pain of surgery is strongly accompanied by emotional elements of fear, anxiety and depression.

The common methods adopted for giving postoperative pain relief are:

1. By increasing the pain threshold:

This is done by:

a) *Pharmacologic means:*

   i) Centrally acting analgesics.

   ii) Peripherally acting analgesics.

b) *Non-pharmacologic means:*

   i) Counselling

   ii) Hypnosis

2. By modulating the pain pathways:

This includes:

a) Transcutaneous electrical nerve stimulation (TENS)

b) Acupuncture

c) Cryotherapy

d) Heat therapy

e) Narcotics

3. By Interrupting the nociceptive pathway:

a) Nerve blocks and Neurolysis

b) Surgical ablation – Cryoanalgesia

i) By increasing the pain threshold:

a) *Pharmacological Means:*

i) Centrally Acting Analgesics:

Traditionally, postoperative pain has been treated with opiate analgesics. In the light of the discovery of opioid receptors, opiate analgesics are divided into agonist, partial agonist, agonist-antagonist, and antagonist. Till to date, opioids usage in postoperative pain relief stands ahead of the various other methods described above for the simple reasons of easy availability, practicability and efficacy.

Commonly available opioids are:

a) Morphine

b) Pethidine

c) Pentazocine and

d) Buprenorphine

Opioid analgesics can be given by various means:

- **Oral:** Due to erratic absorption of the drug it is unsuitable for postoperative pain relief.
- **Intramuscular:** Commonest mode of administration, again having the drawbacks of erratic absorption, over dosage, and frequent occurrence of respiratory depression.
- **Intravenous:** This has short duration of action with rapid onset of action of and the recently developed patient controlled analgesia system requiring extensive monitoring facilities and vigilant watch. Tolerance and addiction are common.

- **Neuraxial:** This route has gained popularity because of the longer duration of segmental analgesia with smaller doses. The cardiovascular and respiratory complications are less if used judiciously.

b) Non-pharmacological Means:

Hypnosis:

In this state the body and mind differ from wakefulness and sleep endorsed with profound physical and mental relaxation. When used in postoperative patients, hypnosis has additional advantages of having the patient mobile and able to look after themselves, obviously preventing deep vein thrombosis and pulmonary complications.

ii) By Modulating the Pain Pathways:

a) TENS (Transcutaneous Electrical Nerve Stimulation)

By stimulating large fibers (A Beta) electrically using flexible carbon electrode, the onward transmission of noxious impulses conducted by small fibers are prevented, thereby producing analgesia. Production of endogenous opiates by electrical neuromodulation also produces pain relief. The problem with this is that it needs skilled personnel and special equipments.

b) Acupuncture:

Mechanical and low frequency electro acupuncture at points called acupuncture points cause release endorphins and thus produce analgesia. High frequency acupuncture is associated with metenkephalin release which acts on the serotonegeric fibers and produces analgesia for shorter duration. Acupuncture also produces antipeptidases which retard the elimination of endorphins. It also modulates

pain at substantia gelatinosa cell level in the spinal cord. This method needs skilled persons and specialized equipments.

c) Cryotherapy:

Cooling peripheral nerves to temperatures between -5 to -20^0 C causes disintegration of axons and breakdown of myelin sheaths while the perinerium and epineurium remain intact. Interruption of conduction is prolonged, lasting an average of several weeks.

d) Heat Therapy:

Bonica 1953 quotes the usefulness of applying warmth locally which provided pain relief especially in anal and rectal operations.

iii) By Interrupting the Nociceptive Pathway:

Nerve Blocks and Continuous Interpleural Analgesia:

This involves either intermittent or continuous administration of local anaesthetics in order to interrupt sensory transmission. The important drawback of this technique is the accompanying motor and sympatheric blockade which can increase the incidence of postoperative complications. Moreover, these techniques are not pain specific; intercostals nerve block in particular bears the risk of pneumothorax, local anaesthetic toxicity. Extradural block offers complete pain relief, permits effective coughing and better ventilation. But the incidence of total spinal, by accidental dural puncture is more with inexperienced hands.

METHODS OF PAIN MEASUREMENT [7]

Merskey of international association for the study of pain (ISAP) defined pain **"as the sensory and emotional experience associated with actual of potential tissue damage or described in terms of such damage".** One cannot determine for the individual patient how much nociception occurs in response to tissue damage for which we have to rely on the expression of the patient to accurately measure the subjective nature of pain.

Loser, of multidisplinary pain center. University of Washington put forward a multifaceted model as depicted in this figure. The core of the model is the immeasurable nociception resulting from tissue damage. The next layer is the human experience of emotional and sensory components integrated pain which is not available for direct inspection. Pain leads to suffering and suffering leads to painful behaviours which is available for observation in the form of:-

- ✓ Withdrawing
- ✓ Grimacing
- ✓ Crying
- ✓ Asking for analgesics

Thus if one relies on the patient's report of pain, it is possible to measure pain intensity and the response to analgesic medications.

Introspective Method:

Patient or trained attender attempts to assess pain.

Behavioural Method:

Some physical parameters which get altered in the presence of pain are objectively measured and correlated with the severity of pain e.g., like tachypnoea and increased blood pressure.

Pain as self-Report on a Single Dimension:

Verbal Descriptor Scales – Melzack and Torerson introduced the following scale for pain intensity: "Mild, Discomforting, Distressing, Horrible, Excruciating".

Numeric Rating Scale (NRS) – Here patients are asked to indicate how strong their pain is on a scale from 0 to 10 on which 0 represents "no pain at all" and 10 "the worst pain imaginable".

Visual Analog Scale (VAS) – Currently, the most commonly used method, first described by AITKEN is 1966. The subject makes a mark on a 10 cms line-horizontal or vertical, one end of which is marked as "No Pain" and the other as "The worst pain one can imagine". The position of the mark on the line measures how much pain the subject experiences.

Oral Analog Scale (OAS) – First put forward by AUSTIN et al., it is simple and clinically 'relevant rating scheme'. Absence of pain, presence of pain, and it the patient desired more analgesics are rated 0, 1 and 2 respectively. This rating is simple, yet addresses the essence of problem for the patient whether pain present and if it is, does the patient desire more pain relief with more analgesic medications.

Pain as Self – Reports on Multiple Dimensions

McGill Pain Questionnaire:- It scales pain in three dimensions: Sensory, Affective, and Evaluative.

West Haven – Yale Multidimensional Pain Inventory: It has been designed to be briefer and more classical in its – psychometric approach.

Brief Pain Inventory: is a quick, multidimensional pain measurement that has demonstrated reliability and validity. Memorial Pain Assessment Card – It scales pain, pain relief and mood on VAS and adds a set adjectives reflecting pain intensity.

***Cross* – Modality Matching:** a psychophysical technique in which a sensory experience is quantified by matching it to the experience of a precisely controlled stimulus in a different sensory modality.

Pain Perception Profile – is a based on cross modality matching.

Other methods used are:

TOTPAR (TOTAL PAIN RELIEF AND ANALGESICS)

SPID (SUM OF PAIN INTENSITY DIFFERENCES)

The preoperative personality assessment is also helpful in assessing the patients psychological background and his psycho to surgery and the pain that follows it. Although there is no absolute consensus on how clinical pain should be measured, there is enough agreement that clinicians and researchers do not have to despair of being able to measure the subjective phenomenon of pain.

PATHOPHYSIOLOGY OF POSTOPERATIVE PAIN [14]

Pain produces discomfort, psychological trauma and fear which discourage activity, breathing or the urge to cough. The somatic and visceral sites of the operation become a source of chronic irritation which constantly stimulates the spinal cord resulting in hyperactivity of the anterior and anterolateral motor cells and consequent skeletal muscle spasm and vasospasm in a manner similar to that of causalgic state. The muscle spasm becomes a source noxious stimuli which gives rise to pain which in turn causes more muscle spasm thus setting up a vicious cycle. Muscle spasm cause hypoventilation by splinting the thoracic, abdominal and diaphragmatic muscles. Cutaneous pain initiates cutaneovisceral reflex to aggravate visceral dysfunction produced by the visceral pain.

- **Cardiovascular:** Increased myocardial work mediated by catecholamines, angiotensin II, ADH, aldosterone which cause dysrhythmia, angina, myocardial infarction and congestive heart failure.

- **Pulmonary Complications:** Pain induced reflex increase in skeletal muscle tension lead to decreased total lung compliance, splinting and hypoventilation. These promote atelectasis, pneumonitis and hypoxaemia.

- **Gastro-intestinal complication:** Pain induced sympathetic hyperactivity cause reflex inhibition of GI function. It results in distension, nausea, vomiting, inadequate digestion and absorption.

- **Urinary complications:** Increased sphincter tone and decreased smooth muscle tone – urinary retention.

- **Vascular Complications:** thrombophlebitis and embolism.

- **Neuroendocrine:** There is increased level of catabolically active hormones like catecholamines (vasoconstriction) cortisol (lipolysis), ACTH (protein catabolism), glucagon (hyperglycemia), ADH (salt and water retention) and angiotensin II (increased myocardial contractility). There is decreased insulin and testosterone level (decreased protein anabolism).

Factors influencing postoperative pain:

1. The psychologic make up of the patient and the threshold for pain: constitutional status e.g.: age, sex, temperament.
2. The site and nature of the operation.
3. The amount of surgical trauma.

Elderly people react less to postoperative pain than young people. Probably they develop a philosophy with age of accepting the stresses of life. Sex also is a variable. Men show an evident circadian rhythm to thermal stimulation.

Postoperative pain and pulmonary complications are more in thoracic and abdominal operations. Anorectal operations are next, followed by operations on back. Type of incision also decides the severity of pain. Incisions which involve cutting or damaging nerves produces more pain. Thus transverse incisions in the abdomen produce less postoperative pain then vertical or diagonal incisions.

PHARMACOLOGY OF TRAMADOL [10,11,12,15]

Tramadol is a centrally acting analgesic with a low affinity for opioid receptors. It is a synthetic analogue of codeine. It has a unique dual mechanism. Tramadol is a recemic mixture of 2 enantiomers.

- **Chemical Name:** Tramadol belongs to the aminocyclohexanol group.

- **History:** Tramadol was introduced in late 1970's by Grunenthal in German Market.

Mechanism of action:

Tramadol has both opioid actions

1. Tramadol has a low affinity for opioid receptors. It acts as a selective μ-receptor agonist, but also binds weakly to Kappa and Delta receptors.

2. Non-opioid mechanism is a monoaminergic pathway. It inhibits noradrenaline and 5-hydroxy tryptamine (serotonin) neuronal reuptake and facilitates serotonin release. The two enantimoers of tramadol i.e., tramadol (+) and tramadol (-) have complementary and synergistic anti-nociceptive interaction. Tramadol (+) has greater affinity for μ receptors and inhibits serotonin reuptake tramadol (-) inhibits norepinephrine reuptake. The synergistic effect of both these enantiomers may be responsible for its low potential for the development of tolerance, dependence, and abuse and production of analgesia with the absence of depression of ventilation. Interestingly, the racemate may produce less sedation and gut inhibition than either enantiomer alone.

Pharmacodynamics:

Effects on respiration: Opioid analgesics cause respiratory depression by decreasing the sensitivity of the respiratory centre to CO_2. This results in a decrease in respiratory rate and tidal volume. There is increased alveolar CO_2, $PaCO_2$ and decreased transcutaneous phase oxygen saturation.

In clinically recommended doses, tramadol is unlikely to produce relevant respiratory depression.

Effects on Cardiovascular System:

Tramadol transiently increases heart rate, both systolic and diastolic blood pressure. It increases peripheral vascular resistance, decreases pulmonary arterial resistance, and exerts a negative inotropic effect on left ventricular myocardium.

Tolerance and Dependence: Tolerance is minimal with tramadol. It has low physical and psychic dependence.

Other Effects: Tramadol in clinical dosage has no effect on plasma histamine levels and it does not cause any systemic anaphylactiod reactions. There is no increase in base line pressure or duration, frequency and amplitude of contractions of the bile duct sphincter in patients undergoing ERCP.

Pharmacokinetics:

Absorption and Distribution:

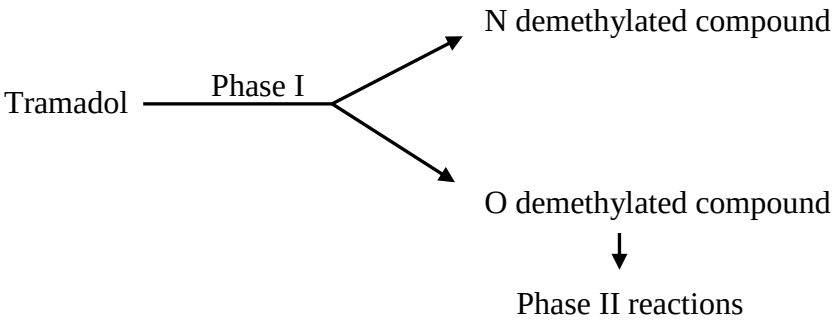
Tramadol is rapid and completely absorbed on oral administration. Peak plasma concentration are achieved in 2 hours and t½ of tramadol is 6.2 hours and has

mean oral bioavailability of 68% after single administration half life of tramadol is slightly prolonged in persons above 75years. In case of renal or hepatic impairment half life is increased twice or thrice.

Tramadol is rapidly distributed after intravenous administration, with distribution half life in α phase is minutes followed by slower distribution half life in β phase of 1.7hrs. Tramadol crosses the placenta with serum concentration in umbilical vein being 80% of that in maternal veins.

Metabolism and Elimination:

Tramadol is metabolized in liver. The major metabolite O-desmethyl tramadol is produced by O-demethylation. It shows 200 times higher affinity for μ receptors than the parent tramadol.



Tramadol is excreted by the kidney. 15-30% as unchanged and only 0.1% of tramadol dose is excreted in milk of lactating women, an amount which is unlikely to produce significant effects in neonates. In patients with chronic renal failure and a creatinine clearance of less than30ml/min, the dose of tramadol should be reduced to a maximum of 200mg/day in 12 hour divided doses. With hepatic cirrohosis, the elimination half life is doubled and maximum dose of tramadol should be further reduced to 50mg every 12^{th} hourly. When induction of hepatic enzymes for example

with carbamazapine 400mg BD occurs the dose of tramadol can be doubled to compensate for enhanced hepatic clearance.

Therapeutic Efficacy: on intravenous administration – tramadol is equivalent to pethidine, $1/5^{th}$ as potent as nalbuphine, $1/10^{th}$ as potent as morphine.

Dosage and Routes of Administration:

Tramadol can be given in doses of 50-100mg upto 4 times a day. Total daily dose should not exceed 400mg for adults.

In children > 1yr of age a dosage of 1 to 2 mg/kg.

Routes: oral, parenteral, epidural, rectal

Adverse effects: Mild, Transient and Rare.

1. **CNS:** nonspecific CNS irritation, dizziness, sedation, euphoria, dysphoria.
2. **GIT:** Nausea, vomiting, constipation, GI irritation
3. **ANS:** Dry mouth, sweating (due to its monoaminergic effects)
4. **CVS:** Orthostatic hypotension, tachycardia
5. **Others:** Motor weakness, urinary retention

Respiratory depression with tramadol is less than with morphine, respiratory depression is unusual in recommended doses and was not found in neonates whose mother had been given tramadol. The advantage of tramadol over opioids with respect to reduced respiratory depression is limited by lack of efficacy of tramadol in severe pain where opioids are more effective.

Drug Interactions:

Tricyclic antidepressants, selective serotonin reuptake inhibitors, neuroleptics: tramadol when given to patients on these drugs decreases the seizure threshold. Concomitant administration of tramadol and SSRI causes serotonin syndrome.

Concomitant administration of tramadol with monoamino oxidase inhibitors causes hypertensive reactions. Quinidine inhibits tramadol metabolism, hence serum tramadol concentration increases, when these 2 drugs are used. Carbamazapine enhances tramadol metabolism, hence tramadol half-life is decreased as much as 50%. When these two drugs are used concomitantly, tramadol dose should be increased.

Overdosage: Symptoms are similar to other opioids. Miosis, vomiting, coma, respiratory depression, respiratory arrest and cardiovascular collapse. Opioid antagonist naloxone will reverse coma and respiratory depression.

Advantage:

1. Can be given through different routes – oral, parenteral.
2. Low respiratory depression.
3. Low dependence, abuse, tolerance.
4. Less secretion in the milk of lactating restriction.
5. Freely available. No narcotic prescription restriction.
6. Cheap.

Indications:

Tramadol indicated for moderate to severe pain in adults. It has same analgesic potency as pethidine, 1/5 of that of nalbuphine, 1/1000 that of fentanyl and 1/10 that of morphine. IV tramadol 50-150mg IV was equivalent to morphine 5-15 mg but a preservative free preparation had 1/13 of the potency of morphine extradurally.

Despite being relatively less potent than pure opioids, tramadol has achieved efficacy when used to treat moderate pain after surgery. In treating pain after thoracotomy, tramadol 150mg IV was no different in effect to morphine 2mg extradurally, combined with a extradural infusions of 2mg/hr. After hysterectomy, Tramadol 50mg IV was as effective as morphine 5mg IV is treating pain described as moderate – pain assessment was by serial changes in verbal rating scores after analgesic administration. Because of its efficacy as an analgesic, tramadol is considered to be effective in step two of the world health organization guideline for treatment of patients with cancer pain.

Contraindication:

As tramadol enhances monoaminergic transmission, the drug is contraindicated in patients receiving mono-amino inhibitors and caution advised in patients with epilepsy. Not recommended in children.

Summary:

The lack of analgesic efficacy limits tramadol as a sole agent to treat severe pain. However it has a relative lack of respiratory depression and constipating effect compared with morphine and codeine and does not share the propencity of

nonsteroidal anti-inflammatory drugs to provoke asthma, gastrointestinal mucosal damage and renal impairment. It may well have a place in the management of pain after surgery, after the control of worst pain by a regional anaesthetic technique.

Extensive clinical experiences with tramadol has shown the drug to be an effective analgesic agent for postoperative pain as well as other acute pain syndromes. For patients with severe pain, more potent opiates such as morphine are preferable. Tramadol is not recommended as the sole analgesic during general anaesthesia, because of high incidences of recall and dreaming.

It has also been confirmed that tramadol is associated with low incidence of respiratory depression and lack of dependence.

PHARMACOLOGY OF BUPRENORPHINE [10,11,12,15]

Buprenorphine is a semisynthetic highly lipophilic opioid derived from thebaine, an opium alkaloid related to morphine, and is a long acting analgesic with narcotic agonist and antagonist actions. It is a white powder weakly acidic and with limited solubility in water.

It has similar structure to morphine. It is a partial agonist of μ-receptor.

Formula: C29H42NO4HCL

Mol. Wt: 504.09

Pka: 9.4

Free base 9%, unbound form in plasma 4%

Diffusible fraction 0.366%

Half life of dissociation 166mts

Volume of distribution Vd: 2.8 lit/kg

Clearance (Cl): 20ml/kg/mt

It is a white powder, weakly acidic with limited solubility in water.

Chemical Structure:

Buprenorphine HCL chemically is 17 cyclopropylmethyl α 1, 1- dimethyl ethyl 4,5-epoxy-18,19-dihydro3-hydroxy6-methoxy-2-methyl -6,14ethanomorphinan-7 methanol hydrochloride.

Mechanism of action:

Buprenorphine appears to have a high affinity for both mu- and k-receptors and low to moderate intrinsic activity at mu and k receptors. In contrast the drug appears to have low affinity and low intrinsic activity at δ receptors. Buprenorphine binds slowly with and dissociates slowly from the μ receptors. Though it is highly lipophilic, onset of action is slow. Peak effect occurs in 3 hours.

Absorption, fate, excretion: It can be given orally, sublingually, parenterally, Metabolism occurs in liver with biliary excretion of most metabolites, Metabolites of buprenorophine are buprenorphine 3-glucuronide and norbuprenorphine. They are less potent and have lower affinities for μ-receptor. They are excreted in faeces and small amounts in urine.

Preparation, route of administration and dosage:

It is available as buprenorphine hydrochloride 0.3 mg/ml ampoules. It is a clear, sterile solution for i.v and i.m administration and each ml contains 0.324 mg buprenorphine hydrochloride, equivalent to 0.3mg buprenorphine, 50 mg anhydrous dextrose, water and HCl to adjust pH. Also available as sublingual tablets (0.2mg).

Dosage: premedication 5-6 μg/kg/intramuscularly

As analgesic component of balanced anaesthesia 4.5 to 12 μgm/kg

For postoperative analgesia 2-3μg/kg epidurally

Sublingual more than 15years 0.2 to 0.4 mg 6^{th} hourly

Effects

Effects on CVS: In therapeutic doses, it will not produce any significant effect on blood pressure or cardiac rate and rhythm.

Effect on respiratory system: In therapeutic doses respiratory depression does not occur. The mechanism of respiratory depression involves depression of medullary and pontine centres and a reduction in responsiveness of brainstem respiratory centre to increased CO2 tension. Buprenorphine induced respiratory depression is characterized by decrease in respiratory rate, arterial PO2 and increase in arterial PCO2. Respiratory depression is lower in onset and lasts longer than that of morphine and maximal respiratory depression if observed after 3 hours. With higher doses, duration of respiratory depression becomes less and ceiling effects occur such that the maximum effects produced were less than those obtained with morphine. Respiratory depression reversal with naloxane and / or doxapram may be required for full reversal.

Effects on C.N.S: Buprenorphine produces similar type of action as morphine but it is 25-30 times more potent than morphine after parentral injection. It produces analgesia, sedation, miosis and a lesser degree of nausea and vomiting, which appears exacerbated by movements. It may also produce side effects like dizziness, sweating and headache.

No major psychomimetic effects and dysphoria have been observed after buprenorphine.

Effects on GIT: It decreases gut motility and increases the tone of smooth muscle of gut.

Labour and delivery: The study of buprenorphine given during labour and delivery has not been established.

Tolerance and physical dependence: Although specific information is not presently available, care should be taken when buprenorphine is used in combination with CNS depressant drugs and MAO inhibitors. Drug interactions common to other opiate analgesics can occur.

Adverse effects:

- Nausea and vomiting – It stimulates chemoreceptor trigger zone in area postrema of the medulla through delta receptors.
- Central nervous system – confusion, blurred vision, euphoria, slurred speech, nervousness.
- Cardiovascular system – tachycardia, bradycardia
- Respiratory system – hypoventilation, cyanosis, apnoea
- Skin – pruritus, rash, sweating
- Genitourinary – urinary retention
- Opiate withdrawal symptoms develop slowly 5 – 10 days after buprenorphine is discontinued, following prolonged use.

Uses : used in the management of postoperative pain to provide preoperative sedation and analgesia as a part of premedication.

As analgesic for the relief of moderate to severe pain associated with malignancies, trigeminal neuralgia, ureteric colic, pain associated with myocardial infarction.

HISTORICAL REVIEW: [7]

Man has been afflicted with this EVIL (pain) since his origin. Prayers, exorcisms and incantations bearing testimony to the prevalence and scourge of pain are found in Babylonian clay tablets, and in papyri written in the days of pyramid builders, in Persian leather documents, on parchment rolls from Troy. Such records continue down through the age in every civilization and in every culture.

The cause of painful disease in pre-historic time was linked with intrusions of magic fluid, evil spirits or pain demons into the body. Treatment was to extract the intruding object or frighten away the pain demons.

The ancient Egyptians believed that painful afflictions other than wounds were due to religious influences of god or spirits of dead. The route of departure of the demons was via vomit, urine, sneeze of nose or sweat of limbs.

According to Ebers papyrus, a widely distributed network of vessels called 'metu' carried the breath of life and sensation to heart. This was the beginning of the concept that the heart was the centre of sensation, an idea that lasted more than 2000 years.

In ancient India the earliest concept of pain were attributed to the God Indra, as recorded in Vedas and Upanishads. Buddha about 500 B.C., attributed the university of pain in life to the frustration of desires. Charaka the first of India's great teachers of medicine, stated that all joy and pain was experienced in the heart, which was considered the seat of consciousness.

The ancient Chinese thought, any imbalance of two forces (yin and yang), results in deficiency or outpouring (excess) in the circulation of the CHI (the vital energy), which ends up in disease and pain. Acupuncture therapy at one or more of the 365 specific points located along meridians, corrects the imbalance and eliminates the disease and pain.

In Greece – Alcameon produced the idea that the brain and not heart was the centre for pain. Herophilus and Bristratus of Alexandria provided anatomic evidences that the nerves attached to the neuraxis are two kinds, those for movement and those for feeling.

The first authentic reference on use of opium for pain relief is found in writings of Theophrastus in 3 rd century BC.

During first century A.D., reference to analgesic pills were done by celsus in his book "De Medicana". A century later Galen re-established the physiological importance of the central nervous system, suggested natural basic of pain due to disease and injury, wrote a book on pain as a diagnostic symptom and spoke of analgesic effects of opium and mandragora.

In the middle ages, the centre of medicine shifted to Arabia. Avicenna modified all available medical knowledge and described aetiology of 15 different types of pain in his book "Cannon of Medicine".

Remarkable advances were made in anatomy particularly of the central nervous system, physiology, chemistry and physics.

In 1804 Descartes in his book “L’Homme (man)” described the conduction of sensation including pain via delicate threads contained in the nerves which connected tissues to the brain.

During the 18th and 19th centuries several developments pertaining to pain and its control took place. The new era of analgesia was initiated with Joseph Priestley’s discovery of nitrous oxide.

Modern approach to the scientific study of pain and its control began in the 19th century. Charles Beu described that functions of dorsal root are distinct from those of the ventral root. After 15 years Johannes Muller fully expanded this idea. The modern era of systemic analgesia began in 1806 when morphine was isolated by Sertuner and it was frequently used intramuscularly for preoperative medication and postoperative analgesia.

Prior to 1846, attempts to provide comfort during operative procedures were minimally effective and the development of surgery was necessarily limited. William T. G. Morton’s public demonstration of ether in that year revolutionized medical care throughout the world. The evolution of anaesthesiology as a medical specialty has facilitated the success of modern, complex surgical procedures, beyond the obtundation of consciousness and creation of a quiescent surgical field. Anaesthesiology applies principles of physiology, pathophysiology and pharmacology to assess and reduce surgical risk, maintain homeostasis, attenuate the surgical stress response, and provide analgesia.[11]

Regional analgesia for the management of intractable pain was also introduced in the last century. In 1900 Losser began experimenting in alcholisation of nerves for

the treatment of neuralgia. In 19th century, yet another greater advancement to conquer pain came up – using neurosurgical techniques. Surgeons started interruption of afferent pathways to control pain.

During the first 50 years of 20th century neuroanatomic, neurophysiologic and psychologic research on pain continued at progressively faster pace. Extensive knowledge became available on nervous system and its functions.

The funding of the International Association for the study of Pain (ISAP) in 1974 and publication of its journal PAIN since 1975 must be considered among the most important developments in the field of pain research and therapy.

Great studies are being made in understanding the structure – function relationships between opioids and endogenous opioid peptides and their receptors. The complex signalling mechanisms and neural circuitry mediating both the salutary and undesirable effects of opioids also are beginning to be understood. The recent discovery of new μ - receptor – selective endogenous opioid ligands and the opioid – related N/OFQ system also will provide opportunities to improve our understanding of opioid pharmacology and physiology. The development of new opioid analgesics and novel delivery routes are improving the care and quality of life for patients requiring opioids.

MANAGEMENTS OF POST – OPERATIVE PAIN

From time to time man has restored to many means in his search for relief of pain. Painless surgery and painless post – operative period is probably the greatest boon that has been granted to the patients and indirectly to the surgeons. There are various methods used, each one carrying its merits and demerits.

In 1806, Setruner isolated morphine and it was frequently used intramuscularly for preoperative medication and postoperative analgesia. After the introduction of the syringe and hollow needle in 1853, the opioids could be administered in carefully measured doses.

In 1939, Eisleb and Schaumann introduced pethidine, which was also used intramuscularly. Intermittent intramuscular injections have been shown to produce unpredictable and fluctuating blood levels. Parenteral administration of opiates has been the strong anchor for the treatment of postoperative pain after the introduction of the syringe and hollow needle.

Opioids have been administered for hundreds of years to allay anxiety and reduce pain associated with surgery.

In 1954, Lasagna et al. showed that some patients, so called ‘Placebo reactors’ apparently obtained pain relief from the injection from normal saline. This made the comparison of the analgesic drugs difficult.

In 1960, Keats et al. Described a drug (WY - 2247), which showed a marked dissociation of analgesia and subjective side effects such as nausea and dry mouth. It

suggested that a potent analgesic devoid of some of the undesirable effects of morphine might one day be found.

In 1962, Archer introduced pentazocine, which also produced same amount of respiratory depression as morphine in equivalent, equianalgesic doses. Many other drugs like fentanyl, methadone, diamorphine, butorphanol were studied, but all were associated with the major disadvantages of respiratory and/ or circulatory depression.

No drug seems to have exceeded the therapeutic ratio of morphine or combined its analgesic properties with a comparable degree of mental sedation and feeling of well being. The pharamacological plot has thickened with the finding that some opiate antagonists can actually be analgesic in themselves.

Buprenorphine, a potent long acting, partial agonist antagonist, synthetic analgesic drug, was synthesized in 1966 by Rockitt and Colman. This compound was shown to have substantial advantage over morphine and related potent analgesic in animals. In 1974 Yusuke administered ketamine for postoperative pain relief.

In general, extradural analgesia has developed slowly in surgical patients, despite enthusiastic reviews. (P. Bromage 1967). Extradural blockade offers considerable improvement in respiratory function in these cases. The technique of injecting analgesics below each rib was described by Moore and Baiden Bough (1962) and Hblonde et Al. (1966).

Baskett and Bennett (1971) used Entonox the premixed 50% mixture of nitrous oxide and oxygen in pain relief. Lower concentrations of Nitrous oxide (20-25%) may provide postoperative analgesia equivalent to routine narcotics. Self

administration through draw-over vaporizers can produce analgesia equivalent to routine narcotic drugs without respiratory depression.

Finer (1972) has defined Hypnosis, which has long been used in relief of pain as a stage of selective concentration and detachment which can be learned under deep muscular and mental relaxation.

Acupuncture, a Chinese medical art is not understood despite considerable present day interest (Dimond 1971, Cheng and Ding 1973). It has been suggested that hypnosis plays a major part and that the explanation lies in the diminution of pain transmission by nociceptive stimulation of the gate control mechanism.

The identification of specific receptors in the substantia gelatinosa of posterior horn cells of spinal cord and in the brain by S. M. Synde (1975) which are sensitive to narcotics and isolation of endogenous lipids in brain by Synder and Simon (1976) has opened up new concepts for the treatment of pain.

A study regarding treatment of postoperative pain with peridural administration of opioids was done. They postulated that there is no ideal opioid available for epidural use and the advantages and disadvantages associated with epidural opioids require careful selection of appropriate opioids. Morphine (provided it is given in small doses and volumes) is very appropriate for epidural pain treatment, especially in longer periods of treatment, due to the excellent analgesia and very low systemic concentrations. The faster onset of analgesia makes the epidural application of pethidine, alfentanil and fentanyl recommendable. However due to the increased risk of respiratory depression during continuous treatment, these opioids should not be given over longer treatment periods. Epidural administration of methadone, sufentanil

and buprenorphine cannot be recommended since the advantages over systemic use do not outweigh the risks. Epidural tramadol in clinical routine is recommended when supervision of the patient is not guaranteed, because the opioid is not restricted by law and has a low potential for central depressive effects[16].

A study investigated epidural buprenophine as a postoperative analgesia in 158 patients. Patients were given 0.15mg or 0.3 mg of buprenorphine in 15ml saline or no injection control group. 0.3 mg of buprenophine was superior to both no injection group and 0.15 mg buprenorphine[17].

In another study the efficacy of epidurally administered buprenorphine (0.2mg) after combined spinal epidural anaesthesia (CSE group) and that after general anaesthesia combined with epidural anaesthesia (EPI+GEN group) was compared. Postoperatively the duration of pain relief with epidural buprenorphine was similar in both group (about 11 hours).However onset of pain relief was faster in CSE group, and explained that it might be due to flux of buprenorphine through a dural hole just after epidural administration[18].

In a study which compared analgesic efficacy as well as side effects circulatory and respiratory parameters of 50mg epidural tramadol with 0.3 mg epidural buprenorphine for the relief of postoperative pain, buprenorphine produced more potent and longer acting analgesic compared to tramadol, although slightly delayed. There were only few and slight side effects and no influence on the circulation and respiration. In the search for new long acting and strong analgesic, tramadol proved to be unable to replace buprenorphine in the control of postoperative pain[19].

Another study compared analgesic action of tramadol and buprenorphine + diazepam in extracorporeal impulse lithotripsy. Opiate agonist antagonist buprenorpine provided high quality analgesia with a drastic lowering of Sp02. It was found that tramadol does not depress respiration and provided adequate analgesia[20].

In another study extradural buprenorphine was compared against pentazocine for postoperative analgesia. The duration of analgesia was longer with buprenorphine than pentazocine and no serious side effects were reported[21].

A study compared the analgesic efficacy, side effects and plasma concentration of buprenorphine and fentanyl in 78 parturiants receiving Patient Controlled Analgesia in epidural infusion following cesarean section. Patients were put into 3 groups, group 1 (n=26), 3µg/mL buprenorphine, 0.0015% bupivacine and 1µg/mL epinephrine. Group 2 (n = 26), 3 µg/mL fentanyl and with 0.015% bupivacine and 1µg/mL epinephrine. Group 3 (n = 26) 3 µg/mL fentanyl with 0.015% bupivacine. Pain relief was similar and satisfactory in all the three groups. Pruritus was more common in the fentanly group. However vomiting was more disturbing to the patients and seen only with buprenorphine. No patient had a respiratory rate less that 12 bpm. Mean opioid plasma concentration did not exceed 1.5ng/mL. They concluded that epidural PCA in all the 3 groups provided excellent analgesia without serious side effects. Epidural buprenorphine offer no advantage over epidural fentanyl[22].

Another study compared the efficacy of epidural fentanyl and buprenorphine for postoperative pain relief. It was performed on 177 patients after upper and lower abdominal surgery. In the fentanyl group (F) 73 patients epidurally receive 0.1mg of fentanyl with 8 ml of saline postoperatively, followed by a constant rate infusion of

0.025mg/ hr for 18-24 hours. In the buprenorphine (B) group, 104 patients received 0.2mg of burpenorphine with 9ml of saline epidurally. After upper abdominal surgery, 33 patients (76.7%) in the F group and 27 patients (52.9%) in the B group obtained satisfactory analgesia ($p < 0.05$). As assessed by the verbal analogue score. Respiratory depression occurred in the 19 patients in the B group and 5 patients in the F group ($p < 0.005$). It was seen that epidural fentanyl offered a significant advantage compared with epidural buprenorphine for postoperative pain relief after upper abdominal surgery. However the difference in the degree of analgesia after lower abdominal surgery was not significant. This was probably because of difference in lipid and water solubility (buprenorphine being less water soluble)[23].

In another study by Hayashi et al, the major site of action of epidurally administered buprenorphine appears to be enhanced by the supraspinal action while the major site of action of epidurally administered fentanyl is spinal cord[24].

A study to clarify the site of analgesic action of epidural buprenorphine and its spinal segmental analgesia in 50 gastrectomy patients was done. Their study supports the hypotheses that buprenorphine administered epidurally is rapidly absorbed from epidural space into systemic circulation and produces systemic (supraspinal) analgesia on par with intravenous buprenorphine at the supraspinal region of central nervous system. Epidural buprenorphine also produces spinal segmental analgesia which developed 2-6 hours after administration[25].

Epidural morphine and epidural buprenorphine was compared for postoperative analgesia. Is this study 60 adult patients undergoing various surgical procedures were chosen. In the recovery room, when analgesia was requested by the patient, either 4mg morphine or 0.12 mg buprenorphine was injected through the

epidural catheter. The patients were evaluated for onset, duration, quality postoperative analgesia and side effects. They found that mean duration of postoperative analgesia with epidural buprenorphine was 19.9 ± 8 hours, in comparison to epidural morphine which produced postoperative analgesia for 15.85±7.36 hours. The incidence of side effects was also less with epidural buprenorphine. Respiratory depression was not found in any case, urinary retention occurred in 8 case (26.7%), pruritis found in 1 case (3.3%), Nausea and vomiting in 2 cases (6.7%), hypotension occurred in one case (3.3%), in buprenorphine group. The incidences of side effects were more with morphine. They concluded that epidural buprenorphine provided longer duration of analgesia with lower incidence of side effects[26].

In another study epidural buprenorphine had a mean duration of analgesia of 31.24hours which was longer duration than morphine[27].

A study was conducted to study the analgesic efficacy of addition of 0.1% bupivacaine to Patient Controlled Epidural Analgesia using buprenorphine and droperidol after gynaecological surgery. They concluded that addition of 0.1% bupivacaine to Patient Controlled Epidural Analgesia using buprenorphine (20 µg) and droperidol (0.1 mg) provided better analgesia on coughing when compared to Buprenorphine and droperidol combination alone[28].

Another study compared the effects of extradural with intravenous buprenorphine on postoperative pain and recovery characteristics in 11-13 years age group undergoing inguinal hernia repair. They found that nausea, vomiting and urinary retention and pururitus were more common in the extradural buprenorphine

group. Their analgesic effects were comparable. They concluded that the administration of buprenorphine resulted in higher incidence of side effects[29].

Kumar et al studied patients for the effectiveness and duration of postoperative pain relief by epidural buprenorphine and ketamine. All patients had satisfactory analgesia after 0.15 mg buprenorphine, so it was recommended for the postoperative pain relief. Mean duration postoperative analgesia with epidural buprenorphine was 13.1 hours[30].

Tramadol is a cyclohexanol derivative with Mu-agonist activity. It has been used as analgesia for post – operative or chronic pain since the late 1970's and became one of the most popular analgesics of its Germany. It was discovered that tramadol not only acts on opioid receptors but also inhibits and noradrenaline reuptake[31].

In patients with moderate postoperative pain, i.v. or i.m. tramadol is roughly equal in efficacy to meperidine or morphine. Common adverse effects of tramadol include dizziness, nausea, dry mouth and sedation. The abuse potential is low[32].

In another review a similar finding was observed. The overall analgesic efficacy of tramadol was similar to that of morphine or alfentanil and superior to that of pentazocine. The most common adverse effects (incidence of 1.6 to 6.1%) were nausea, dizziness, sweating, vomiting and dry mouth and no clinically relevant effects on respiratory or cardiovascular parameters noted at recommended dose in adults or children. Tramadol also has a low potential for abuse or dependence[33].

In a study on postoperative pain relief 50mg and 100mg of tramadol epidurally was compare and changes in blood pressure, pulse rate, respiratory rate,

pain scores were found. The changes were significantly less($p < 0.05$) at 3, 12, 24 hours in patients receiving tramadol 100mg than in those receiving tramadol 50mg. The duration of post– operative analgesia was 7.40 hours with 50mg tramadol and 9.36 hours with 100mg tramadol[34].

In a study on postoperative pain relief following cesarean section they compared 100mg vs 200 mg epidural tramadol with saline and with placebo. Pain scores and side effects were evaluated at 1, 2, 4, 8, 12 and 24 hr after surgery. The mean time to first analgesic administration was longer in patients who received 100 mg tramadol (4.5 ± 3.1hr) and the 200 mg tramadol (6.6 ± 3.4hr) than in those who received placebo (2.8 ± 2hr). No difference was obtained between patients receiving 100 mg and 200 mg tramadol concerning all parameters studied. It was concluded that epidural tramadol 100mg can provide adequate postoperative analgesia without respiratory depression in patients after cesarean delivery[35].

In another study two groups of 25 patients each posted for elective surgery below the level of umbilicus received postoperative epidural analgesia. Group – I (received 100 mg Tramadol Hydrochloride diluted in 10ml normal saline) was found to be safe with rapid onset of action, adequate and prolonged intraoperative analgesia extending into the postoperative period allowing good cardiovascular and respiratory stability with a few side effects when compared to Group-II patients (Received 10 ml drug free, normal saline postoperatively through epidural catheter)[36].

A study compared IV tramadol infusion with epidural tramadol for postoperative analgesia after gastrectomy. One patient in epidural group developed respiratory depression 8 hours after the operation. They concluded that intravenous tramadol infusion provided effective and safe postoperative analgesia[37].

The efficacy and side effects of epidural tramadol and morphine were compared in patients undergoing laminectomy. The time to first supplementary dose was significantly shorter in the tramadol group compared to the morphine group ($p<0.05$).No patient in either group suffered respiratory depression[38].

Turker G et al did a study to compare lumbar epidural morphine (4mg) and lumbar epidural tramadol (100mg) with respect to onset and duration of analgesia, analgesic efficacy and drug related side effects after muscle sparing thoracotomy. The study revealed that the quality of analgesia achieved with repeated doses of lumbar epidural tramadol was comparable to that achieved with lumbar epidural morphine. Compared with morphine lumbar epidural tramadol resulted in less sedation and a less pronounced decrease in oxygenation[39].

Epidural administration of single dose tramadol (2mg/Kg) with morphine (0.1mg/Kg) in children undergoing urological surgery with respect to preoperative haemodynamic effects, postoperative analgesia and side effects were compared. During the 24 hour postoperative period, heart rate, systolic blood pressure, respiration rate, pain score and sedation level of the patients were monitored. In the postoperative period, the pain scores and the average time for analgesic requirement were similar. However the incidence of allergic rash, itching, sedation and respiratory depression and sedation score were greater in morphine group than in tramadol group. It was concluded that greater epidural use of tramadol was preferred to morphine for postoperative analgesia[40].

A similar conclusion was reached by Baraka et al. He compared epidural tramadol and epidural morphine for postoperative analgesia in 20 patients undergoing major abdominal surgeries. In 10 patients 100 mg tramadol diluted in 10ml normal

saline was injected in epidural space, while 4 mg epidural morphine was used in the other 10 patients. In all patients, the visual analogue pain score, PaO2, PaC02, and respiratory rate were monitored every hour for the first 24 hours postoperatively. In both tramadol and morphine groups, the mean hourly pain scores ranged from 0.2 - 0.6 to 1.4-2.5 throughout the period of observations. However the mean PaO2 was decreased postoperatively in the epidural morphine group. The results suggest that epidural tramadol can be used to provide prolonged postoperative analgesia without serious side effects[41].

A study regarding the efficacy and safety of tramadol versus morphine for moderate and severe postoperative pain with special regard to respiratory depression was conducted. It was concluded that both drugs produced acceptable analgesia and there were no clinically significant adverse events and no clinically relevant respiratory depression with tramadol. They underlined its safety for postoperative pain relief[42].

A study compared oral tramadol and morphine for strong cancer related pain. They concluded that in certain cancer patients with strong pain tramadol achieved good pain control with fewer side effects than morphine[43].

In another study 2 trials were conducted simultaneously. In first, tramadol and pethidine was compared in 30 patients by Patient Controlled Analgesia during the first 24 hours following abdominal surgery. In the second trial, they compared tramadol with morphine sulphate at approximately 1.5 times the equipotent dose as estimated from the first trial. Tramadol transiently depressed the rate of respiration but had no effect on end tidal carbon dioxide tension. Morphine causes apnoea or considerable

depression of ventilation. The results suggest that mechanisms other than opioid receptor activity play a significant role in the analgesia produced by tramadol[44].

Rajiv et al studied forty adult male patients undergoing elective abdominal, pelvic or lower limb surgery. The patients were randomly allocated into two groups. The patients in group-I received 2% lignocaine 20ml epidurally and the patients in group – II received 2 % lignocaine 20ml with tramadol hydrochloride 5 mg epidurally. The pain scores were significantly less at 3,6,12 and 24 hours in the tramadol group. The incidence of nausea and urinary retention was more in the tramadol group but no clinically significant respiratory depression or sedation was observed in the tramadol group[45].

A study regarding the safety of patient controlled epidural analgesia by using tramadol alone and combined with bupivacaine for postoperative pain relief after major urological surgeries was done. They concluded that a combination of tramadol with bupivacaine can provide the most effective and safe postoperative analgesia with minimal risk for side effects[46].

A study was carried out in 57 circulatory risk patients with different opioids with clinical equipotent dose range (buprenorphine, fentanyl, morphine, nalbuphine, pentazocine, pethidine, tramadol, alfentanyl) to compare the central and peripheral hemodynamic effects. A complete hemodynamic and blood gas status as obtained prior to as well as at 5^{th}, 10^{th}, 15^{th} and 20^{th} minute following opioid administration. Significant time effects were observed for heart rate and total peripheral resistance while significant group and time effects were noted for mean pulmonary artery pressure, pulmonary capillary wedge pressure, stroke volume index and PaO2.No major effects were observed following morphine, fentanyl, alfentanyl, tramadol and

nalbuphine . Buprenorphine caused distinct respiratory depression than tramadol and nalbuphine. Buprenorphine caused distinct respiratory depression accompanied by an increase in MPAP and peripheral vascular resistance while pethidine also caused significant respiratory depression. It was concluded that for interpretation of the results factors such as respiratory depression, histamine release, excretion of endogenous catecholamine , Hypoxia induced pulmonary vasoconstriction have to be discussed .Tramadol an opioid with moderate potency seems to offer some advantages due to its minor cardiovascular side effects and respiratory side effects[47].

METHODOLOGY

This study was carried out in the Department of Anaesthesiology, B.L.D.E.U's Shri. B. M. Patil Medical College, Hospital and Research Centre, Bijapur from Dec 2008 to June 2010.

Selection of Patients

Patient selected for the study were those undergoing lower abdominal and lower limb surgeries in the age group of 20-50yrs of both sexes were included with ASA grade I and grade II. There were total 105 patients, 53 patients in group (B) and 52 patients in group (T) were allocated alternatively. Group B patients received Buprenorphine 150µgm epidural, group T patients received Tramadol 50mg epidural for postoperative analgesia.

All the patients were thoroughly examined and investigated to rule out any systemic disorder. All the patients were explained about the procedure and its complications and informed consent was obtained.

Equipments Used

- Sterile gown and gloves
- Sterile drape
- Syringes: 2cc, 5cc, 10cc
- Loss of resistance technique
- 18G Tuohy epidural needle
- 18G epidural catheter with filter
- Sterile steel bowl
- Spinal needle (25G)

Monitor Used

- Non Invasive Blood Pressure
- Pulse oximeter
- VAPS – Visual Analog Pain Scale

Drugs Used

- 2% Xylocaine with adrenaline
- Bupivacaine hydrochloride 0.5% (Heavy)
- Tramadol hydrochloride ampoule (Preservative free)
- Buprenorphine hydrochloride ampoule (Preservative free)
- Normal Saline

All the patients were allocated into 2 groups randomly. The patient in Group B received Burenorphine 150µgm diluted in normal saline and patients in group T received Tramadol 50mg diluted in normal saline viz epidural catheter postoperatively.

Anaesthesia machine, resuscitation equipment and drugs were checked and kept ready, before undertaking the procedure.

Procedure

All the patients were preloaded with 10ml/Kg infusion of ringer lactate solution. All the patients were administered combined spinal epidural anaesthesia. An 18G Epidural Catheter was introduced in L3-L4 space and subarachnoid block was given in L4-L5 space using 2.5 – 3.0 ml of 0.5% heavy bupivacaine. Level of sensory block and haemodynamic parameters will be monitored intra-operatively.

All surgeries were performed under spinal Anaesthesia. No narcotics were administered throughout intra-operative period.

In the postoperative, at Visual Analogue score of >4, patient were administered 150µgm of buprenorphine diluted to 10ml with normal saline, in group B and 50mg of tramadol diluted to 10ml with normal saline in group T through epidural catheter. Both drugs used in the study for epidural injection were preservative free patients were observed for 24hrs postoperatively.

The following variables were assessed at 1/2 hr, 1hr, 2hr, 4hr, 6hr, 8hr, 12hr & 24hr in respect to onset, duration, and quality of analgesia.

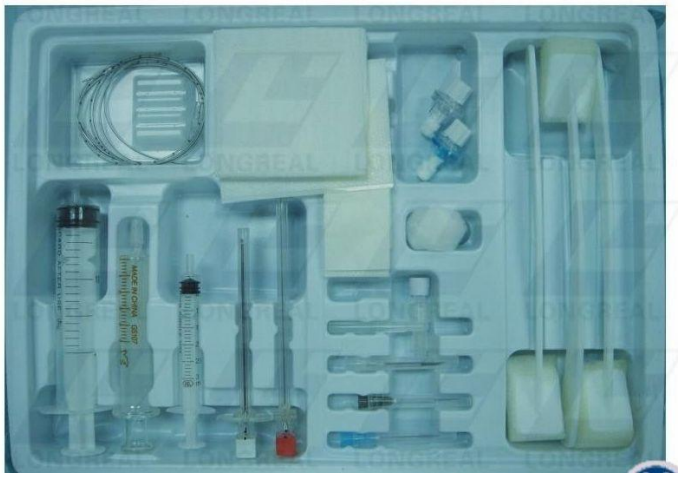
Vital parameters such as pulse rate, BP, respiratory rate were recorded at 1/2hr, 1, 2, 4, 6, 8, 12, 24hr and were noted. Duration of analgesia is calculated as the time gap between the first injection of drug and subsequent dose on demand by patient. Analgesia was scored by visual analog pain scale ranging from 0 to 10.

Assessment of postoperative pain relief was done by verbal response score

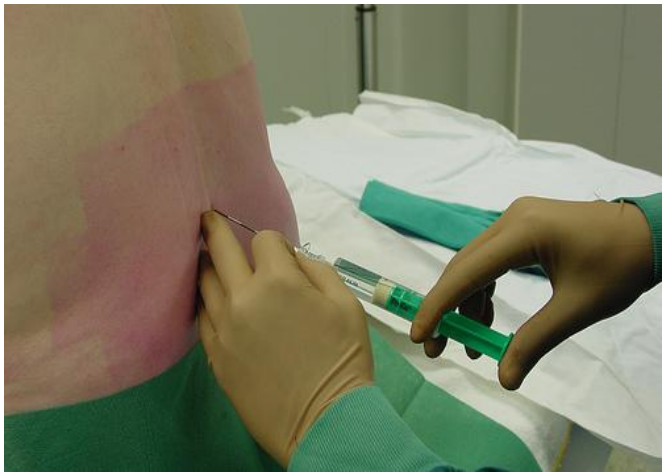
Visual Analog Pain Scale	**Verbal Response Score**
0 – no pain	0 – no pain relief
1, 2, 3 – mild pain	1 – Little pain relief
4, 5, 6 – moderate pain	2 – Some pain relief
7, 8, 9 – Severe pain	3 – A lot pain relief
10 – Worst ever felt pain	4 – Complete pain relief

All the patients were observed for the following side effects throughout the study period- nausea and vomiting, pruritus, respiratory depression, hypotension, bradycardia, sensory blockade, motor blockade.

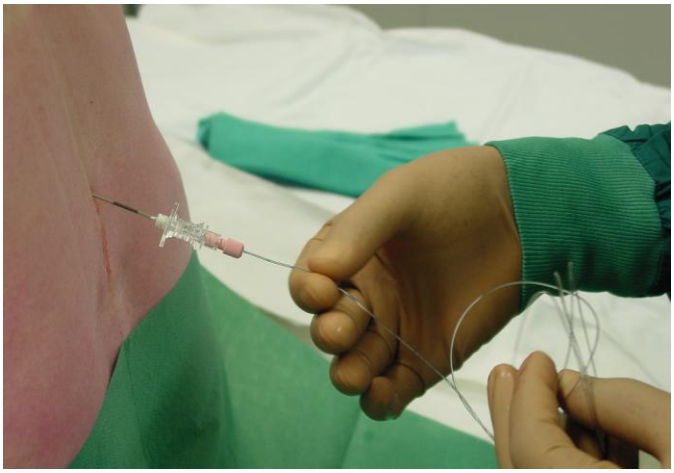
Fig. 11: COMBINED SPINAL EPIDURAL ANAESTHESIA



a) Combined Spinal Epidural Tray



b) Loss of Resistance Technique



c) Insertion of Epidural Catheter

RESULTS

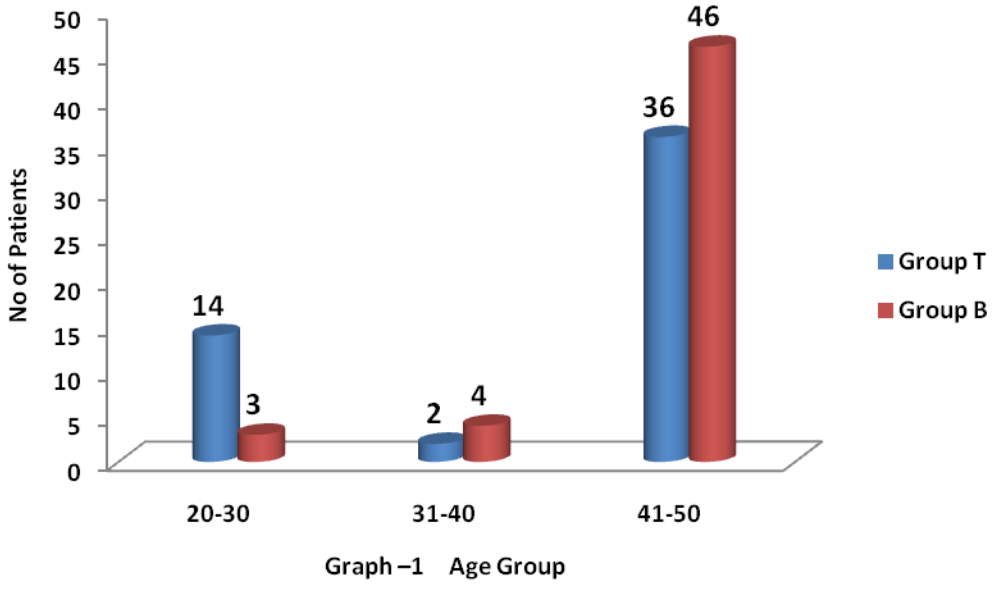
This study consisted of 105 adult patients posted for lower abdominal and lower limb surgeries divided into two groups, 53 in group B and 52 in group T. Group B received buprenorphine 150µgm, Group T 50mg tramadol epidurally postoperatively. The effect of postoperative analgesia was compared and contrasted.

Age Distribution

The minimum age of the patient was 20yr and the maximum was 50yrs. The mean age of the patient in group-T was 43.44 ± 8.37 and in Group-B 44.75 ± 6.0.

Table. 1: Age Distribution of samples

Age group (in years)	Group T	Group B
20-30	14	03
31-40	02	04
41-50	36	46



Graph –1 Age Group

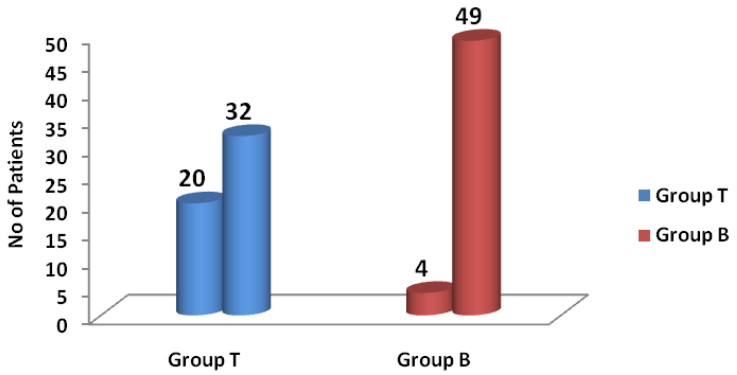
Sex Incidence

In group-T, 20 were males 32 were females.

In group-B, 4 were males 49 were females.

Table.2: Sex Incidence of samples

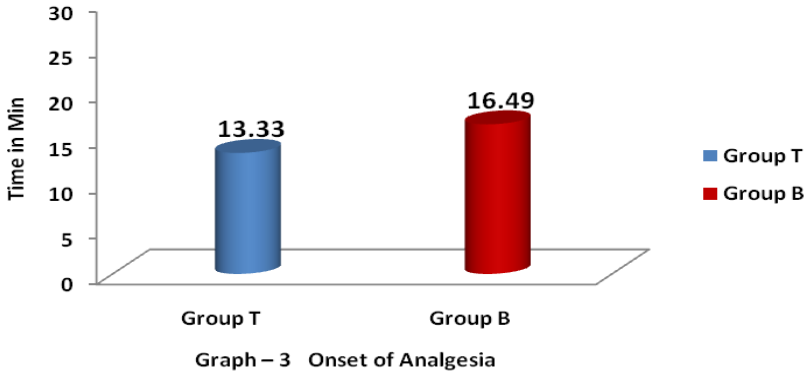
Sex	Group T (Tramadol) n=52	Group B (Buprenorphine) n=53
Male	20	04
Female	32	49
Total	52	53



Graph –2 Sex Distribution

Onset of Analgesia

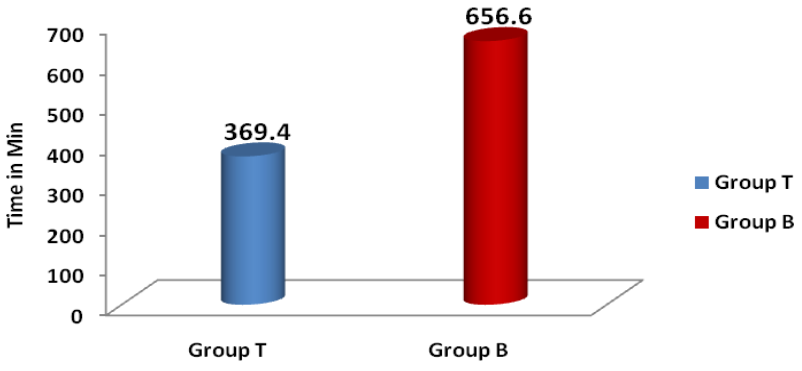
The mean time of onset of analgesia in Group-T was 13.33 ± 2.02(SD)min and in Group-B was 16.49 ± 3.38(SD)min. The statistical analysis by 'T' test showed that difference between the time of onset of analgesia in group B and group-T is =5.89 (P<0.01) which is statistically significant.



Graph – 3 Onset of Analgesia

Duration of Analgesia

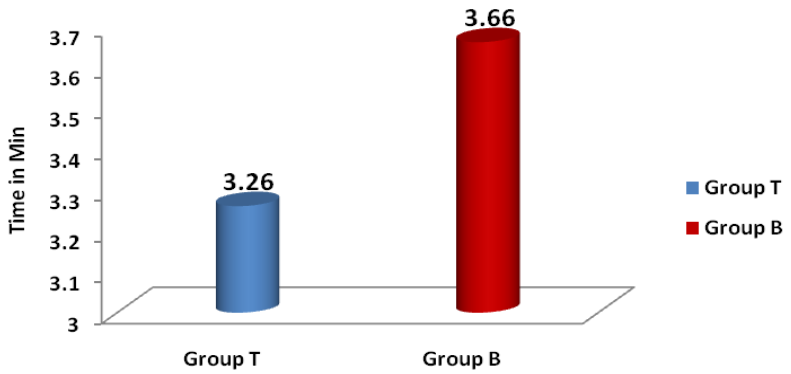
The mean duration of analgesia in Group-T was 369.4 ± 25.5(SD)min and in Group-B was 656.6 ± 97.3(SD)min. The statistical analysis by 'T' test showed that the difference between the duration of analgesia in group B and group T is T=20.78 (P<0.01) which is statistically significant.



Graph –4 Duration of Analgesia

Quality of Analgesia

The quality of Analgesia (VRS) in group-T was 3.26 ± 0.53(SD)min and in Group-B 3.66 ± 0.48 (SD) min. The statistical analysis by 'T' test showed that the difference between the quality of analgesia (VRS) in group B and group T is T=3.98 (P<0.01) which is statistically significant.



Graph – 5 Quality of Analgesia

Table.3: Onset, Duration and Quality of Analgesia (VRS)

Variable	Group-T (Mean ±SD)	Group-B (Mean ± SD)	Statistical test	Significance
Onset of Analgesia (in min)	13.33±2.02	16.49±3.38	T=5.89	P<0.01
Duration of Analgesia (in min)	369.4±26	656.6±98	T=20.78	P<0.01
Quality of Analgesia (VRS)	3.26±0.53	3.66±0.48	T=3.98	P<0.01

Cardiovascular and Respiratory Effects:

In Group T, before giving tramadol pulse rate was 81.20 ± 4.66(min), systolic BP 118.65 ± 6.58 (mm of Hg), diastolic BP 80.50 ± 6.12 (mm of Hg), Respiratory rate was 14.69 ± 1.09 (min). After giving tramadol pulse rate was 80.50 ± 5.48(min), systolic BP 118.69 ± 6.47 (mm of Hg), diastolic BP 79.92 ± 6.38 (mm of Hg), respiratory rate 14.78 ± 1.14 (min).

In Group B, before giving buprenorphine pulse rate was 76.60 ± 5.88(min), systolic BP 116.26 ± 8.53 (mm of Hg), diastolic BP 75.06 ± 7.37 (mm of Hg), respiratory rate 14.47 ± 1.17 (min). After giving buprenorphine pulse rate was 76.90 ± 4.73(min), systolic BP 75.06 ± 7.37 (mm of Hg), diastolic BP 74.45 ± 5.75 (mm of Hg), respiratory rate 14.25 ± 1.17 (min).

In our study there was no statistically significant change in group T,

In Group B, statistically significant change is seen with systolic BP and Respiratory rate.

No statistically significant change is seen with diastolic BP and pulse rate.

Table.4: Cardiovascular and Respiratory Effects:

variable	Groups	Before the drug	After the drug	Statistical test (paired 't' test)	'P' value
Pulse Rate (/min)	Group-T	81.20 ± 4.66	80.50 ± 5.48	1.08	P > 0.01
	Group-B	76.60 ± 5.88	76.90 ± 4.73	0.79	P > 0.01
Systolic BP (in mm Hg)	Group-T	118.65 ± 6.58	118.69 ± 6.47	0.05	P > 0.01
	Group-B	116.26 ± 8.53	75.06 ± 7.37	57.76	P < 0.01
Diastolic BP (in mm Hg)	Group-T	80.50 ± 6.12	79.92 ± 6.38	0.78	P > 0.01
	Group-B	75.06 ± 7.37	74.45 ± 5.75	1.44	P > 0.01
R.R. (/min)	Group-T	14.69 ± 1.09	14.78 ± 1.14	0.76	P > 0.01
	Group-B	14.47 ± 1.17	14.25 ± 1.17	2.13	P < 0.01

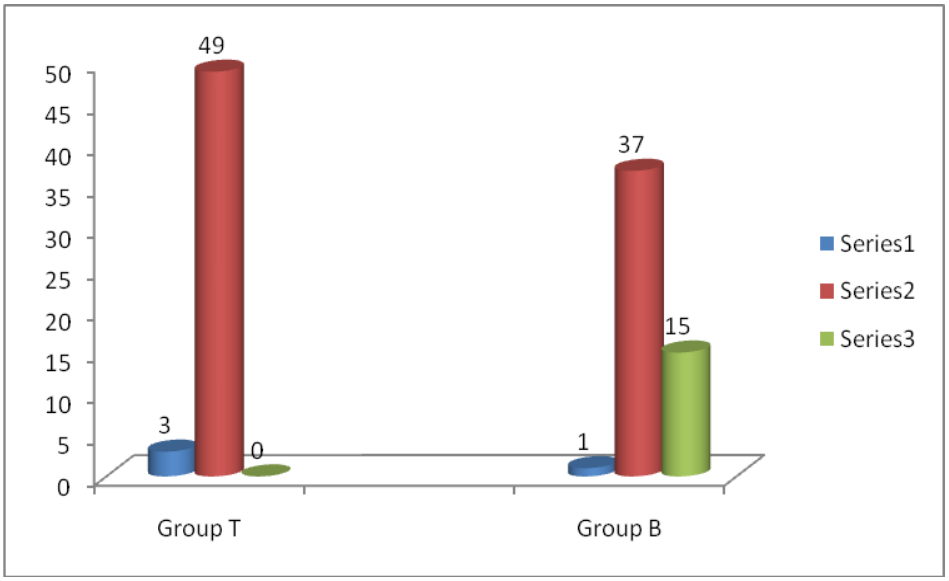
Level of consciousness

In group T after ½hr of giving drug 34, after 1hr 49, after 2hr 40 and after 4hr 8 of the patients were sleeping normally. None of the patients in group T had sedation score of 1.

In group B after ½hr of giving drug 39, after 1hr 37, after 2hr 36 and after 4hr 18 of the patients were sleeping normally. 15 of the patients after 1hr 9 of the patients after 2hr had sedation score of 1. Sedation score was higher and was maximum at 1hr with group B which was statistically significant. (Chi-Square test$X^2 = 17.66$, $p<0.01$)

Table.5: (Sedation Score)

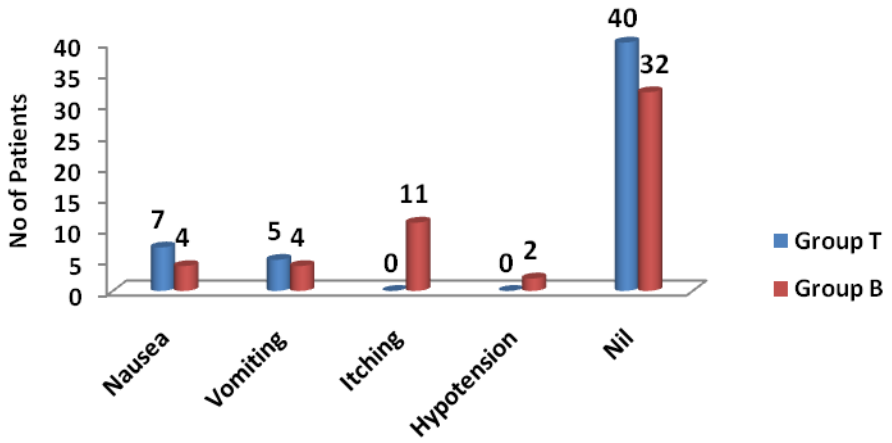
Sedation Score	After ½ hr			After 1hr			After 2hr			After 4hr		
	0	S	1	0	S	1	0	S	1	0	S	1
Group-T	18	34	0	3	49	0	12	40	0	44	8	0
Group-B	14	39	0	1	37	15	8	36	9	35	18	0
Chi-Square test(X2)	0.833			17.66			10.002			4.862		
Test of Significance	P > 0.01			P < 0.01			P < 0.01			P < 0.01		



Graph-6 Sedation Score

Side effects

In group T 7 of the patients had Nausea, 5 had Vomiting compared to which group B 4 of the patients had Nausea, 4 had Vomiting, 11 had Itching and 2 had Hypotension. None of the patients in either group had respiratory depression or any other side effects in this study. Urinary retention could not be commented as few of the patients had indwelling urinary catheter.



Graph-7 Side Effects

Table.6: Side effects

Side Effects	Group T	Group B
Nausea	7	4
Vomiting	5	4
Itching	--	11
Hypotension	--	2
Nil	40	32
Total	**52**	**53**

DISCUSSION

This study compares the efficiency of epidural buprenorphine hydrochloride and tramadol hydrochloride for postoperative pain relief. Various studies have shown that epidural buprenorphine is the most effective drug for postoperative pain relief. Similarly many studies have proved that epidural tramadol can give sufficient duration of analgesia with minimal side effects.

Hundred and five patients posted for elective surgeries were selected randomly who had no complicating systemic disorders.

The dose of the drugs selected was:

- Buprenorphine hydrochloride – 150 µgm.
- Tramadol hydrochloride – 50 mg.

All the patients were explained about the procedure and the confidence gained. In the postoperative period, immediately after the patient complained of pain, group T tramadol and group B buprenorphine were given via epidural catheter diluted in normal saline to make 10cc. The onset and duration of analgesia were studied. Vital data like pulse rate, systolic and diastolic blood pressures, respiratory rate, visual analog score, and side effects were recorded at regular intervals.

ONSET OF ANALGESIA

Rathie P et al (1998) studies the effectiveness and duration of postoperative analgesia with epidural tramadol and they found that epidural tramadol has rapid onset of action and adequate analgesia.

In our study mean onset of analgesia with epidural tramadol was 13.33 ± 2.02minutes, whereas with epidural buprenorphine it was 16.49 ± 3.38 minutes. We found that epidural tramadol has rapid onset of analgesia when compared to epidural buprenorphine.

Duration of Analgesia

Siddik-sayyid et al (1999) studied the analgesic effect of epidural tramadol in patients who underwent elective caesarean section. They concluded that epidural tramadol provided postoperative analgesia for a period of 4.5 ± 3.1 hours.

Rathie P et al (1998) studied 50 patients for effectiveness and duration of postoperative pain relief by tramadol. The mean duration of postoperative analgesia with tramadol 100mg was 10.26 ± 2.73 hours.

Delilkan et al studied the analgesic effects of epidural tramadol and concluded that 100mg of tramadol provided postoperative analgesia for 9.46 hours.

Koshy T et al in 1994 compared epidural morphine and epidural buprenorphine for postoperative pain relief. They found that longer duration of analgesia was with epidural buprenorphine i.e., 19.9 ± 8 hours.

Kumar D et al (1997) studied the effectiveness of epidural buprenorphine and Ketamine. The mean postoperative analgesia obtained with epidural buprenorphine was 13.1 hours.

Agarwal M et al in 1998 compared epidural morphine and epidural buprenorphine for postoperative pain relief. They found that mean duration of analgesia was longer with epidural buprenorphine (31.24 hours).

In this study, the mean duration of postoperative analgesia obtained with epidural tramadol was 369.4 ± 25.5 min and with buprenorphine was 656.6 ± 97.3 (SD) min. The mean duration is correlating with the studies conducted by Siddik et al, Rathi P et al, Delikan et al, Kumar et al, Koshy T et al and Agarwal M et al. The longer duration of action of buprenorphine can be well explained on the basis of high lipid solubility and high affinity for opiate receptors.

Complications:

Nausea and vomiting:

Delikan AE et al in 1993 studied the efficacy of epidural tramadol in patients undergoing abdominal surgery and found longer duration of postoperative relief and high incidence of nausea.

Rathie P et al in 1998 studied effectiveness and duration of postoperative pain relief by epidural tramadol and found that nausea and vomiting were common side effects.

In our study the incidence of nausea and vomiting was more with tramadol group than buprenorphine group. In tramadol group, 12 cases complained of nausea and vomiting. In buprenorphine group 8 cases complained of vomiting.

Haemodynamic changes:

Koshi T et al in 1994 compared epidural morphine with epidural buprenorphine for postoperative analgesia and side effects. In their study hypotension occurred in 1 case in buprenorphine group.

Churubasik S et al in 1996 studied the pain relief with peridural administration opioids. They felt that epidural tramadol may be useful in clinical routine, because it has cardiovascular stability and has a low potential for central depressive effects, extremely useful where supervision of the patient is not guaranteed.

In our study hemodynamics were stable with epidural tramadol when compared to epidural buprenorphine. Incidence of hypotension was nil with epidural tramadol.

In Buprenorphine group hypotension occurred in 2 cases, which was responded well to intravenous fluid administration.

Respiratory depression:

Vickers MD et al in 1992 compared the effect of tramadol on respiration with morphine. They concluded that equianalgesic dose of tramadol has much less effect on respiratory centre when compared with morphine.

Baraka A et al in 1993 compared epidural tramadol and morphine for postoperative analgesia in patients undergoing major abdominal surgeries. They concluded the absence of clinically relevant respiratory depression with epidural tramadol.

Koshi T et al in 1994 compared epidural morphine with epidural buprenorphine for postoperative analgesia and side effects. The incidence of respiratory depression was zero with epidural buprenorphine.

Demirarean Y et al in 2005 compared epidural tramadol with epidural morphine for postoperative analgesia in children undergoing urological surgery. They concluded that incidence of respiratory depression was more in morphine group than in tramadol group.

In our study either with tramadol or with epidural buprenorphine the incidence of respiratory depression was zero. Our study results are correlating with the Vickers MD, Baraka A, Koshi T et al studies.

Other complications:

Koshi T et al in 1994 compared epidural morphine with epidural buprenorphine for postoperative analgesia and side effects. They found side effects like pruritus occurred in 1 case and urinary retention occurred in 8 cases.

In our study pruritus occurred in 11 cases with epidural buprenorphine. Our study results are closer to Koshi T et al study. These complications were not observed with epidural tramadol.

CONCLUSION

The advantage of epidurally administered opiates would seem to be it's high quality of analgesia in low dosage.

The results of our study in confirmed our expectations that buprenorphine provided excellent analgesia given epidurally in incremental low dosage. Its quality of analgesia and duration of action was better and longer than tramadol. It has added advantages like.

1. Preservative free form available.
2. No motor or sensory blockade.
3. No haemodynamic alteration.
4. Thirty times more potent than morphine in controlling postoperative pain.

Therefore we conclude that epidural buprenorphine provides adequate and prolonged postoperative analgesia. The only appreciable side effect being nausea and vomiting which can be obtunded by an antiemetic.

SUMMARY

This study entitled “A COMPARISON OF EPIDURAL BUPRENORPHINE AND EPIDURAL TRAMADOL FOR POSTOPERATIVE ANALGESIA IN LOWER ABDOMINAL AND LOWER LIMB SURGERIES” was conducted in 105 adult patients of ASA I and ASA II. They were divided into 2 groups. This study aimed at postoperative analgesia was conducted at Shri. B. M. Patil Medical College Hospital and Research Centre B.L.D.E.U’s Bijapur.

Group B – 53 patients buprenorphine 150µgm.

Group T – 52 patients tramadol 50mg.

These drugs were given via epidural catheter in postoperative period when patients complained pain for the first time.

In the present study with epidural tramadol the mean duration of postoperative analgesia was 369.4 ± 25.5 minutes. The onset of analgesia was fast and majority of patients experienced excellent analgesia with few complications like nausea and vomiting in some cases. None of them had motor blockade. No other complications were found.

In the other group with epidural buprenorphine the mean duration of postoperative analgesia was 656.6 ± 97.3 minutes. The onset of analgesia with epidural buprenorphine was little late when compared to epidural tramadol. Most of the patients had excellent analgesia. Complications like nausea and vomiting occurred in few cases. The incidence of other complications like hypotension, pruritus, were minimal. None of them had motor blockade.

- **Onset of analgesia –** The mean (S.D) time of onset of analgesia with tramadol (13.33 ± 2.02 min) was significantly faster when compared with buprenorphine (16.49 ± 3.38 min) [t=5.89, p < 0.01].

- **Duration of analgesia –** Study revealed that mean (S.D) duration of analgesia was significantly higher with buprenorphine (656.6 ± 97.3 min) than with tramadol (369.4 ± 25.5 min) [t=20.78, p<0.01].

- **Cardiorespiratory effects –** Both buprenorphine and tramadol had no significant effects on the hemodynamic and respiratory system.

- **Side effects –** It is observed that frequencies of side effects (nausea, vomiting, pruritus) were common with buprenorphine.

In our study single dose of epidural buprenorphine was found to give significantly longer duration of postoperative pain relief with better quality of analgesia and minimal side effects: whereas epidural tramadol needs repeated administration because of its short duration of action and quality of analgesia is less when compared to epidural buprenorphine.

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ANNEXURE I

PROFORMA FOR EVALUATION OF POSTOPERATIVE ANALGESIA

Name: Date:

Age: I.P. No.:

Sex: Hospital:

PREOPERATIVE OBSERVATIONS:

General Physical Examination

Pulse Rate: bpm B.P.: mm of Hg R.R.: cycles/ min

Temperature: Weight: Kg Spine:

Systemic Examination:

C.V.S.:

R.S.:

Others:

Investigations:

Hb%: F.B.S./ R.B.S.: E.CG.:

Blood Urea: S. Creatinine: Urine:

Others:

Preoperative Diagnosis:

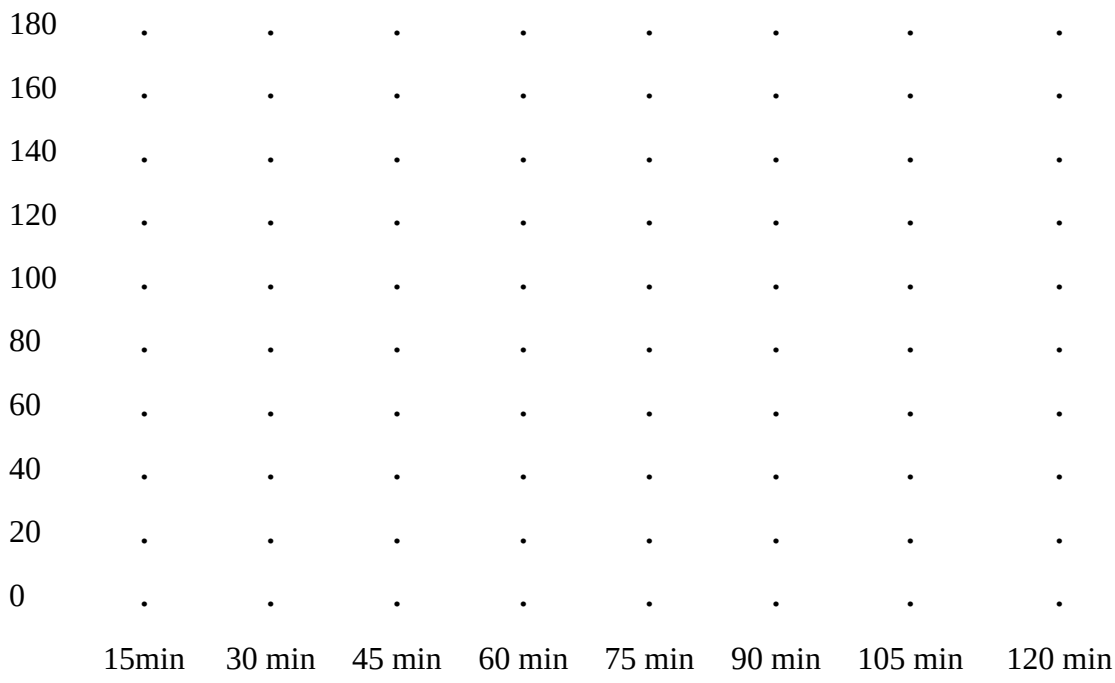
Proposed Surgery :

Premedication : Inj. Glycopyrrolate 0.2mg and Inj. Ondansetron 4mg IV

ASA Grade :

Anaesthetic Technique: Combined Spinal Epidural Anaesthesia

INTRAOPERATIVE OBSERVATION:



STUDY PROTOCOL:

Epidural Buprenorphine 150µgm or epidural Tramadol 50mg diluted to 10ml with normal saline.

Time of administration:

Onset of Analgesia:

ASSESSMENT OF POSTOPERATIVE PAIN RELIEF:

VERBRAL RESPONSE SCORE:

Grade	*Response*	*½ hr*	*1 hr*	*2 hrs*	*4 hrs*	*6 hrs*	*8 hrs*	*12 hrs*	*24 hrs*
0	*No Pain relief*								
1	*Little Pain relief*								
2	*Some Pain relief*								
3	*A lot Pain relief*								
4	*Complete Pain relief*								

VITAL PARAMETERS:

P.R (bpm) :

B.P. (mm of Hg) :

R.R (cycles/min) :

Level of consciousness:

0 – None (Patient alert)

1 – Mild (Patient may be sleepy but easy to arouse)

2 – Moderate (Patient frequently drowsy, but still fully arousable)

3 – Severe (Difficult to arouse)

S – Sleeping normal

SIDE EFFECTS:

Nausea :

Vomiting :

Resp. depression :

Hypotension :

Pruritus :

Urinary retention :

Neurological deficits :

Others :

DURATION OF ANALGESIA:

QUALITY OF ANALGESIA:

Signature of Investigator **Signature of Guide**

ANNEXURE II

SAMPLE INFORMED CONSENT FORM

Title of Project : "A COMPARATIVE STUDY OF EPIDURAL BUPRENORPHINE AND TRAMADOL FOR POSTOPERATIVE ANALGESIA IN LOWER ABDOMINAL AND LOWER LIMB SURGERIES."

Guide : Dr. VIDYA PATIL

P.G. Student : Dr. JAYALAXMI

PURPOSE OF RESEARCH:

I have been informed that this study will comparatively evaluate postoperative analgesia between epidural buprenorphine and epidural tramadol in patients undergoing lower abdominal and lower limb surgeries.

PROCEDURE:

I understand that I will be given either epidural buprenorphine or epidural tramadol for comparison of duration of postoperative analgesia.

RISKS & DISCOMFORTS:

I understand that I may experience some pain, discomforts and cardiovascular effects during procedure. This is mainly the result of my condition and procedures of this study are not expected to exaggerate these feelings, which are associated with the usual course of procedure.

BENEFITS:

I understand that my participation in this study will help in finding out the efficacy of epidural buprenorphine and epidural tramadol for postoperative analgesia.

CONFIDENTIALITY:

I understand the medical information produced by this study will become part of my hospital record and will be subject to the confidentiality. Information of sensitive and personal nature will not be part of the medical record, but will be stored in the investigator's research file.

If the data are used for publication in the medical literature or for teaching purpose, no names will be used and other identifiers, such as photographs will be used only with my special written permission. I understand that I may see the photographs before giving the permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time. Dr. Jayalaxmi at the department of Anaesthesiology is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation. A copy of this consent form will be given to me to keep for careful reading.

REFUSAL FOR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice. I also understand that Dr. Jayalaxmi may terminate my participation in this study at any time after he has explained the reasons for doing so.

ANNEXURE III

INJURY STATEMENT

I understand that in the unlikely event of injury to me resulting directly from my participation in this study, if such injury were reported promptly then appropriate treatment would be available to me. But no further compensation would be provided by the hospital. I understand that by my agreement to participate in this study and not waiving any of my legal rights.

I have explained to _____ the purpose of the research, the procedures required and the possible risks and benefits to the best of my ability.

_____ _____

Investigator Date

I confirm that Dr. Jayalaxmi has explained to me the purpose of the research, the study procedure that I will undergo and the possible risks and discomforts as well as benefits that I may experience in my own language. I have been explained all the above in detail in my own language and I understand the same. Therefore I agree to give my consent to participate as a subject in this research project

_____ _____

Participant Date

_____ _____

Witness to signature Date

MASTER CHART BUPRENORPHINE (GROUP B)

Sl No	Name	Age (yrs)	Sex	IP No	Surgery	OOA (Min)	Duration (Min)	QOA (VRS)	Side Effects	PULSE RATE (/Min)							SYSTOLIC. B.P. (in mm Hg)							DIASTOLIC B.P. (in mm Hg)							RESPIRATORY RATE (/Min)							SEDATION SCORE						
										Before	After						Before	After						Before	After						Before	After						Before	After					
											1/2 hr	1 hr	2 hr	4 hr	6 hr	8 hr		1/2 hr	1 hr	2 hr	4 hr	6 hr	8 hr		1/2 hr	1 hr	2 hr	4 hr	6 hr	8 hr		1/2 hr	1 hr	2 hr	4 hr	6 hr	8 hr
1	RAKUMABAI	45	F	6118	AMP	15	720	4	ITCHING	80	82	82	80	78	78	80	120	122	120	120	124	124	124	80	78	76	76	74	74	76	16	15	15	15	16	15	15	0	S	S	S	0	0	0
2	CHANDRAM	50	M	7523	AMP	18	660	4	NAUSEA	82	82	84	82	80	78	80	110	114	112	114	114	116	114	70	68	70	70	72	72	70	17	16	15	15	14	15	16	0	S	1	1	S	S	0
3	RAGHAVENDRA	50	M	8512	HEMIARThrOPLASTY	16	780	4	NO	74	76	76	74	72	74	74	114	116	114	112	112	114	114	72	70	70	72	72	70	72	15	14	14	14	15	14	15	0	0	S	S	0	0	0
4	YAMUNABAI	50	F	8403	HEMIARThrOPLASTY	18	540	4	ITCHING	76	74	74	72	72	74	76	112	116	112	110	110	112	112	70	70	72	72	70	70	72	14	13	13	13	12	13	13	0	0	S	S	0	0	0
5	MUMTAZ	40	F	####	TAH	20	600	3	NO	78	76	76	78	74	76	74	118	120	118	116	116	118	118	68	66	68	70	70	70	70	16	15	14	14	15	15	16	0	S	S	1	S	0	0
6	ARCHANA	35	F	437	TAH	22	720	3	NO	76	74	76	74	72	70	72	130	132	130	128	128	126	128	90	88	90	88	86	86	86	14	13	13	13	14	14	14	0	0	S	1	S	0	0
7	LAKSJMIBAI	35	F	31	TAH	25	780	3	NO	78	76	78	76	76	74	74	126	128	128	126	126	124	126	84	82	82	80	80	80	82	13	12	12	12	13	12	13	0	S	S	0	0	0	0
8	SHANTABAI	40	F	86	TAH	15	660	4	ITCHING	80	80	82	82	80	82	80	124	128	126	122	120	120	120	82	80	82	80	78	78	80	12	11	11	12	11	12	12	0	0	S	S	S	0	0
9	GANGAWWA	45	F	456	TAH	12	720	4	NO	74	74	76	72	72	74	72	120	124	122	118	120	118	120	78	76	76	74	74	76	76	14	13	13	12	13	13	12	0	S	1	S	S	0	0
10	LATHABAI	35	F	725	TAH	10	780	4	VOMITING	68	70	72	70	70	72	70	118	120	116	118	116	118	118	74	72	72	72	70	70	72	14	13	13	12	13	13	13	0	S	1	S	S	0	0
11	CHANABAWWA	45	F	966	TAH	10	600	4	NO	64	68	70	70	72	74	72	116	118	116	114	112	110	112	72	70	70	72	72	72	70	15	14	14	15	14	15	15	0	0	S	S	0	0	0
12	GANNIBAI	40	F	860	TAH	15	540	4	NO	72	70	70	72	70	72	72	110	114	112	110	110	112	110	70	68	70	70	72	70	72	14	14	13	13	14	14	14	0	S	S	S	0	0	0
13	KALLAWWA	50	F	5953	VH	18	540	3	NO	78	76	74	74	76	76	76	114	116	112	110	110	112	112	70	70	72	70	72	70	72	13	12	12	12	13	12	12	0	S	S	S	0	0	0
14	KALAVATHI	42	F	4841	MAYWARD'S	18	720	4	ITCHING	76	74	76	74	76	74	74	112	114	110	112	114	112	110	70	68	70	70	72	72	70	14	13	13	12	13	14	14	0	S	S	0	0	0	0
15	MANGALABAI	50	F	7410	VH	20	840	3	NO	70	72	72	72	74	72	74	110	114	110	110	110	112	112	70	70	72	70	72	72	72	14	14	14	13	13	13	14	0	0	S	S	0	0	0
16	SANTA	44	F	6301	VH	15	780	4	NO	70	72	70	72	70	70	72	114	116	112	114	110	110	110	72	70	72	70	70	72	72	13	12	12	11	12	12	12	0	S	1	S	0	0	0
17	MALLAMMA	40	F	5145	VH	18	720	3	NO	76	74	74	72	72	74	76	116	118	114	114	114	112	112	70	68	70	70	70	70	70	14	13	13	14	14	13	13	0	0	S	S	0	0	0
18	BOURAMMA	29	F	5254	VH	16	720	4	NO	78	76	76	74	72	74	76	118	118	112	110	110	110	112	68	66	68	68	70	68	70	15	14	14	15	14	15	15	0	S	S	S	0	0	0
19	PRABHA	50	F	5221	WERTHEIM'S HYSTERECTOMY	20	660	3	HYPOTENSION	68	70	72	70	68	70	72	90	86	82	80	84	86	90	60	54	54	50	54	56	58	15	14	14	14	15	15	15	0	S	1	S	0	0	0
20	HANAMAWWA	45	F	5502	VH	15	720	4	NO	70	72	70	72	70	70	72	124	124	120	122	124	124	124	76	74	72	70	72	74	74	16	15	15	16	16	16	16	0	S	S	0	0	0	0
21	BARAMMA	50	F	5254	VH	20	780	4	ITCHING	72	74	72	70	72	70	72	126	128	124	120	122	120	122	78	76	74	76	74	76	74	15	14	14	14	15	15	15	0	S	S	S	0	0	0
22	MAREWWA	50	F	5011	VH	16	660	4	NO	76	76	74	74	72	74	74	128	130	126	124	124	122	124	84	82	82	80	82	82	80	14	13	13	13	14	14	14	0	0	S	1	S	0	0
23	MAHADEVI	50	F	4890	VH	15	600	3	ITCHING	80	78	76	74	74	74	76	124	126	124	126	128	128	126	84	82	80	82	82	84	82	15	14	14	15	15	14	15	0	S	S	1	S	S	0
24	SUSHILABAI	50	F	5167	VH	18	540	3	NO	84	82	80	80	80	82	84	122	124	120	118	118	120	124	82	80	82	80	80	80	82	14	13	13	12	13	13	14	0	S	S	1	1	S	0
25	RAVMA	48	F	5866	VH	14	660	4	ITCHING	82	80	80	82	82	82	82	130	130	128	126	128	126	120	90	88	88	86	86	86	88	16	15	14	14	13	15	15	0	S	S	S	0	0	0
26	MAMTAZ	47	F	5652	VH	10	720	4	ITCHING	80	78	78	80	80	80	80	126	124	122	124	120	120	124	84	86	82	80	80	84	84	15	14	14	13	13	14	14	0	0	S	S	0	0	0
27	KALLAWWA	50	F	5953	VH	18	600	4	VOMITING	76	76	76	76	78	78	78	110	110	110	114	110	110	110	84	84	82	80	80	78	80	15	14	14	14	16	16	16	0	0	S	S	0	0	0
28	SANTA	44	F	6301	VH	15	540	4	NO	88	86	86	86	88	86	86	120	118	116	118	116	114	112	80	80	78	76	76	78	80	14	13	13	12	13	14	14	0	S	S	S	0	0	0
29	VIDYA	44	F	6307	VH	18	540	4	NAUSEA	80	82	80	82	84	82	84	110	110	112	114	108	110	110	78	76	76	74	74	76	76	16	16	15	14	16	15	16	0	S	S	0	0	0	0
30	BHEMABAI	40	F	1897	TAH	15	600	4	NO	84	84	84	82	84	84	82	110	110	112	114	108	110	112	74	76	74	72	72	74	74	13	12	13	14	12	14	14	0	S	S	S	S	0	0
31	SUVARNA	45	F	2176	TAH	20	720	4	ITCHING	74	72	72	74	76	76	78	120	120	118	120	118	114	110	76	78	76	74	74	72	76	14	14	13	13	13	14	14	0	S	S	S	S	0	0
32	SHANTAWWA	40	F	2663	TAH	15	720	3	NO	86	84	82	84	86	84	82	130	132	130	132	128	128	128	80	78	78	76	74	72	78	15	15	15	15	16	16	15	0	S	S	S	0	0	0
33	MANGALABAI	32	F	2794	TAH	10	540	3	VOMITING	82	82	80	82	84	84	82	118	120	122	122	120	118	120	84	84	82	80	82	80	82	16	14	13	14	15	15	15	0	S	S	1	S	S	0
34	NAGARATNA	50	F	3359	TAH	14	600	4	NAUSEA	80	80	82	84	84	82	84	116	118	116	118	114	112	114	82	80	80	80	82	80	82	13	12	12	12	12	13	13	0	0	1	S	0	0	0
35	SOUMYA	40	F	3885	TAH	13	540	4	NO	78	76	74	76	76	78	76	114	116	114	116	112	110	112	70	72	70	70	72	70	72	14	14	14	15	15	16	16	0	0	1	1	S	0	0
36	SANTA	44	F	3668	TAH	15	780	4	NO	76	76	74	76	78	76	74	112	114	114	116	112	110	114	72	74	72	70	72	70	72	15	14	14	14	15	16	16	0	S	S	0	0	0	0
37	PADMAVATHI	44	F	4119	TAH	20	840	3	ITCHING	70	72	72	72	74	74	72	116	114	116	116	114	110	114	64	66	66	64	66	68	70	14	13	14	12	14	14	14	0	S	S	S	0	0	0
38	KAMALABAI	50	F	6444	VH	20	660	4	NO	74	74	72	74	76	74	76	120	118	120	122	118	116	120	68	70	70	68	68	70	70	13	13	13	14	14	13	13	0	S	1	S	0	0	0
39	KARENA	48	F	6596	VH	20	780	4	NO	76	76	74	76	76	74	74	110	112	114	116	112	110	114	70	72	70	70	72	72	70	14	13	13	13	14	14	14	0	S	S	1	S	0	0
40	RUKMINI	50	F	6482	VH	25	720	4	NO	78	76	74	74	76	76	78	112	110	114	116	110	108	110	72	74	70	70	70	72	72	15	15	16	16	15	15	15	0	S	S	0	0	0	0
41	SHOBHA	50	F	6928	VH	15	540	4	NO	74	72	72	74	76	76	74	114	112	116	118	110	108	110	74	76	72	70	70	72	70	16	15	15	16	16	16	15	0	S	S	S	0	0	0
42	RENUKA	50	F	7107	VH	14	720	3	NO	70	70	72	72	74	72	74	116	114	116	118	110	110	112	72	70	70	68	70	72	72	14	14	13	13	12	12	13	0	S	S	S	S	0	0
43	SIDDAPPA	50	M	####	KNEE AMPUTATION	15	660	4	HYPOTENSION	66	68	68	70	72	70	70	90	90	80	84	88	90	90	60	56	50	54	60	60	60	12	13	13	13	13	12	13	0	0	S	S	0	0	0
44	DEEPA K	27	M	####	TRENDELENBERG OPERATION	12	600	3	NAUSEA	68	66	68	70	70	72	72	118	116	118	118	114	114	112	80	80	78	76	78	76	78	15	15	15	16	15	15	15	0	S	S	0	0	0	0
45	LINGAMMA	49	F	7235	VH	15	540	4	NO	70	72	70	72	74	76	76	124	122	122	124	120	120	122	82	84	82	80	80	78	80	17	16	16	16	17	16	16	0	S	1	S	0	0	0
46	VAISHALI	46	F	7608	VH	16	540	3	NO	74	72	72	72	74	76	76	126	124	124	126	122	120	124	84	82	80	80	78	76	80	15	14	14	13	14	14	14	0	S	1	S	0	0	0
47	SHARANAMMA	43	F	7678	VH	18	480	3	NO	86	86	86	84	86	84	86	130	126	128	128	126	124	126	90	90	88	86	84	88	76	13	13	12	13	13	13	13	0	0	0	S	S	0	0
48	AMBABAI	40	F	7910	VH	15	480	4	ITCHING	88	88	86	84	86	86	88	110	112	112	114	108	108	110	70	72	70	72	74	76	74	14	14	15	15	14	15	15	0	S	S	1	S	S	0
49	KAMALA	46	F	5102	TAH	16	540	4	NO	82	80	82	80	82	84	84	116	114	116	118	110	108	110	72	70	70	72	70	72	72	16	15	14	15	14	14	14	0	S	S	1	S	0	0
50	SANJANA	56	F	5421	TAH	16	780	4	NO	84	82	80	82	84	84	82	106	108	110	110	100	100	102	68	70	70	70	72	74	72	13	12	14	13	12	13	13	0	S	S	1	S	0	0
51	JYOTHI	43	F	5868	TAH	15	720	3	NO	88	86	84	82	84	86	84	104	106	108	110	100	100	104	64	66	68	70	72	70	70	14	15	14	14	14	15	15	0	S	S	S	0	0	0
52	NEELAMMA	48	F	6028	TAH	20	660	4	VOMITING	72	70	72	72	74	76	72	110	112	110	112	102	100	104	70	68	70	72	74	76	72	16	16	15	15	15	15	15	0	S	S	0	0	0	0
53	NEELA	48	F	5951	TAH	20	600	3	NO	74	72	74	74	76	78	76	108	110	110	112	104	102	104	70	70	70	72	74	72	70	14	14	14	14	13	13	13	0	S	1	S	0	0	0

MASTER CHART TRAMADOL (GROUP T)

Sl No	Name	Age (yrs)	Sex	IP No	Surgery	OOA (Min)	Duration (Min)	QOA (VRS)	Side Effects	PULSE RATE (/Min)							SYSTOLIC. B.P. (in mm Hg)							DIASTOLIC B.P. (in mm Hg)							RESPIRATORY RATE (/Min)							SEDATION SCORE						
										Before	After						Before	After						Before	After						Before	After						Before	After					
											1/2 hr	1 hr	2 hr	4 hr	6 hr	8 hr		1/2 hr	1 hr	2 hr	4 hr	6 hr	8 hr		1/2 hr	1 hr	2 hr	4 hr	6 hr	8 hr		1/2 hr	1 hr	2 hr	4 hr	6 hr	8 hr		1/2 hr	1 hr	2 hr	4 hr	6 hr	8 hr
1	SUNIL DAS	34	M	15959	ORIF WITH PLATING	12	380	3	NO	78	72	72	78	78	80	80	120	120	116	110	110	110	110	78	70	70	78	74	78	78	15	15	15	15	15	16	15	0	S	S	S	0	0	0
2	BABAMA	25	M	16043	ORIF WITH K-NAIL	16	320	3	NO	80	82	76	74	76	80	80	120	116	118	118	120	120	120	80	84	80	82	82	86	78	13	13	14	14	14	14	14	0	S	S	S	0	0	0
3	BASAVANTAPPA	50	M	16510	HEMIARTHROPLASTY	12	360	4	NO	86	82	88	88	86	88	88	118	116	110	116	118	120	120	78	72	74	76	76	78	80	16	14	14	14	15	16	15	0	S	S	S	0	0	0
4	MUTTAPPA	28	M	16708	IM NAILING	14	360	3	NO	80	82	80	80	82	84	84	120	116	118	118	120	120	120	78	70	70	68	68	70	70	14	13	14	13	14	14	14	0	S	S	0	0	0	0
5	DEVENDRAPPA	50	M	17085	IM NAILING	16	360	4	NAUSEA	70	68	70	70	70	74	72	110	104	102	106	106	110	108	70	66	67	64	68	70	72	13	12	12	12	12	13	13	0	S	S	S	0	0	0
6	GODHUBAI	37	F	16927	VH	9	360	4	NO	82	78	76	76	74	80	80	106	104	104	106	110	110	110	70	70	70	70	70	72	70	13	13	13	14	14	13	13	0	S	S	0	0	0	0
7	SHANKRAMA	50	F	16634	WERTHEIMS HYSTERECTOMY	16	380	3	NO	76	80	74	76	76	76	78	120	110	110	110	112	120	120	70	70	78	78	80	80	80	14	14	13	13	12	14	14	0	S	S	S	0	0	0
8	PARVEENA	28	F	17205	VH	15	420	4	VOMITING	82	68	64	68	70	70	70	110	118	114	114	114	116	118	90	88	80	80	80	82	72	14	13	13	12	12	13	13	0	S	S	S	0	0	0
9	SHIVAMMA	50	F	762	VH	12	360	3	NO	84	80	80	80	80	80	80	116	110	110	110	110	110	110	90	80	80	80	80	78	80	15	14	14	14	15	16	16	0	S	S	S	0	0	0
10	RUDRAMMA	35	F	967	VH	12	400	2	NO	90	86	90	90	90	92	90	124	120	118	118	118	120	120	92	78	74	76	90	90	90	16	14	14	18	16	16	16	0	S	S	S	S	0	0
11	MUNNAYYA	50	M	8673	B/ L HERNIOPLASTY	12	360	3	NO	86	84	82	86	86	86	86	110	116	112	110	110	116	116	80	78	80	80	80	90	80	15	13	13	14	14	14	14	0	S	S	S	S	0	0
12	BOURAMMA	30	F	11563	B/ L HERNIOPLASTY	14	360	3	NO	80	74	70	70	78	78	78	110	110	110	110	110	110	116	70	70	64	68	70	70	70	14	12	12	14	14	14	14	0	S	S	S	0	0	0
13	BASAVARAJ	49	M	579	KNEE AMPUTATION	14	360	3	NO	82	82	80	80	84	84	84	120	118	114	114	118	118	120	82	80	78	78	78	80	80	15	14	14	14	14	15	15	0	0	S	0	0	0	0
14	BHIMANNA	35	M	3304	B/ L HERNIOPLASTY	10	400	3	NO	86	70	70	68	70	78	80	126	120	120	120	126	126	130	84	84	80	80	82	80	90	14	16	14	14	14	16	16	0	0	S	S	S	0	0
15	BALAKRISHNA	50	M	3020	TRENDELENBERG OPERATION	12	360	4	NO	82	88	82	80	86	88	88	126	120	120	126	126	104	126	86	78	78	84	84	86	84	14	13	13	14	14	14	14	0	S	S	S	0	0	0
16	BASAMMA	38	F	3113	TRENDELENBERG OPERATION	13	360	2	NO	88	74	70	70	70	70	80	118	110	110	110	112	110	110	78	70	70	70	70	72	70	16	14	14	14	15	15	15	0	S	S	S	0	0	0
17	PARASAPPA	50	M	3975	EXPLORATORY LAPROTOMY	14	380	3	NO	76	74	74	78	78	78	80	118	106	104	106	106	110	108	78	72	72	72	72	76	70	14	14	13	13	13	14	14	0	S	S	0	0	0	0
18	CHANDAWWA	50	F	4444	EXPLORATORY LAPROTOMY	15	360	3	NO	74	68	68	68	68	70	70	110	102	102	102	106	110	110	80	72	72	68	60	68	70	13	13	13	13	13	13	13	0	S	S	S	0	0	0
19	SHANKARAPPA	35	M	16917	KNEE AMPUTATION	14	330	3	NO	86	84	84	84	84	80	80	126	110	110	118	118	120	120	80	84	84	88	90	90	90	14	14	14	14	13	14	14	0	S	S	S	S	0	0
20	MONUBAI	50	F	16975	HEMIARTHROPLASTY	14	360	4	NO	80	84	84	82	80	80	80	120	110	110	110	116	116	116	70	70	70	70	70	80	80	16	15	15	15	15	15	15	0	0	0	S	0	0	0
21	SHIVAKKA	50	F	988	VH	12	360	3	NO	94	80	80	80	92	90	90	130	120	120	126	126	128	130	88	80	80	88	90	90	90	17	15	14	14	16	16	16	0	0	S	S	0	0	0
22	LOKAWWA	50	F	812	VH	16	300	3	NO	76	78	76	80	76	76	80	118	120	114	116	116	118	120	70	74	70	76	76	76	76	14	13	14	14	14	14	14	0	S	S	S	0	0	0
23	INDUMATI	50	F	1211	VH	12	380	4	NO	70	82	76	70	70	70	70	110	110	110	116	110	110	120	70	64	64	64	70	70	70	13	13	13	13	13	14	13	0	0	S	S	0	0	0
24	GEETA	30	F	1374	VH	14	360	4	NO	80	68	68	68	68	70	70	110	110	110	110	110	120	120	80	76	76	76	80	80	80	15	15	15	15	16	15	16	0	0	S	S	0	0	0
25	BASAMMA	50	F	1759	AMP	10	380	3	NO	86	88	82	82	88	88	88	126	110	110	120	124	124	124	80	82	84	84	84	84	80	16	15	14	14	14	15	14	0	S	S	0	0	0	0
26	PARANNA	24	M	4718	TRENDELENBERG OPERATION	14	360	4	VOMITING	78	72	64	64	70	70	68	114	106	106	108	108	110	110	78	74	74	74	76	76	78	14	14	13	13	13	14	14	0	0	S	S	0	0	0
27	KASTURI	45	F	5579	EXPLORATORY LAPROTOMY	15	360	3	NO	80	82	80	82	80	82	82	110	116	116	116	110	110	110	80	80	70	70	72	70	70	16	13	12	14	14	14	16	0	0	S	0	0	0	0
28	HANAMANTH	50	M	7236	TRENDELENBERG OPERATION	8	380	3	VOMITING	80	72	72	70	70	72	74	120	124	120	118	126	124	126	84	82	80	80	82	84	86	15	14	14	14	14	16	16	0	0	S	S	S	0	0
29	LALITHA	35	F	7294	EXPLORATORY LAPROTOMY	16	400	3	NO	78	80	84	84	84	86	88	116	112	110	110	116	118	120	90	90	82	82	84	90	90	16	14	14	16	16	16	18	0	S	S	S	S	0	0
30	MAHADEVAPPA	45	M	5749	KNEE AMPUTATION	9	360	3	NAUSEA	86	80	78	78	80	80	84	126	120	120	122	122	120	124	90	86	84	84	86	90	90	16	14	14	14	16	16	16	0	0	S	S	0	0	0
31	MAIBOOB	50	M	7370	KNEE AMPUTATION	15	360	3	NO	78	82	80	80	80	80	84	130	130	126	124	130	130	130	80	80	74	74	78	78	80	15	14	14	15	16	18	16	0	0	0	S	0	0	0
32	PARAMAWWA	45	F	1415	VH	12	420	4	NAUSEA	80	72	70	70	72	74	72	110	120	120	120	124	120	124	78	76	74	74	80	80	80	16	16	16	15	16	17	17	0	0	0	S	0	0	0
33	NELAMMA	45	F	1510	VH	15	360	4	NO	78	80	68	64	68	68	74	110	116	112	110	110	110	110	80	80	80	80	82	82	80	16	15	15	15	14	14	15	0	0	S	S	0	0	0
34	SHANTAMMA	50	F	19603	VH	14	360	3	NO	84	82	82	80	80	80	84	130	126	120	120	124	124	128	90	90	88	90	90	90	90	14	14	12	12	14	14	14	0	0	S	0	0	0	0
35	CHANDRABAGH	50	F	243	VH	13	420	4	NAUSEA	82	84	80	80	84	82	82	120	118	120	120	130	130	130	82	80	80	80	84	84	84	14	14	14	14	14	16	16	0	S	S	S	0	0	0
36	MALLAMMA	50	F	21	VH	12	420	4	NO	84	80	80	80	80	82	84	120	110	110	110	116	118	120	80	80	80	80	80	82	82	15	14	14	14	15	15	15	0	S	S	S	0	0	0
37	ARJUN	40	M	1395	ORIF	16	380	3	NO	74	74	72	72	76	76	76	116	110	104	104	106	110	110	78	70	70	70	70	74	74	13	13	12	13	14	14	14	0	0	S	S	0	0	0
38	DONAPPA	50	M	2182	AMP	13	360	3	NO	84	80	80	80	86	86	84	120	110	110	110	118	118	120	74	76	74	74	76	76	74	15	14	14	16	16	16	15	0	0	S	S	0	0	0
39	GANGABAI	50	F	2602	AMP	15	360	3	NO	82	84	82	82	86	86	86	110	106	106	110	110	110	110	84	80	80	84	80	84	84	15	14	14	14	14	14	14	0	S	S	S	0	0	0
40	SOMAPPA	50	M	2281	HEMIARTHROPLASTY	14	360	3	NO	84	84	84	76	84	84	86	110	110	110	110	110	116	116	70	70	70	78	78	78	80	16	15	15	15	15	16	16	0	S	S	S	S	0	0
41	MALLESH	50	M	4250	AMP	14	400	3	VOMITING	80	74	72	72	76	76	78	118	114	112	112	116	112	116	84	80	76	76	78	80	80	15	14	14	14	14	14	15	0	S	S	S	0	0	0
42	MALLAMMA	50	F	4368	HEMIARTHROPLASTY	16	400	4	NAUSEA	86	80	80	78	76	80	78	120	122	114	114	118	120	124	90	84	82	82	80	86	86	16	15	15	15	15	15	16	0	S	S	0	0	0	0
43	RUDRAPPA	35	M	4162	ORIF	10	320	3	NO	82	80	82	82	82	80	82	130	128	124	130	130	130	130	86	88	86	86	84	86	86	15	14	14	14	14	14	16	0	S	S	0	0	0	0
44	DHANIBAI	50	F	908	VH	12	360	4	NO	80	80	80	80	80	86	82	120	110	110	110	110	110	110	84	86	80	78	78	80	80	13	13	13	14	14	13	13	0	0	S	S	0	0	0
45	CHANNAMMA	40	F	1554	VH	15	360	3	NO	80	76	74	74	76	80	80	120	124	116	116	118	120	120	80	80	80	80	80	80	78	14	13	13	13	13	13	15	0	0	S	0	0	0	0
46	LAXMIBAI	35	F	1858	VH	14	380	3	NAUSEA	76	76	74	76	76	76	80	130	124	124	124	126	126	124	84	84	82	82	84	84	88	16	14	14	14	14	16	15	0	S	S	S	0	0	0
47	RAYAMMA	30	F	1836	VH	15	360	3	NO	86	84	84	84	86	86	86	120	106	106	108	110	120	116	82	80	76	74	76	78	80	14	13	13	13	13	14	13	0	S	S	S	S	0	0
48	PRABHAVATI	50	F	2872	VH	12	420	4	VOMITING	80	82	82	82	82	82	86	118	112	114	112	114	114	118	76	70	72	72	67	72	78	13	13	14	14	14	14	15	0	S	S	0	0	0	0
49	YAMUNAVVA	50	F	2326	VH	14	360	3	NO	84	80	82	80	80	80	80	120	116	120	120	120	120	120	86	80	80	80	80	88	86	15	14	13	14	14	14	14	0	0	S	S	0	0	0
50	JAYASHREE	46	F	3134	VH	11	360	3	NO	86	78	78	80	80	80	80	120	118	116	118	120	120	120	80	76	72	72	78	76	76	14	13	14	14	14	14	15	0	S	S	S	0	0	0
51	YAMUNAWWA	40	F	3392	VH	15	360	3	NAUSEA	80	76	74	84	76	80	80	120	124	116	116	118	120	120	80	80	80	80	80	80	78	14	13	13	13	13	13	15	0	S	S	S	0	0	0
52	SUMANGALA	50	F	3438	VH	14	360	3	NO	76	76	74	76	76	76	80	130	124	124	124	120	126	124	84	84	82	82	84	84	88	16	14	14	14	14	16	15	0	S	S	S	0	0	0

KEY TO MASTER CHART

SI. No	- Serial Number
IP. No	- Inpatient Number
Min	- Minutes
VRS	- Verbal Response Score
hr	- hours
BP	- Blood Pressure
mm Hg	- millimeters of mercury
OOA	- Onset of Action
QOA	- Quality of Analgesia
yrs	- years
AMP	- Austin Moor's Prosthesis
TAH	- Total Abdominal Hysterectomy
VH	- Vaginal Hysterectomy
ORIF	- Open Reduction Internal Fixation
IM Nailing	- Intra-medullary Nailing
S	- Sleeping normal (Sedation score S)
0	- Awake (Sedation score 0)
1	- Drowsy but arousable (Sedation score 1)