

**A STUDY ON THE EFFICACY OF GABAPENTIN ON
COMBINED SPINAL EPIDURAL ANAESTHESIA FOR LOWER LIMB
ORTHOPEDIC SURGERIES**

A STUDY OF 60 CASES

DISSERTATION SUBMITTED FOR THE DEGREE OF

DOCTOR OF MEDICINE

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INTRODUCTION

“For all the happiness that mankind can gain,

It is not in pleasure but in relief from pain”

-JOHN DYRDEN

“Pain, like pleasure is passion of the soul,

That is an emotion and not one of the senses”

-PLATO AND ARISTOTLE (a 375 B.C)

Pain is a fundamental biological phenomenon .The International Association for the study of pain has defined Pain as an unpleasant sensory and emotional experiences associated with actual or potential tissue damage. Pain is always underestimated and undertreated.The relief of pain during surgery as well as in the post operative period is the main part of anesthesia.

Orthopedic patients can be particularly challenging for anesthesiologists. These patients represent a broad scope of problems, ranging from an elderly patient with multiple co-morbid conditions to a young.

Many orthopedic procedures are well suited for regional anesthetic techniques. Regional anesthesia may reduce the incidence of major peri operative complications like ,deep vein thrombosis (DVT), pulmonary embolism (PE), blood loss. In addition, regional anaesthesia provides superior post operative pain relief.

Eventhough there are various methods of providing post operative pain relief, like intravenous opioids, NSAIDS, patient controlled analgesia, continuous peripheral nerve blocks, epidural analgesia etc, Epidural analgesia is the one method which can be performed easily ,can provide intraoperative and postoperative analgesia better than other methods with better patient comfort.

But in epidural analgesia , it needs higher volume or higher dosage and sometimes it may exceed toxic dosage . So as to reduce the requirement of post operative epidural analgesic supplementation there are drugs that can be used as preemptive analgesia like opioids, NSAIDS etc.

This study involves, using Gabapentin, (An atypical anticonvulsant Which was originally used for chronic pain) and the effects of Gabapentin on combined spinal epidural anaesthesia in respective of post operative epidural analgesic requirements.

AIM OF THE STUDY

To study the efficacy of Gabapentin on combined spinal epidural anaesthesia for lower limb orthopedic surgeries with respect to post operative epidural analgesic requirements

HISTORY

1. 1885-CORNING first used epidural analgesia
2. On August 15, 1898, AUGUST BIER and AUGUST HILDEBRANDT injected 5mg and 15mg of cocaine intrathecally to reproduce spinal anesthesia .
3. In 1901, JEAN ENTHUSE SICARD and FERNAND CATHELIN independently, introduced cocaine through the sacral hiatus.
4. ACHILLE MARIO DOGLIOTTI described epidural infusion of local anesthetics in 1931.
5. 1963, Bupivacaine introduced clinically by TELIVERO.
6. MELZACK AND WALLS (1965), Propounded The Gate Control Theory Of Pain.
7. REYNOLDS (1969), Described the endogenous neuronal system of Analgesia & HUGHES et al, Discovered the specific opioid receptor in the substantia gelatinosa of spinal cord and the brain .
8. BEHAR, OLSHWANG (1979) et al, First reported epidural opioids in human (morphine).
9. GARY A. MELLICK and LARRY B. MELLICK have published the first literature on pain, Gabapentin for Neuropathic pain on October, 1997

ANATOMICAL CONSIDERATIONS

SUBARACHNOID BLOCK

In Encyclopaedia Britannica (1771), the word 'subarachnoid' means 'privation of senses', not necessarily implying loss of consciousness.

VERTEBRAL COLUMN

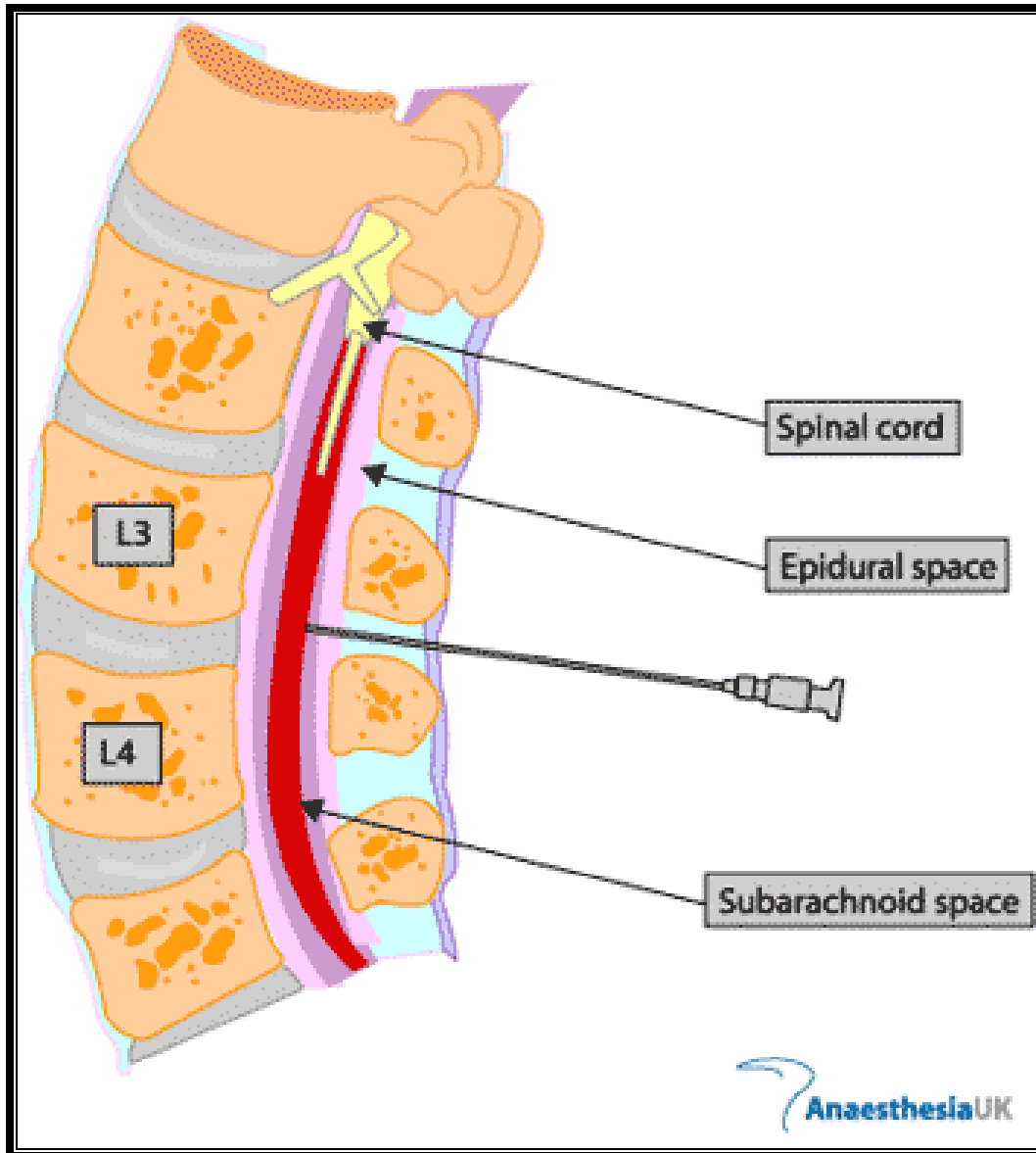
Vertebrae are 33 in number – 7 cervical, 12 thoracic, 5 lumbar, 5 sacral and 4 coccygeal. Each vertebra is composed of a 'body' separated from the adjacent vertebra by intervertebral disc and 'vertebral arch' formed by pedicles and laminae, which surround and protect the cord laterally and posteriorly.

There are seven projections from these vertebral or neural arches. They are

- (a) Three muscular processes – two transverse and one spinous – for the attachment of muscles and ligaments and
- (b) Four articular processes – two upper and two lower – which in the lumbar region prevent rotation but allow limited flexion and extension between contiguous vertebrae.

Spinal cord is the direct continuation of medulla oblongata extending from upper border of atlas to 1st lumbar vertebra, below which there is leash of nerve roots termed cauda equina. Spinal nerves are 31 pairs, 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 1 coccygeal, each composed of anterior and posterior roots

FIG .1.ANATOMY OF SUB ARACHNOID SPACE



uniting at the intervertebral foramina and form nerve trunk. Membranes covering the spinal cord are the outer most duramater, middle arachnoidmater and inner

most piamater. Dura and arachnoid end at S2 level. Pia is closely applied to the spinal cord. **(figure 1)**

Blood supply of cord is by anterior spinal artery and by a pair of posterior spinal arteries. The peculiarity is that, there is no anastomosis between these arteries. Spinal veins comprise of anterior and posterior plexus draining into vertebral, azygos and lumbar veins.

CerebroSpinal fluid is the ultrafiltrate of plasma from choroids plexus of lateral ventricles with pH of 7.4. The amount of CSF in spinal canal is 75ml with a pressure of 70-170 cm of water in lateral position. It contains 20-40mg% of protein, 45-80mg% of sugar and 5 lymphocytes /cu.mm normally.

An important factor that determines the spread of the drug in CSF is specific gravity of the drug in relation to that of CSF (baricity) which 1.003-1.009 (average 1.004). Hyperbaric solution is the one which is denser than CSF at 37°C, specific gravity around 1.034.

PHYSIOLOGY OF SUBARACHNOID BLOCK

Drugs deposited at the subarachnoid space acts on the nerve roots and blocks the nerve conduction. The blockade occurs in the preganglionic B fibres, temperature, pain, proprioception and then motor fibres in that order.

Factors controlling the extent and duration of anaesthesia:

1. Specific gravity of the solution – the most important
2. Position of the patient during and immediately after injection
3. Site of injection
4. Volume and concentration of the solution : increasing the dose and concentration prolongs the block.

Cardiovascular effects :

B fibres are more sensitive than A fibres causing a higher sympathetic block (zone of differential blockade) resulting in vasodilatation and a fall in blood pressure especially if a substantial number of thoracic segments are blocked. Due to Bainbridge reflex, the fall in blood pressure is associated with bradycardia. Blockade of cardiac sympathetic fibres is from T1 – T4 an additional factor, that causes bradycardia.

Respiratory effects :

Normally respiration is not depressed. High spinal can cause blockade of intercostal nerves but not phrenic nerves. Hypoxia may accompany hypotension and is corrected by Oxygen supplementation through face mask.

Metabolic and Hormonal effects :

Regional blockade minimizes the rise in blood sugar, cortisol, catecholamines, renin and aldosterone release associated with stress. Postoperative negative nitrogen balance and secretion of antidiuretic hormone are inhibited.

Genito – Urinary system :

Sphincters of bladder are not relaxed and tone of ureters are not greatly altered. Penis is often engorged and flaccid due to paralysis of nervi erigentes (S2, S3). Postspinal retention of urine may be moderately prolonged as L2 & 3 contain small autonomic fibres and their paralysis lasts longer than that of the larger sensory & motor fibres. Uterine tone is unchanged in pregnancy.

Gastro intestinal effects :

Sympathetic blockade leads to contracted bowel with relaxed sphincters. Handling of viscera causes discomfort since vagus is not blocked.

ANATOMICAL CONSIDERATIONS

EPIDURAL ANALGESIA

The epidural space is a potential space within the bony cavity of the spinal canal and outside dural sac. It extends from the foramen magnum to the coccyx. Within the cranium the endosteal and meningeal layers are united but below the foramen magnum the two layers are separate, the outer becoming the periosteal lining of spinal canal while the inner layer forms the spinal duramater. Between these two layers lies the epidural space.

The spinal canal is triangular in cross section and epidural space is widest in midline posteriorly in the lumbar region averaging about 5 to 6 mm in diameter. In the midthoracic region the distance is somewhat less in the range of 3 to 5 mm in the midline.

BOUNDARIES OF THE EPIDURAL SPACE (figure 2)

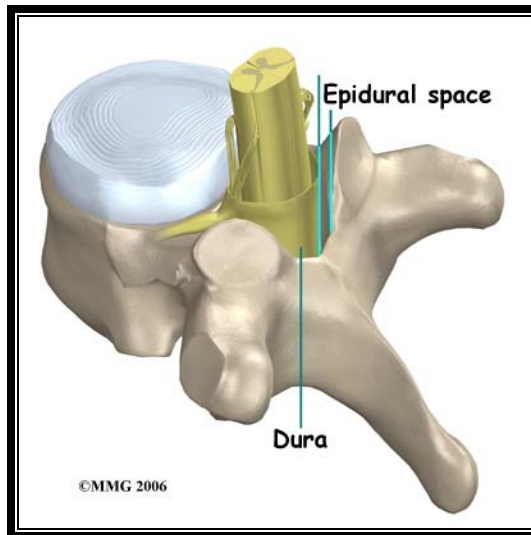
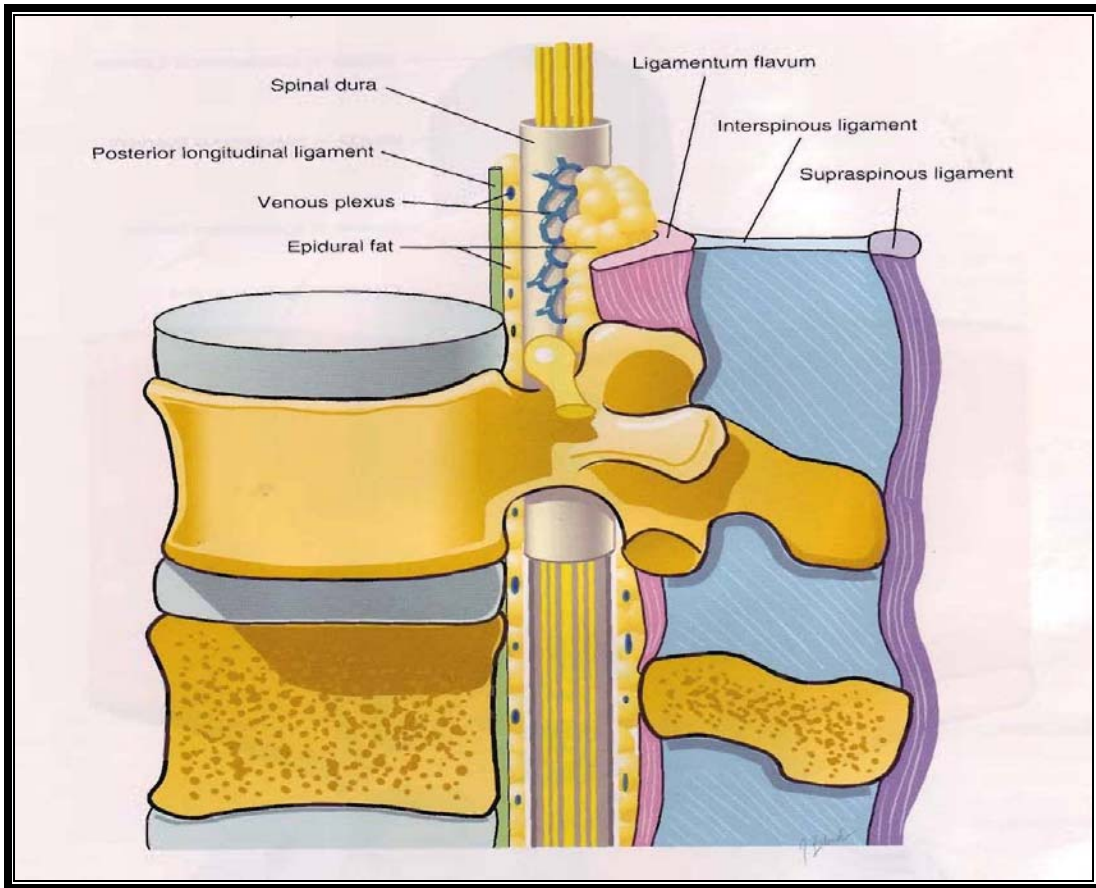
Superior : The foramen magnum where the periosteal and spinal layers of the dura fuse together.

Inferior : The sacrococcygeal membrane.

Anterior : The posterior longitudinal ligament covering the posterior aspect of vertebral bodies and intervertebral discs.

Posterior : The anterior surface of vertebral lamina and ligamentum flavum.

FIG .2.BOUNDARIES OF EPIDURAL SPACE



Laterally : The pedicles of vertebra and intervertebral foramina.

It communicates via the intervertebral foramina with the paravertebral spaces. Fibrous strands anchoring the dura posteriorly, partly divide the epidural space in the midline so that injected fluid frequently distends the space laterally rather than in the midline.

Ligamentum flavum is concerned with the identification of the epidural space. It is composed of yellow elastic fibres. It is thinnest in the cervical region becoming progressively thicker lower down the spine and is thickest in the lumbar region.

SIZE OF THE EPIDURAL SPACE

Region	Epidural space	Thickness of duramater
Cervical	1 – 1.5 mm	1.5 – 2 mm
Upper Thoracic	2.5 – 3 mm	1 mm
Lower Thoracic	4 – 5 mm	1 mm
Lumbar	5 – 6 mm	0.66 0.33 mm

CONTENTS OF THE EPIDURAL SPACE

It includes dural sac and spinal nerve roots, extradural plexus of veins (BATSON'S) lymphatics and fat. The 31 pairs of spinal nerves with their dural cuff traverse the space on their way to intervertebral foramina. The veins form a network which run in four main trunks along the space.

The veins receive tributaries from the adjacent bony structures and the spinal cord. They communicate with venous plexuses at each vertebral level, with the basivertebral veins on the posterior aspect of each vertebral body and with the ascending, deep cervical, intercostals, ilio-lumbar and lateral sacral veins. The veins have no valves and constitute the valveless vertebral venous plexus of Batson. They connect the pelvic veins below with the intracranial veins above, so that air or local analgesic solution injected may ascend to the brain. They drain into inferior vena cava via the azygos vein.

The epidural veins become distended during coughing and straining and also when inferior vena cava is obstructed or in late pregnancy. The intrathoracic pressure is conducted via the paravertebral spaces to the thoracic epidural space and to diminishing extent to cervical and lumbar region.

CAUSES OF NEGATIVE PRESSURE IN THE EPIDURAL SPACE

1. The degree of negative pressure obtainable is dependent upon the type of needle used. Blunt needles gave greater negative pressure than the sharp ones and needles with side openings gave better readings than those with the end openings.
2. Slow and careful introduction give the greatest negative pressure.

3. Greater negative pressures were recorded with low CSF pressures than with high ones.

THEORIES OF NEGATIVE PRESSURE

1. Cone theory : (Eaton – Lawrence) Dimpling of the dura by the needle. The advancing needle dented a cone of resilient dura within the unyielding walls of spinal canal.
2. Transmission theory : (Macintosh – Bryce smith) Negative pressure in the epidural space is caused by transmission of negative intra-pleural pressure through the intervertebral foramina into the epidural space.
3. Full flexion of the back.
4. The initial bulging forward of the yellow ligament in front of the advancing needle, followed by its rapid return to the resting position once the needle has perforated the ligament.
5. Redistribution of CSF in the intradural space: Negative pressure was readily recorded in the cervical and the thoracic regions, when the patients were sitting up. But the negativity becomes less marked in the lumbar region and nonexistent in the sacrum.

6. Recorded pressures are as follows

Thoracic: - 1 to 9.6 cm of H₂O

Lumbar : +2 to 6 cm H₂O

ANATOMY OF THE LUMBAR VERTEBRA

The bodies of the lumbar vertebra are large and kidney shaped. The vertebral foramen is roughly triangular. The transverse processes are slender. The lamina are short, broad and strong and do not overlap each other. The spinous processes are horizontal and oblique.

Location of spinal segments in relation to the vertebrae

Spinal cord	Segment	Vertebral level
Cervical	1 – 8	Cervical 1 – 7
Thoracic	1 – 4	Thoracic 1 - 3
Thoracic	5 – 12	Thoracic 4 – 8
Lumbar	1 – 5	Thoracic 9 – 11
Sacral	1 – 5	T12 – L1

PHYSIOLOGY OF PAIN

PAIN

International association for study of pain has defined pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or defined in terms of such damage.

There are two components of pain. Neuro physiologically mediated sensory component and an emotional component.

There are two types of pain

1. Physiological pain is a transient sensation due to noxious mechanical, thermal, chemical stimulus each with a clearly defined threshold and without causing damage to the nervous system.
2. Pathological pain is an inflammatory response to tissue injury or damage to central nervous system with an alteration in perception. Pain following surgery is pathological.

There are two major theories of pain.

1. Specificity theory proposed by von Frey states that pain is due to stimulation of specific end organs.

2. Intensive / summation / pattern theory proposed by Gold Scheider states that there are no specific pain receptors and any sensory stimulus if sufficiently severe would produce pain.

ORGANISATION OF PAIN PATHWAYS:

According to the recent theory, pain pathway is organized as follows(**figure 3,4**)

RECEPTORS:

Nociceptive receptors are fine, profusely branched, free nerve endings covered by Schwann cells with little or no myelin. They are present in skin, viscera and other organs.

There are three types of receptors

1. Mechanosensitive nociceptors activated by mechanical stimuli.
2. Mechanothermal nociceptors activated by mechanical and thermal stimuli $>43^{\circ}\text{C}$.
3. Polymodal pain receptors respond to mechanical, thermal and chemical stimuli like hydrogen and potassium ions, histamine, serotonin, bradykinin, prostaglandins and substance P.

FIRST ORDER NEURONS:

Mechanosensitive and mechanothermal pain receptors transmit impulses through thinly myelinated A delta fibres of $1-5\ \mu$ diameter with conduction velocity

FIG.3.PAIN PATHWAY

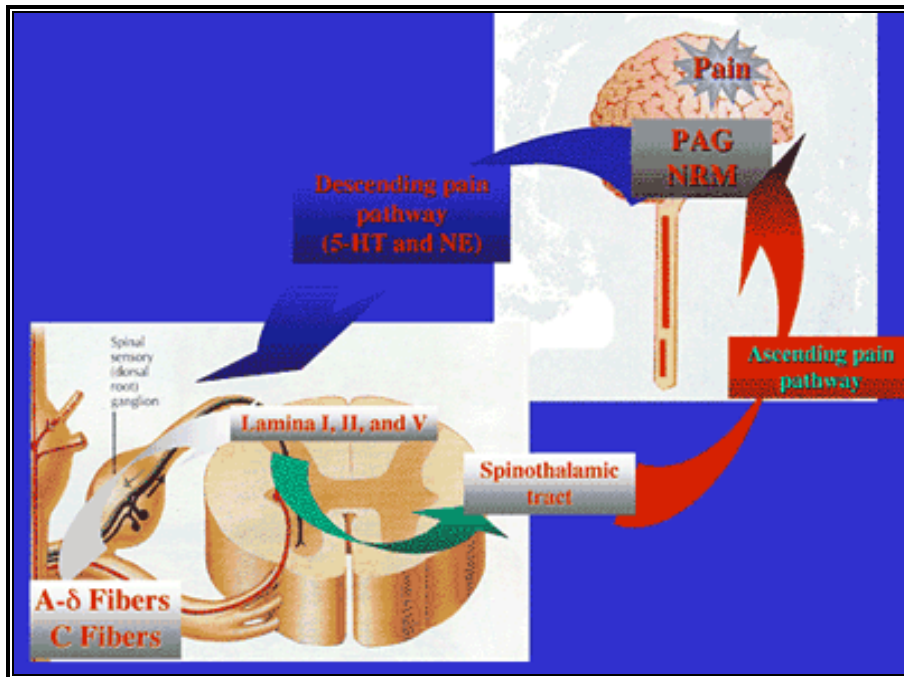
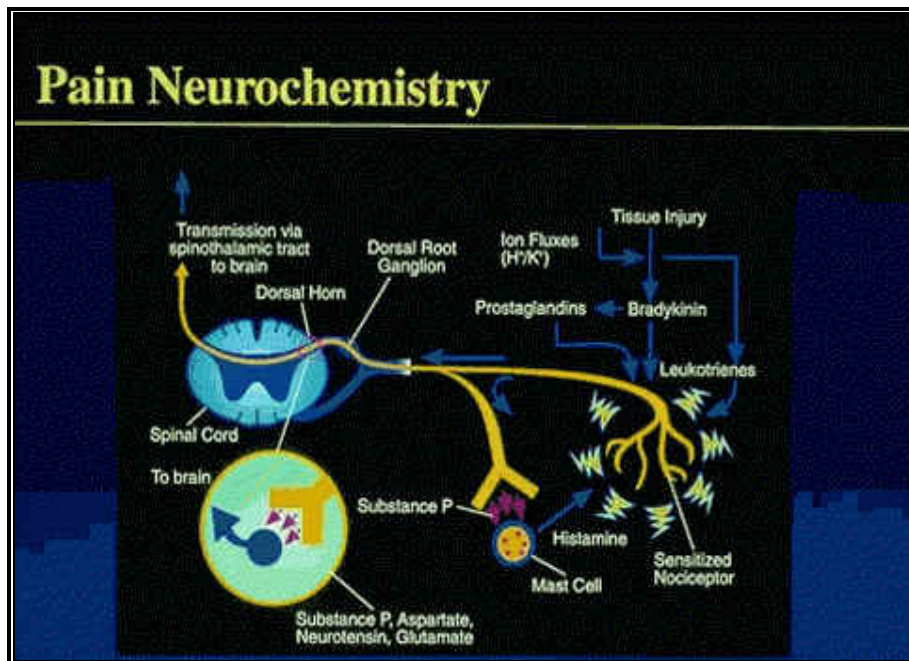


FIG.4.



of 15-30 metres per second. This is responsible for fast pain which is sharply localized. Polymodal pain receptors transmit impulses through unmyelinated C fibres of 0.4-1.1 μ diameter with conduction velocity of 0.5 – 2 meters per second.

This is responsible for the poorly localized slow pain. Transmission through both these fibres causes the “ Double response of Lewis”.

The peripheral afferent fibres have their cell body in the dorsal root ganglion and project via the lateral part of the dorsal root called “ Tract of Lissauer”. They terminate in dorsal horn of spinal cord within 1 to 2 segments of entry.

A delta fibres terminate in lamina 1 (marginal cell layer of Waldeyer) and lamina 5 (wide dynamic range of neurons which respond to other modalities also).

Unmyelinated C fibres terminate in lamina 2 & 3 (substantia gelatinosa).

SECOND ORDER NEURONS :

They arise from the cell and connect with ventral and lateral horn cells in the same and adjacent spinal segments and subserve both somatic and autonomic reflexes. Around 75% of other sensory neurons project contralaterally after decussating in the anterior commissure

1-3 segments higher than the root of entry and divide into two ascending tracts.

Neospinothalamic / Lateral spinothalamic tract: It ascends in the anterolateral funiculus of spinal cord to brain stem and thalamus and contains fast conducting

fibres which transmit specific localised pain, identifiable in quality and intensity causing “ First Pain “. The fibres are arranged in such a way that fibres from lower part of the body are superficial and from upper part of the body are innermost.

Palaeospinothalamic/Ventral spinothalamic/Spinoreticulothalamic tract:

It is medially placed and contains slowly conducting fibres responsible for “ Second Pain” and has connections with reticular core or brainstem, limbic and subcortical regions.

Thalamic terminus: Most of the fibres of spinothalamic tract terminate in the nucleus ventro posterolateralis which is the major sensory relay nucleus. The other fibres terminate in the posterior group of nuclei, ventrobasal complex and hypothalamic nuclei.

THIRD ORDER NEURONS / THALAMOCORTICAL PROJECTIONS:

Posterior thalamic nuclei project to the post central cortex and upper bank of sylvian fissure and subserve tactile and proprioceptive stimuli with discriminative sensory function. Pain afferents received from mesencephalic offset of anterolateral funiculus project to the amygdaloid nuclei and other areas related to affect the emotion.

PERCEPTION OF PAIN :

The threshold for the perception of pain is the lowest intensity of stimulus recognized as pain. The conscious awareness or perception of pain occurs at the thalamic level and thalamic pain occurs when the thalamocortical pathway is destroyed. Somatosensory cortex is essential for the accurate localization, appreciation of intensity and other discriminative aspects of pain. Prefrontal cortex subserves the unpleasant affective and emotional reaction to pain.

GATE CONTROL THEORY OF PAIN:

It was propounded by Melzack and Walls in 1965. It states that modulation of pain impulses in the dorsal horn can control further synaptic transmission via the spinothalamic tract. It states that stimulation of large afferent fibres (myelinated) excite the I cells (inhibitory cells) in the lamina 2 and 3 of dorsal horn which in turn cause pre and post synaptic inhibition of secondary transmission neurons(T cells) in lamina 5 of dorsal horn and interrupt pain pathway. Conversely stimulation of small pain afferents (C fibres) inhibit the I cells leaving the T cells in the excitatory state thus facilitating transmission of pain.

CENTRAL SENSITISATION OR ‘WIND UP’:

Prolonged nociceptive stimulation leads to hyperexcitability of dorsal horn cells and increased cephalad transmission resulting in increased pain sensation.

This is responsible for chronic pain syndromes. There are two mechanisms for this chronic pain syndromes. Descending inhibitory pathways and endogenous pain control mechanisms. Endogenous neuronal system of analgesia was described by Renolds in 1969. It extends from the hypothalamus along the peri ventricular and periaqueductal grey matter which communicates through dorsolateral funiculus to end in the nucleus raphe magnus and locus ceruleus. Stimulation anywhere along this tract releases endogenous opioid like peptides called endorphins which activate serotonergic pathways via descending reticulobulbar spinal system and interact with lamina 1 and 2 of the dorsal horn and exert analgesia. Another descending inhibitory pathway arises from locus ceruleus in Pons and projects directly to spinal cord. Here the neurotransmitter is noradrenaline and this pathway inhibits pain responses in spinal cord by Alpha 2 adrenergic mechanisms.

Endogenous opioids and other neurotransmitters and spinal modulation of pain perception:

Hughes et al described endogenous morphine like substances with analgesic activity called endorphins. There are 5 endorphins, **Metenkephalin, Leuenkephalin, Betaendorphin, L endorphin and R- endorphin.**

Met-enkephalin and Leu-enkephalin: They are inhibitory neurotransmitters at the primary afferent nociceptive site. They act through release of substance P.

Dynorphins: Control nociception at the spinal cord level through activation of kappa receptors. It is present in lamina 1 to 5 of dorsal horn.

L-endorphin and R-endorphins are breakdown products of beta endorphins.

Substance P (Substance preparation): It is a 11 amino acid peptide. It acts as an excitatory transmitter in lamina 1,2,4 and 5 of dorsal horn, spinal trigeminal nucleus and type B cells in dorsal root ganglia. It is released in vivo by the activity of A delta and C fibers. Endogenous opiates inhibit presynaptic release of substance P. Serotonin released from descending inhibitory pathways inhibit the action of substance P at the post synaptic level thus inhibiting pain transmission.

Somatostatin: It is a 13 amino acid peptide found in lamina 2 of dorsal horn and inhibits function of afferent pain fibres.

PHARMACOLOGY

BUPIVACAINE

Bupivacaine is an amide linked local anaesthetic. It is a hydrochloride salt of d(1)-1-butyl 2'6' pipercoloxylidide and is presented as a racemic mixture

(figure 5)

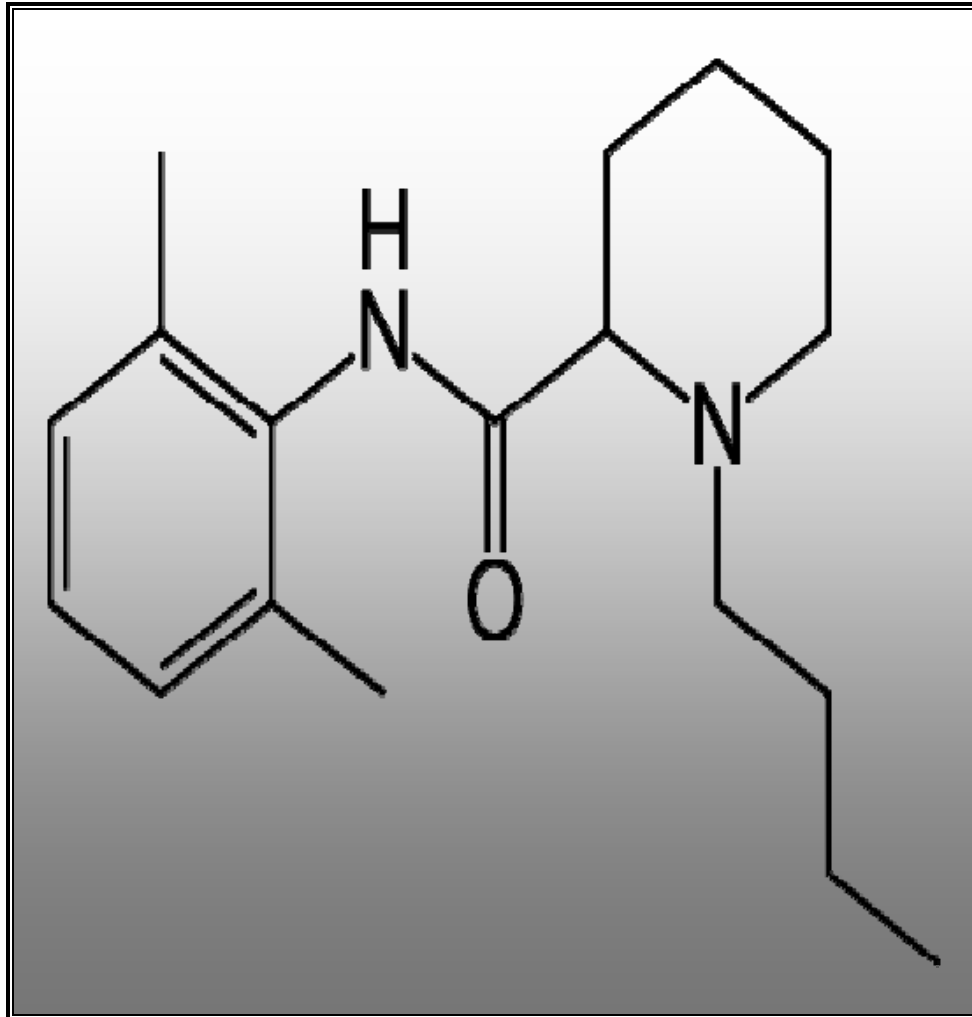
- Bupivacaine was synthesized by Ekenstam in 1957.
- First report of its use was published in 1963 by Telivuo.
- It is derived from Mepivacaine and is very stable compound and may be autoclaved repeatedly.

Pka	-	8.1
Molecular weight	-	288
Protein binding	-	95%
Lipid solubility	-	28
Elimination half life	-	210mts
Toxic plasma concentration	-	>1.5µg/ml
Approximate duration of action	-	175mts

Availability:

- Ampoules - 0.5% Bupivacaine hydrochloride 4cc
- 0.5% Bupivacaine hydrochloride with dextrose (heavy) 4cc

FIG.5.STRUCTURE OF BUPIVACAINE



Vials - 0.25% and 0.5% Bupivacaine hydrochloride 20cc

Dosage - Maximum dosage 3mg/kg body weight.

Onset time and duration of action

Site of action	Onset (minutes)	Duration (minutes)
Intrathecal	5	180-240
Epidural	15-20	165-225
Brachial plexus	10-20	600

PHARMACOKINETICS:

Once injected intrathecally, it gets absorbed by the nerve rootlets and results in the desired effect. It is rapidly absorbed from the site of injection, but the rate of absorption depends on the vascularity at the site and presence of vasoconstrictors. High lipid solubility of bupivacaine makes it easy for nerve and vascular tissue penetration. 80-95% of the absorbed bupivacaine binds to the plasma.

Distribution:

Rapid distribution phase: (α) - In this phase the drug is distributed to highly vascular region $t_{1/2}$ of α - being 2.7 minutes.

Slow disappearance phase: (β)-In this phase the drug is distributed to slowly equilibrating tissues $t_{1/2}$ of β – being 28 minutes.

Biotransformation and excretion phase : (δ)-T_{1/2} of δ is 3.5hours. Clearance is 0.47 litres / minute.

Biotransformation:

Possible pathways of metabolism of bupivacaine include aromatic hydroxylation and conjugation. Only the N-dealkylated metabolite, N-desbutyl bupivacaine has been measured in blood (or) urine after epidural (or) spinal anaesthesia. Alpha-1 acid glycoprotein is the most important plasma protein binding site of bupivacaine and its concentration is increased by many clinical situation including post operative trauma.

Excretion:

It is through the kidney, 4-10% of the drug is excreted unchanged.

MODE OF ACTION:

a) Site of action:

- i) Peripheral nerve rootlet fine nerve filaments
- ii) The spinal nerve rootlet fine nerve filaments
- iii) Posterior and lateral aspects of the spinal cord itself.

b) Sodium Channel blockade:

They impede sodium ion access to the axon interior by occluding the transmembrane sodium channels thus delaying the process of depolarization and axon remains polarized. It is a non-depolarization blockade.

PHARMACODYNAMICS:

It has got a longer duration of action but a slower onset.

Cardio vascular system: It reduces cardiac output by reducing the sympathetic tone, by slowing the heart rate and by reducing the venous return, it produces a fall in arterial blood pressure but it is relatively slow and is seldom very profound.

It produces a fall in central venous pressure. It causes an increase in lower limb blood flow. It causes a reduction in incidence of deep vein thrombosis.

Respiratory System: Spinal blockade seldom, if ever causes respiratory problem.

Gastro intestinal tract: There is an increase in gastro intestinal motility and emptying of the gastric contents is better.

TOXICITY:

Toxicity is related to plasma level of unbound drug and more likely due to an inadvertent intravenous injection. Systemic toxicity reactions primarily involve central nervous system and cardio vascular system. The blood level required to

produce central nervous system toxicity is less than that required to produce circulatory collapse.

Central Nervous System Toxicity: Initial symptoms include feeling of light headedness and dizziness, followed by visual and auditory disturbances. Objective signs are excitatory and include shivering, muscle twitching and tremor. Ultimately generalized tonic, clonic seizure occurs.

Cardiovascular System Toxicity: The rate of depolarization in fast conducting tissue of Purkinje fibres and ventricular muscle is decreased. The rate of recovery of bupivacaine induced block is slower than that of lignocaine. Extremely high concentration of the drug causes sinus bradycardia and cardiac arrest.

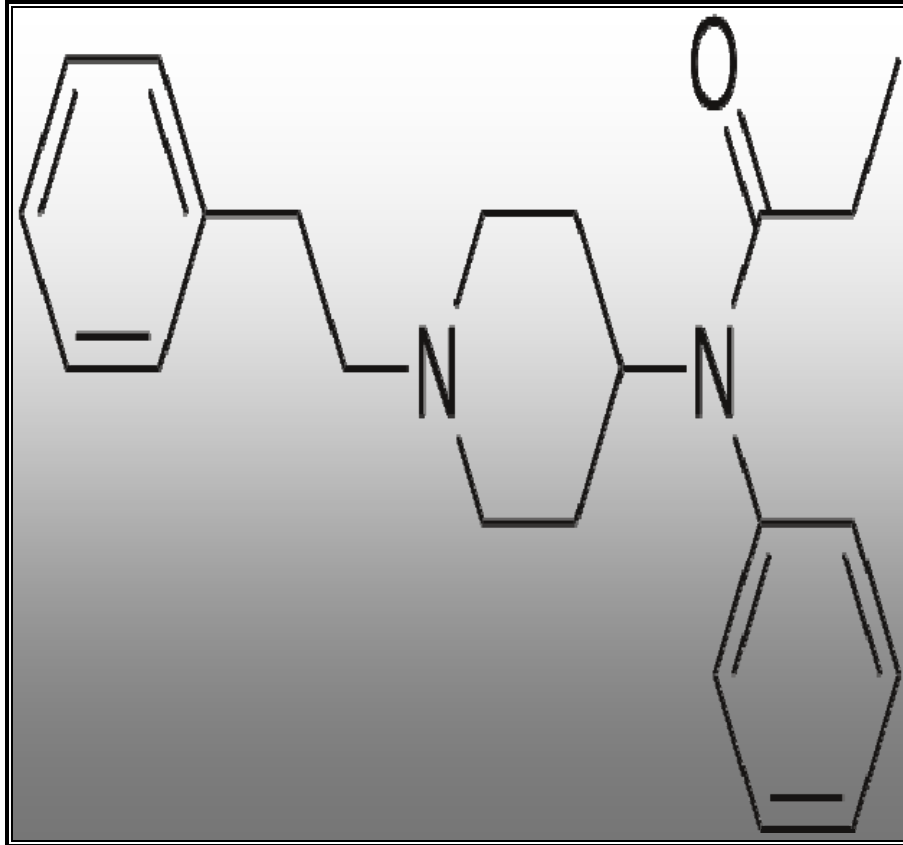
FENTANYL

Fentanyl (**figure 6**) is N-1 (1-Phenethyl-4, piperidylpropionalide citrate). It is a synthetic narcotic agonist that is related to phenylpiperidines. Fentanyl is 100 times more potent than morphine as an analgesic agent. It has got a rapid onset and a shorter duration of action.

Availability

Ampoules : 2 ml containing 100 µg
10ml ampoules : Containing 50 µg/ml

FIG .6.STRUCTURE OF FENTANYL



Lollipop : For paediatric use

Patches : Transdermally delivering a doses of 75 -100 $\mu\text{g}/\text{hour}$

Routes of Administration

Fentanyl is the only opioid available for various forms of administration. It can be used by intramuscular, intravenous, neuraxial, transdermal and transmucosal.

Dosage

Intramuscular : 50-100 μ g (1-2 μ g/kg)
 Intravenous : 50 -100 μ g (1-2 μ g/kg)
 Intrathecal : 10-25 μ g (0.25 -0.5 μ g/kg)
 Epidural : Bolus dose 1 μ g/kg or 2-5 μ g/ml
 Continuous infusion after the bolus : 30 -100 μ g/hr

ONSET TIME AND DURATION OF ACTION

Routes of administration	Onset time(minutes)	Duration of action (hours)
Intramuscular	7-8	1 – 2
Intravenous	Immediate	0.5 – 1
Epidural	10	2 – 3

PHARMACOKINETICS

Molecular weight : 528
 pKa : 8.4

Plasma protein binding	:	84%
$t_{1/2\alpha}$:	1– 2 minutes
t_{β}	:	10 – 30 minutes
$t_{1/2\gamma}$:	2 – 4 minutes

Being a highly lipophilic opioid, the vascular uptake is fast and the rapid circulation to the brainstem is high. These kinetics of Fentanyl is in contradiction to morphine, and clinically produces rapid onset, shorter duration of action, early but not delayed respiratory depression.

Once the Fentanyl is systemically absorbed, it is rapidly redistributed to inactive tissue sites such as fat and skeletal muscles with an associated decline in plasma concentration. The lungs also serve as a large inactive storage site, with an estimated 75% of the initial Fentanyl dose undergoing first pass pulmonary uptake.

Fentanyl is extensively metabolized by dealkylation, hydroxylation and amide hydrolysis to inactive metabolites, including norFentanyl and despropionyl norFentanyl that are excreted in the bile and urine.

The pharmacokinetics of Fentanyl can be described as three compartment model, with a distribution time of 1.7 minutes, redistribution of 13 minutes, and a terminal half time of 219 minutes, The volume of distribution is 4 L/kg.

Gastric acidity can ionize Fentanyl and prevents its systemic absorption and once the acidity is neutralized, the systemic absorption can increase the plasma Fentanyl concentration. Enterohepatic Circulation of Fentanyl can explain the delayed respiratory depression seen in some cases.

MODE OF ACTION

Fentanyl acts on the Mu receptors in the supraspinal areas and on Kappa and Delta receptors in the spinal cord producing spinal analgesia.

Intrathecally administered Fentanyl gets attached to the spinal opioid receptors situated densely in the substantia gelatinosa and systemic absorption of the Fentanyl can lead to supraspinal receptor binding and its effects.

Investigations suggest that different receptors are existing for different opioids. These receptors are distributed throughout the central nervous system and other parts of brain like paleothalamic pathway, limbic system, medial thalamic nuclei, periaqueductal grey matter, reticular formation, periventricular areas of medulla, substantia gelatinosa of spinal cord, lamina I & V of spinal cord.

Opioid receptors in the limbic system and hypothalamus are related to the emotional components of pain. Enkephalin – containing receptors are found in the Meissner's plexus of duodenum, Which probably affects gastro intestinal motility. Opiate receptors are found in large numbers in the area postrema, Which contains

the chemoreceptor trigger zone, the site where opioids are thought to induce nausea and vomiting.

Mechanism and site of action

Recent studies now point to the dorsal horn of spinal cord as the site of action of spinal opiate based upon iontophoretic and microinjection data. Radiolabelled morphine or Fentanyl showed a strong focus of activity on the substantia gelatinosa.

Opiate receptors are located both pre-synaptically at the terminal of primary sensory afferents entering the dorsal horn and on the dendrites of post – synaptic membranes.

Pre-synaptically, opiate peptides inhibit the release of substance –P, glutamate and other neurotransmitters like acetylcholine, noradrenaline, and dopamine from sensory neurons. They also act post-synaptically by decreasing the excitatory post – synaptic potentials induced by persistent afferent stimulation.

Intraoperatively, subarachnoid narcotics potentiate the antinociception provided by the local anaesthetic agent. There is enhancement of comfort and also the visceral manipulations are better tolerated.

Fentanyl also binds to M3 muscarinic receptors in the heart leading to bradycardia which can be prevented by giving atropine to the patients.

Fentanyl also antagonizes 5 hydroxytryptamine levels in the brain, thereby potentiating the analgesic activity of other opioids.

PHARMACODYNAMICS

Cardiovascular system:

It produces bradycardia by binding to M3 receptors. It slows AV node conduction and prolongs PR interval.

Respiratory system:

It can cause early respiratory depression. Peak effect is noted 5 to 15 minutes following intravenous injection. Very rarely delayed respiratory depression can occur.

Musculoskeletal system:

Fentanyl may cause muscle rigidity, particularly involving the muscles of the chest wall by acting on caudate nucleus.

Skeletal muscle movements of various groups in the extremities, in the neck and in extraocular muscles have been reported during induction of anaesthesia with Fentanyl. This effect is related to the dose and speed of injection.

Central nervous system:

It produces euphoria, sedation and miosis. It will not interfere with evoked potential monitoring.

Gastrointestinal tract:

It causes nausea, vomiting and biliary spasm.

ADVERSE EFFECTS

Respiratory depression, urinary retention, pruritus, nausea, vomiting, and hypotension, chestwall rigidity, apnoea, bradycardia, diaphoresis, dizziness, and blurred vision.

OVERDOSAGE AND TREATMENT

The manifestations of Fentanyl over dosage are an extension of its pharmacological actions.

Effects	-	Treatment
Hypoventilation	-	Oxygen therapy or Assisted controlled ventilation
Severe respiratory depression	-	Naloxone
Hypotension	-	Parenteral fluid therapy
Pruritus	-	Chlorpheniramine

GABAPENTIN

Gabapentin , specifically a GABA analogue .It was first synthesized in 1977.It was originally developed for the treatment of epilepsy and First introduced

as an anticonvulsant in 1994, and currently Gabapentin is widely used to relieve pain, especially neuropathic pain, chronic pain and more recently for acute pain relief also.

Gabapentin is described as 1-(aminomethyl)cyclohexaneacetic acid) with a molecular formula of $C_9H_{17}NO_2$ (**figure 7**) and a molecular weight of 171.24

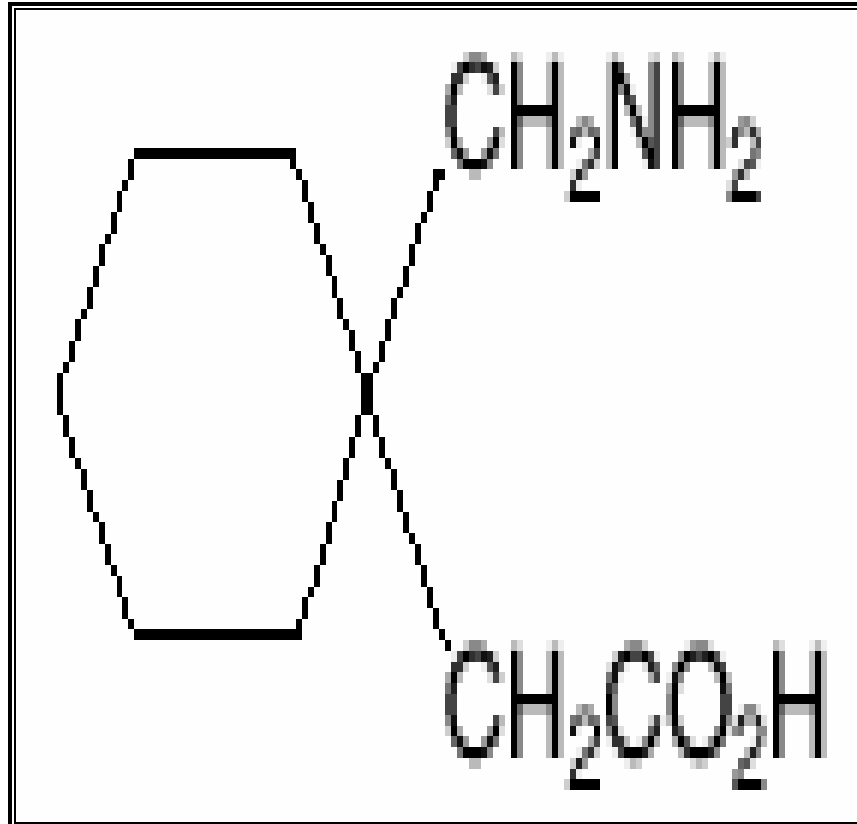
PHARMACOKINETICS

Gabapentin is available in oral preparation (capsules, tablets).

It is orally absorbed in small intestine. Oral bioavailability varies inversely with dose. The bioavailability for the dose of 900 mg is about 60%, whereas that of 1200 mg is about 47% only. Volume of distribution is about 0.6-0.8 litre/kg. Cerebrospinal fluid and brain tissue concentrations are 20%, 80% respectively that of plasma levels.

Gabapentin is not metabolized in humans and excreted unchanged in urine.

FIG.7.STRUCTURE OF GABAPENTIN



Elimination half life is 5-7 hours.

Peak effect will last for 2-4 hours

Duration of action around 8 hours

MECHANISM OF ACTION

Various mechanism of actions are proposed regarding pain relief in acute as well as in chronic pain. Among them antagonism of NMDA receptors and calcium channel blocking actions are the most supporting evidences .

NMDA receptor is a complex ligand gated ion channel that mediates influx of calcium ion when activated.(**figure 8**)

The NMDA receptor complex has a number of binding sites for various ligands that regulate its activity, including the strychnine-insensitive glycine binding site, phencyclidine binding site, polyamine binding site, redox modulatory site and a proton-sensitive site. Partial depolarisation of the neuron after glutamine activation will release a magnesium plug and allow calcium influx into the neuron. These receptors are known to be found in high concentrations in the hippocampus and have been attributed a key role in the process of central sensitisation of painful stimuli, commonly known as the wind-up phenomenon, leading to hyperalgesia. The alpha 2 delta subunit of the voltage-dependent calcium channel is a binding site for Gabapentin (**figure 9**). Because only Gabapentin and the S-isomer of pregabalin

FIG.8. NMDA RECEPTOR

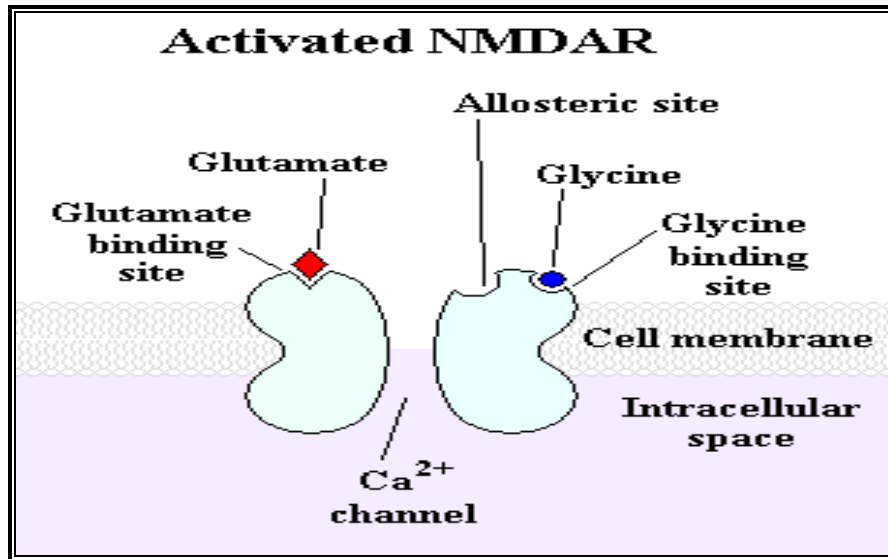
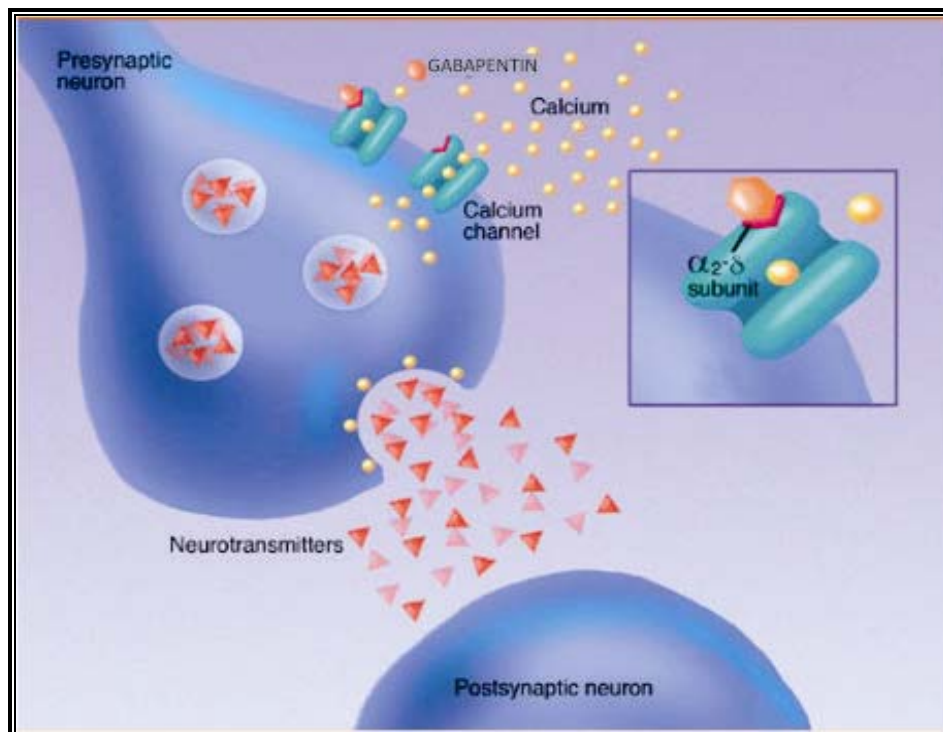


FIG.9.GABAPENTIN ACTION



produce antihyperalgesic effects, it is postulated that the antihyperalgesic action for Gabapentin is mediated by its binding to this site on the voltage-dependent calcium channel. The decreased calcium influx reduces excitatory amino acid (e.g. glutamate) release leading to decreased AMPA receptor activation, and noradrenaline release in the brain. These findings support the hypothesis that calcium channel inhibition mediates the analgesic effects of Gabapentin in chronic neuropathic pain.

DOSAGE AND ADMINISTRATION

Gabapentin is available as capsules or tablets only

For effective pain relief, the recommended adult dose is 900-3600 mg /day in three divided doses. It is not recommended in paediatric age groups, age less than 3 years.

In age group of more than 3 years, the recommended dose is 10-15mg/kg in three divided doses for post herpetic neuralgia

SIDE EFFECTS

Most of the patients tolerate well. Few patients exhibit side effects that are also tolerable. Common side effects are dizziness, drowsiness, coordination problems, fever, nausea or vomiting, pedal edema, asthenia, malaise, arthralgia, vertigo, hyperkinesia, paresthesia.

USES:

1. Gabapentin is frequently used to treat various types of neuralgia. It has been found to be effective in prevention of frequent migraine headaches, neuropathic pain and nystagmus.

2. Gabapentin is widely believed to help patients with post-operative chronic pain, and nerve pain associated with spinal cord injury.

3. It may be effective in reducing pain and spasticity in multiple sclerosis, and has also had success in treating certain instances of Complex Regional Pain Syndrome.

4. Gabapentin is a very promising medication in the treatment of post herpetic neuralgia and pain.

5. Gabapentin has been used to treat symptoms of opiate withdrawal. 6. Gabapentin may help deepen sleep, positively affecting deep, slow wave sleep, and reducing arousals during the night. It could potentially be helpful for both sleep onset and sleep maintenance.

REVIEW OF LITERATURE

1. Canadian journal of anesthesia 2004, 51:4 page: 358-363. Chandra Kant

Pandey MD, Shio Priye MBBS, Surendra Singh MD, Uttam Singh PhD, et al.

Preemptive use of Gabapentin significantly decreases postoperative pain and rescue analgesic requirements in laparoscopic cholecystectomy:

459 ASA I and II patients were randomly assigned to receive 300 mg Gabapentin, 100 mg tramadol or placebo two hours before laparoscopic cholecystectomy under general anesthesia. Postoperatively, patients' pain scores were recorded on a visual analogue scale for the next 12 hr. Patients received Fentanyl 2 µg/kg intravenously on demand. The total Fentanyl consumption for each patient was recorded. Patients in the Gabapentin group had significantly lower pain scores at all time intervals (2.65 ± 3.00 , 1.99 ± 1.48 , 1.40 ± 0.95 , 0.65 ± 0.61) in comparison to tramadol (2.97 ± 2.35 , 2.37 ± 1.45 , 1.89 ± 1.16 , 0.87 ± 0.50) and placebo (5.53 ± 2.22 , 3.33 ± 1.37 , 2.41 ± 1.19 , 1.19 ± 0.56). Significantly less Fentanyl was consumed in the Gabapentin group (221.16 ± 52.39 µg) than the tramadol (269.60 ± 44.17 µg) and placebo groups (355.86 ± 42.04 µg; $P < 0.05$).

2.Canadian journal of anaesthesia . 2004 dec;51(10):986-9.Pandey CK, Sahay S, Gupta D, Ambesh SP, Singh RB, Raza M, Singh U, et al. Preemptive Gabapentin decreases postoperative pain after lumbar discectomy :

56 ASA I and II patients were allocated into two equal groups to receive either Gabapentin 300 mg or placebo two hours before surgery. After surgery, the pain was assessed on a Visual Analogue Scale at intervals of 0-6, 6-12, 12-18, and 18-24 hr at rest. Total Fentanyl consumption in the first 24 hr after surgery was also recorded. Fentanyl 2 µg/kg intravenously was used to treat postoperative pain on patient's demand. Patients in the Gabapentin group had significantly lower VAS scores at all time intervals of 0-6, 6-12, 12-18, and 18-24 hr than those in the placebo group (3.5 ± 2.3 , 3.2 ± 2.1 , 1.8 ± 1.7 , 1.2 ± 1.3 vs 6.1 ± 1.7 , 4.4 ± 1.2 , 3.3 ± 1.1 , 2.1 ± 1.2 ; $P < 0.05$). The total Fentanyl consumed after surgery in the first 24 hr in the Gabapentin group (233.5 ± 141.9 , mean + SD) was significantly less than in the placebo group (359.6 ± 104.1 ; $P < 0.05$).

3.British journal of anaesthesia 2006,96 (2): 242–6 .Effect of oral Gabapentin on postoperative epidural analgesia : A.Turan, G. Kaya, B. Karamanlioglu, Z. Pamukcu and C. C. Apfel.

In this study , 40 patients were posted for lower limb orthopedic procedures of ASA physical status of I &II. Study group patients were given 1.2gram of

Gabapentin capsules, control group patients were given placebo capsules on the day of surgery as well as on first post operative day. Patients were taken under combined epidural general anaesthesia technique. Post operatively pain relief was offered by PCA infusion with lock out interval .The time interval needed for bolus doses was significantly less than that needed for control groups ($p < 0.05$) during the period of 72 hours infusion ,the total PCEA usage also was less in Gabapentin group (38 hours) than that of control group (57 hours),($p < 0.05$).The VRS pain score during first 16 hours following post operative period was significantly lower in Gabapentin group than placebo group ($p < 0.001$)

4. Canadian journal of anesthesia 2006 , 53: 3 , pages 268-273. Hussain Al-Mujadi FRCA, Abdul Rahman A, Refai et al. Preemptive Gabapentin reduces postoperative pain and opioid demand following thyroid surgery:

In this clinical trial, Gabapentin 1200 mg or placebo capsules were given two hours prior to induction of anesthesia to patients undergoing elective thyroidectomy. Post-thyroidectomy pain was assessed on a visual analogue scale at rest and during swallowing in the first 24 hr postoperatively. All patients received morphine 3 mg intravenous every five minutes until visual analogue scale scores were 4 or less at rest, and 6 or less with swallowing. Total morphine consumption for each patient was recorded from zero to 24 hr postoperatively. Overall, pain

scores at rest and during swallowing in the Gabapentin group were significantly lower when compared with the placebo group. Total postoperative morphine consumption in the Gabapentin group was 15.2 ± 7.6 mg (mean \pm SD) vs 29.5 ± 9.9 mg in the placebo group ($P < 0.001$).

4. **Anesthesia-analgesia 2007;104:97–101.**Alparslan Turan, MD,Paul F. White, PhD, MD.,et al . **Premedication with Gabapentin, the effect on tourniquet pain and quality of intravenous regional anesthesia :**

40 Patients undergoing elective hand surgery with IVRA were randomly assigned to one of two study groups. The control group received placebo capsules 1 hour before the surgery, and the Gabapentin group received Gabapentin 1.2 gram orally before the operation. IVRA was achieved in all patients with Lidocaine 3 mg/kg, diluted with saline to a total volume of 40 mL. Fentanyl, 0.5 μ g/kg IV, was administered as a rescue analgesic during surgery. Study showed that tourniquet pain scores at 30, 40, 50, and 60 min after cuff inflation were lower in the Gabapentin group ($P < 0.05$). The time to require intra operative analgesic rescue was prolonged in the Gabapentin group (35 -10 min vs 21 -13min, $P < 0.05$), and less supplemental Fentanyl was required (35 -47 μ g vs 83 -73 μ g, $P < 0.05$). The quality of anesthesia, as independently assessed by the anesthesiologist and the surgeon, was significantly better in the Gabapentin

versus control group. In Gabapentin group, the time to request a rescue analgesic after surgery was prolonged (135 ± 25 min vs 85 ± 19 min, $P < 0.05$), and postoperative pain scores at 60 min (3.8 ± 0.9 vs 2.2 ± 0.5) and 120 min (3.2 ± 1.4 vs 1.8 ± 0.8), as well as diclofenac consumption (30 -38 mg vs 60 - 63 mg), were reduced after surgery

5. **Singapore Medical Journal 2007; 48 (8) ,748.** Montazeri K, Kashefi P, Honarmand A et al . **Pre-emptive Gabapentin significantly reduces post operative pain and morphine demand following Lower extremity orthopaedic surgery :**

70 ASA I and II patients were assigned to receive 300 mg Gabapentin or placebo two hours before surgery under general anaesthesia. Postoperatively, the pain was assessed on a VAS score at 2, 4, 12, and 24 hours at rest. Morphine 0.05 mg/kg intravenously was used to treat postoperative pain on patients' demand. Total morphine consumption in the first 24 hours after surgery was also recorded. Patients in the Gabapentin group had significantly lower Visual Analogue Scale scores at all time intervals of 2, 4, 12, and 24 hours, than those in the placebo group respectively, 55.50 [mean] ± 15.80 [standard deviation], 57.30 ± 19.30 , 45.74 ± 16.00 , 44.60 ± 17.64 , versus 72.30 ± 14.00 , 70.50 ± 18.13 , 62.00 ± 23.32 , 66.50 ± 25.70 , ($p < 0.05$). The total morphine consumed after

surgery in the first 24 hours in the Gabapentin group(15.43 ± 2.54) was significantly less than in the placebo group (17.94 ± 3.00 ; $p < 0.05$).

7. Journal of neurosurgical anesthesiology, 2007, 19(4): 235-8. Prabhakar H, Arora R, Bithal PK, Rath GP, Dash HH et al. The analgesic effects of preemptive Gabapentin in patients undergoing surgery for brachial plexus injury :

20 adult patients undergoing surgery for brachial plexus injury under general anaesthesia were enrolled for the study. Patients randomly received either oral Gabapentin 800 mg or placebo capsules 2 hours before surgery. Intra operative Fentanyl and propofol requirements were noted. Postoperatively, all patients were alert and pain was assessed using Visual Analogue Scale for 24 hours, both during rest and movement. Whenever VAS score was more than 50 or on patients' demand, ketorolac 30 mg was given as rescue analgesic. Significant difference was noted in intraoperative Fentanyl consumption ($p=0.03$), total dose of rescue analgesic ($p=0.004$), and VAS score was less in Gabapentin group as compared with placebo group ($p=0.01$ and 0.04 , at rest and movement, respectively).

8. **Indian journal of anesthesia 2008 , 52 ,Issue 4 ,Page : 428** : Anil Verma, Sangeeta Arya, Sandeep Sahu, Indu Lata, HD Pandey, Harpreet Singh et al. **To evaluate the role of Gabapentin as preemptive analgesic in patients undergoing total abdominal hysterectomy in epidural anaesthesia:**

50 patients with ASA grade I and II were assigned to receive 300mg Gabapentin or placebo 2hr before surgery. Surgeries were conducted under combined spinal epidural anaesthesia. Post operatively, pain was assessed by visual analogue score (VAS). Patients were given epidural boluses of bupivacaine (0.125%) on demand . Patients in Gabapentin group have significantly lower VAS score 2, 4,8,12 and 24hrs postoperatively as compared to the placebo (1.3 ± 1.3 , 2.3 ± 1.4 , 3.2 ± 2.1 , 1.8 ± 1.7 , 1.2 ± 1.3 vs. 2.1 ± 1.7 , 3.2 ± 1.6 , 4.4 ± 1.2 , 3.3 ± 1.1 , 2.1 ± 1.2 respectively; $P < 0.05$). Total numbers of epidural boluses were significantly less in Gabapentin group (3.4 ± 1.6 vs. 5.6 ± 2.1 , $P < 0.05$). They concluded that preemptive use of Gabapentin 300mg orally significantly reduces the number of postoperative epidural bolus requirements and postoperative pain in patients undergoing total abdominal hysterectomy under combined spinal epidural anaesthesia.

9. European Journal of Anaesthesiology ,2009, 26(9):772-6. Sen H,Sizlan A,Yanarates O,Senol MG,Inangil G,Sucullu I, Ozkan S,Dagli G et al .The effects of gabapentin on acute and chronic pain after inguinal herniorrhaphy:

Sixty male patients aged 20-40 years were scheduled for unilateral inguinal herniorrhaphy under spinal anaesthesia were included in this study. The gabapentin group (n=30) received single-dose 1.2 g oral gabapentin 1 h before surgery, and the placebo group received a placebo capsule instead. Spinal anaesthesia was performed with heavy bupivacaine, and all operations were performed by the same surgeon with the same technique. Postoperative analgesia was evaluated during sitting and lying with a visual analogue scale. Assessment of postoperative pain at 1, 3 and 6 months was carried out with an 11-point numerical rating scale; 0 indicating 'no pain' and 10 indicating 'worst pain imaginable'. When compared with the placebo group, the gabapentin group displayed significantly lower visual analogue scale scores (lying and sitting) and total tramadol consumption at 8, 12, 16, 20 and 24 h after surgery ($p < 0.05$) and higher postoperative patient satisfaction scores ($p < 0.05$). Numerical rating scale scores at 1, 3 and 6 months after surgery were lower in the gabapentin group than in the placebo group ($p < 0.05$). They concluded that preoperative single-dose gabapentin decreases the

intensity of acute postoperative pain, tramadol consumption and the incidence and intensity of pain in the first 6 months after inguinal herniorrhaphy.

10. Saudi journal of anaesthesia 2009, volume : 3, issue : 1, page : 25-28.

Sussan Soltani Mohammadi, Mirsadegh Seyedi et al. **Comparing oral gabapentin versus clonidine as premedication on early postoperative pain, nausea and vomiting following general anesthesia:**

120 ASA I and II patients were scheduled for elective abdominal surgery were randomly assigned to receive either 0.2mg oral clonidine (n=40) or 300mg gabapentin (n=40) or placebo (n=40) 1hr before surgery. They were anesthetized using the same technique. Demographic data, post operative visual analogue scale (VAS), PONV and total morphine consumption by PCA pump were recorded in the recovery room and during first 6 hr after surgery. Two patients in gabapentin compared with 13 patients in clonidine group ($p<0.05$) and 29 patients in placebo group ($p<0.05$) had VAS >3 in recovery room. The mean morphine consumptions were 4.75 ± 7.5 , 1.95 ± 5.51 and 1.56 ± 1.5 mg in placebo, clonidine and gabapentin group with significant differences ($p<0.05$). These measurements were 18 ± 15.8 , 13.1 ± 12.6 and 12.1 ± 12.9 mg respectively during first 6 hr after surgery with significant differences ($p<0.05$). PONV was not statistically different between the study groups in the recovery room and during first 6 hr after the surgery.

11. **Saudi journal of anaesthesia 2010 , volume 4, issue 3, page 137-141.**
Harshel G Parikh, Sananta Kumar Dash, Chitra B Upasani. **Study of the effect of oral gabapentin used as preemptive analgesia to attenuate post operative pain in patients undergoing abdominal surgery under general anesthesia.**

In this study 60 patients were divided into two groups. Group A received 600mg gabapentin and group B oral received placebo 1 h prior to surgery. Surgery was done under general anaesthesia. Assessment of post-operative pain was made with the visual analog score (VAS) at extubation (0 h), 2, 4, 6, 12, and 24 h post-operatively. Post-operative analgesia was provided with intravenous Tramadol. The first dose was given in the post anesthesia Care Unit as 2mg/kg, and repeated at 8 and 16 h. Rescue analgesia was given with diclofenac 1.5mg/kg, slow intravenous. The number of doses of rescue analgesia in both the groups was noted. The VAS scores at 0, 2, 4, 6, 12, and 24 h were 1.9 vs. 2.4 ($p=0.002$), 2.3 vs. 3.0 ($p=0.000$), 3.2 vs. 3.7 ($p=0.006$), 2.9 vs. 4.4 ($p=0.000$), 3.6 vs. 4.6 ($p=0.000$), and 3.7 vs.4.6 ($p=0.000$), respectively. Numbers of patients requiring rescue analgesia with diclofenac were 3 vs. 14 ($P=0.004$).

MATERIALS AND METHODS

After Institute ethical committee approval and written consent from the patients, A randomized double blind control study was conducted at Government Rajaji Hospital attached to Madurai Medical College, Madurai.

PROTOCOL

Inclusion criteria

60 patients who were posted for lower limb orthopedic surgeries, in the age Group of 18 – 60 years in the ASA I and II grade were included.

Exclusion criteria

Patients who were contraindicated to central neuraxial blockade

Age > 60yrs

Known allergic patients to local anesthetics, and Gabapentin

DESIGN

Patients were divided into two groups. 30 patients in each group

Group G– Patients received cap. Gabapentin 1200 gram (3 capsules of 400mg)

Group P – Patients received three placebo capsules

METHOD

Preoperatively, patients were given three capsules of 400mg Gabapentin or three placebo capsules according to their group one hour before surgery .

Under strict aseptic precautions patient in sitting position, epidural space identified by using 18G Tuohy needle with loss of resistance technique at L2-L3 inter vertebral space. After the epidural space was identified, epidural catheter was inserted and 4 cm length of catheter kept inside the space. A test dose of 3ml of 1.5% lignocaine with 15µg adrenaline was given .

After excluding inadvertent subarachnoid or intravascular placement of catheter, Subarachnoid block was performed at L3- L4 Inter space by using 23G Quincke type spinal needle. 3ml of Inj. Bupivacaine 0.5% (heavy) was injected into the subarachnoid space. Patient positioned supine gently. When the sensory blockade reached T10 level, surgery was commenced.

Intra operatively pulse rate, respiratory rate, blood pressure , saturation of Hb (**SpO₂**) , urine output were monitored. After the surgery , patient was shifted to ICU for post operative pain management. In the ICU, post operative epidural analgesia was given in the dose of Inj. Bupivacaine 0.125% 8 ml with Fentanyl 2 µg / ml and time of epidural analgesic supplementation was noted.

On next day morning at 8.30am, three Gabapentin capsules (or) Placebo capsules were given respectively according to their groups. If side effects were present they were treated accordingly.

PARAMETERS OBSERVED

1. Time to reach T10 segment sensory block - since the time of subarachnoid block to loss of pin prick sensation at T10
2. Two segment regression time in subarachnoid block (in minutes) - time to regress sensation to pin prick two segments from the highest level of blockade.
3. Time to require first epidural top up since the time of subarachnoid block performed (when VAS score > 5)

Visual analogue pain score :

Patients were asked to mark a point on the 10 point visual analogue scale of Pain according to the intensity of pain . It was observed every hour . The pain relief is graded according to VAPS as follows: (Elbaz. 1984).

VAPS	QUALITY OF ANALGESIA
0 - 1	Excellent
1 - 4	Fair
4 - 6	Good

6 - 8 Slight

8 -10 No relief

4. Ramsay sedation score every 4 hours up to 48 hours since the time the study drug was given

Ramsay Sedation Score

1-Anxious / Restless / Both

2-Cooperative / Oriented

3-Responds to commands only

*4-Brisk response to light touch / Glabellar tap / loud auditory
stimuli*

5-Sluggish response to light touch / glabellar tap

6-No response at all

5. Total number of epidural supplementations

6. Time interval between each epidural analgesic supplementation

7.Side effects like dizziness, headache, nausea, vomiting, ataxia, bradycardia

OBSERVATIONS AND RESULTS

Data analysis was done with the help of computer using **Epidemiological Information Package (EPI 2008)**. Using this software range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. Kruskal Wallis chi-square test was used to test the significance of difference between quantitative variables. A 'p' value less than 0.05 is taken to denote significant relationship.

AGE

Age distribution in the Gabapentin (group G) was between 18 years to 60 years with mean age of 41.5 years \pm 15.8 (S.D.). In the placebo group (group P) age distribution was between 18 years to 60 years with mean value of 41.9 years \pm 10.9(S.D.) The Observed difference between the two groups in age is statistically not significant ('p' = **0.08243**, **>0.05**) (Table 1, **figure 10**)

SEX

Total number of male patients in group G was 19, in group P is 23 and number of female patients in group G was 11, in group P 7. Sex distribution is not statistically significant ('p' = **0.398** **>0.05**) between the two groups.

(Table 1, **figure 11**)

FIG. 10.AGE DISTRIBUTION

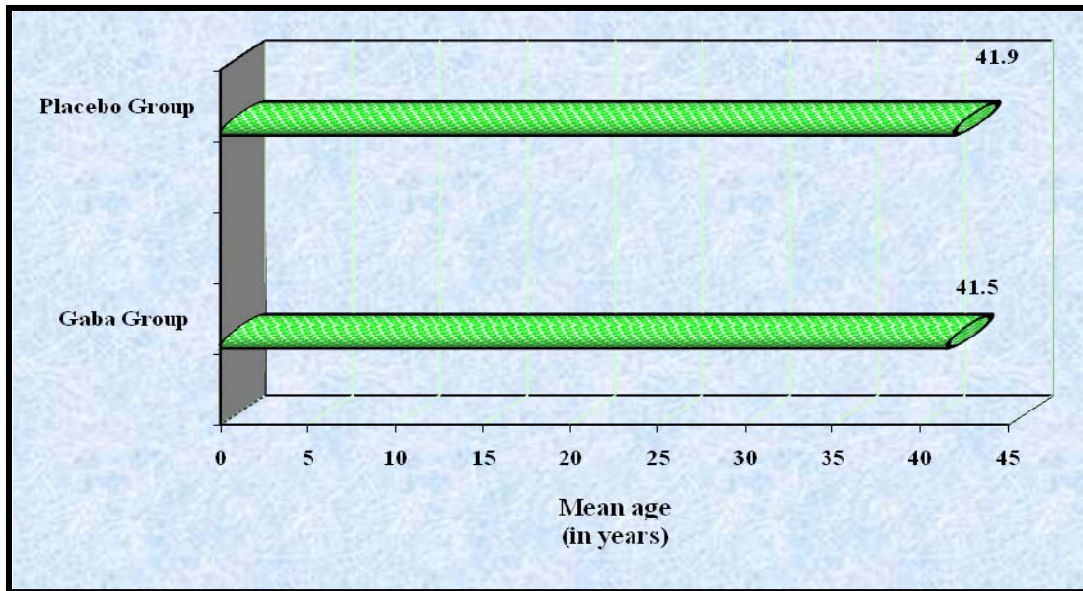
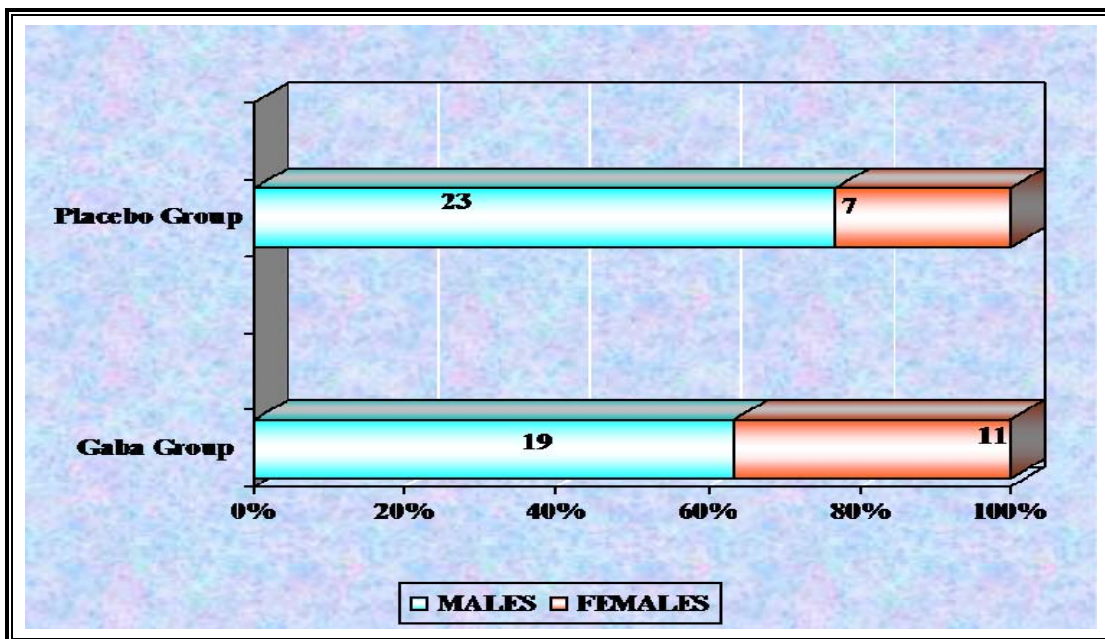


FIG .11.SEX

DISTRIBUTION



HEIGHT & WEIGHT

The height distribution in Gabapentin group (Group G) varied from 154cm - 167cm and the mean height was 160.8 cm \pm 3.8(SD). The height distribution in placebo group (Group P) varied from 156 -167 cm and the mean height was 162.1cm \pm 3.4(SD). (Table 1, **figure 12**)

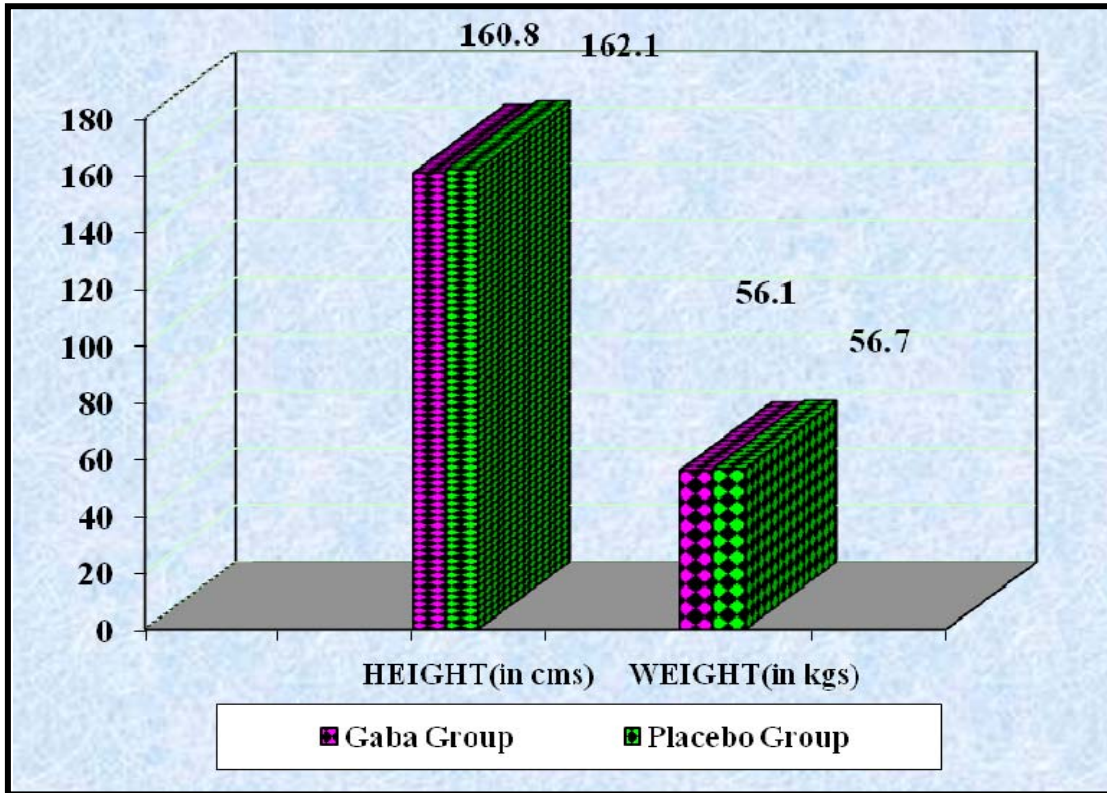
The weight distribution of the patients in Gabapentin Group (GroupG) varied from 50 -62 kgs and the mean weight was 56.1kg \pm 3.3(SD) and placebo Group (GroupP) varied from 52 -62 kg and the mean weight was 56.7 kg \pm 2.8(SD) (Table 1, **figure 12**)

Table 1. AGE,SEX, HEIGHT AND WEIGHT

Group	Age	Sex		Height(cm)	Weight(kg)
	Mean \pm SD	Male	Female	Mean \pm SD	Mean \pm SD
Group G	41.5 \pm 15.8	19(63.3%)	11(36.7%)	160.8 \pm 3.8	56.1 \pm 3.3
Group P	41.9 \pm 10.9	23(76.7%)	7(23.3%)	162.1 \pm 3.4	56.7 \pm 2.8
'p'	0.08243	0.398		0.2243	0.3381

The height (**'p'** =**0.2243**) and weight (**'p'** =**0.3381**) distribution between the two groups are statistically not significant (**'p'**>**0.05**)

FIG.12.HEIGHT AND WEIGHT



DURATION OF SURGERY

Duration of surgery in Galapentin group (Group G) varied from 90 -180 minutes and the mean duration was 134.4 minutes \pm 19.9(SD)

Duration of surgery in placebo group (Group P) varied from 105 -180 minutes and the mean duration of surgery was 138 minutes \pm 18.6(SD).the

observed difference between the two groups in duration of surgery is statistically not significant('p' =0.5346, >0.005) (Table 2,figure 13)

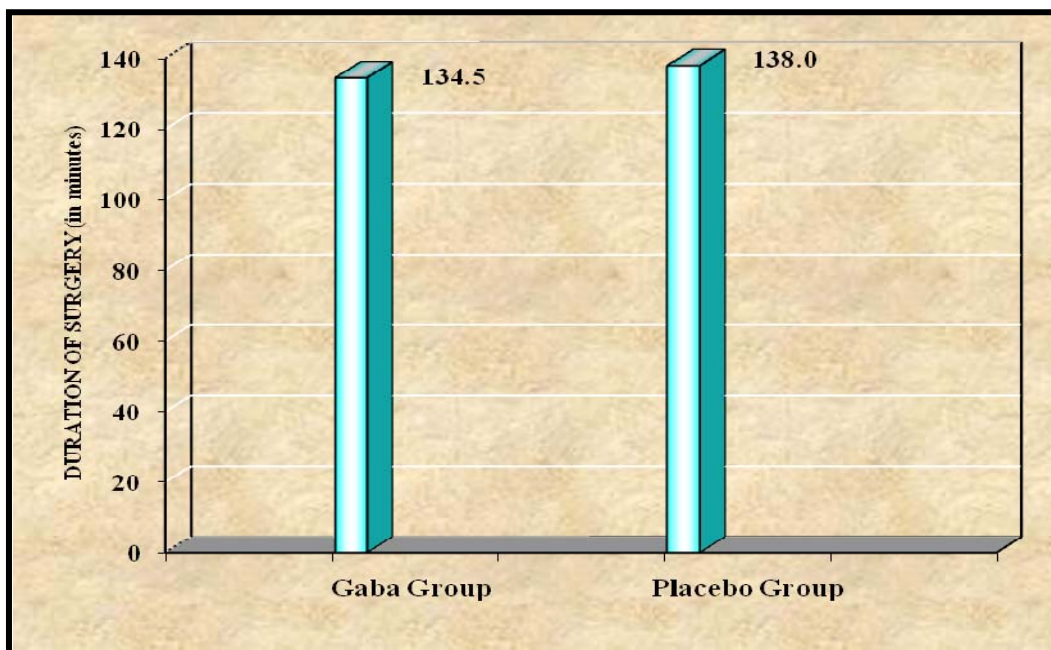
Table.2 . DURATION OF SURGERY

Duration of surgery(minutes)	Group G	Group P
Range	90 -180	105 -180
Mean± S.D	134.5±19.9	138±18.6
'p'	0.5346 (Not significant)	

HEMODYNAMIC PARAMETERS

Pulse rate, blood pressure, respiratory rate, saturation monitored in every 15 mints intra operatively in both groups

FIG .13.DURATION OF SURGERY



PULSE RATE

The changes in intraoperative pulse rate in both group statistically not significant (**'p'** = **0.2287**, > **0.05**) The mean pulse rate in (Group G) Gabapentin group was 86.5 ± 2.8 (SD) whereas in placebo group (group P) was 83.9 ± 6.0 (SD) (Table 3,**figure 14**)

BLOOD PRESSURE

The mean systolic blood pressure during the intra operative period in Gabapentin group (group G) was $116.5 \text{mmHg} \pm 3.1$ (SD).The mean systolic blood pressure in placebo group (group P) was $116.3 \text{mmHg} \pm 3.2$ (SD).The changes in systolic blood pressure during intraoperative period between the two groups is statistically not significant (**'p'** = **0.859**,> **0.05**) . (Table 3,**figure 15**)

The mean diastolic blood pressure in Gabapentin group (Group G) was $74.0 \text{mmHg} \pm 2.8$ (SD) and that in placebo group (group P) was $73.1 \text{mmHg} \pm 2.6$ (SD).Changes in diastolic Blood pressure between the two groups is statistically not significant (**'p'** = **0.8941**, >**0.05**). (Table 3,**figure 16**)

FIG.14.PULSE RATE

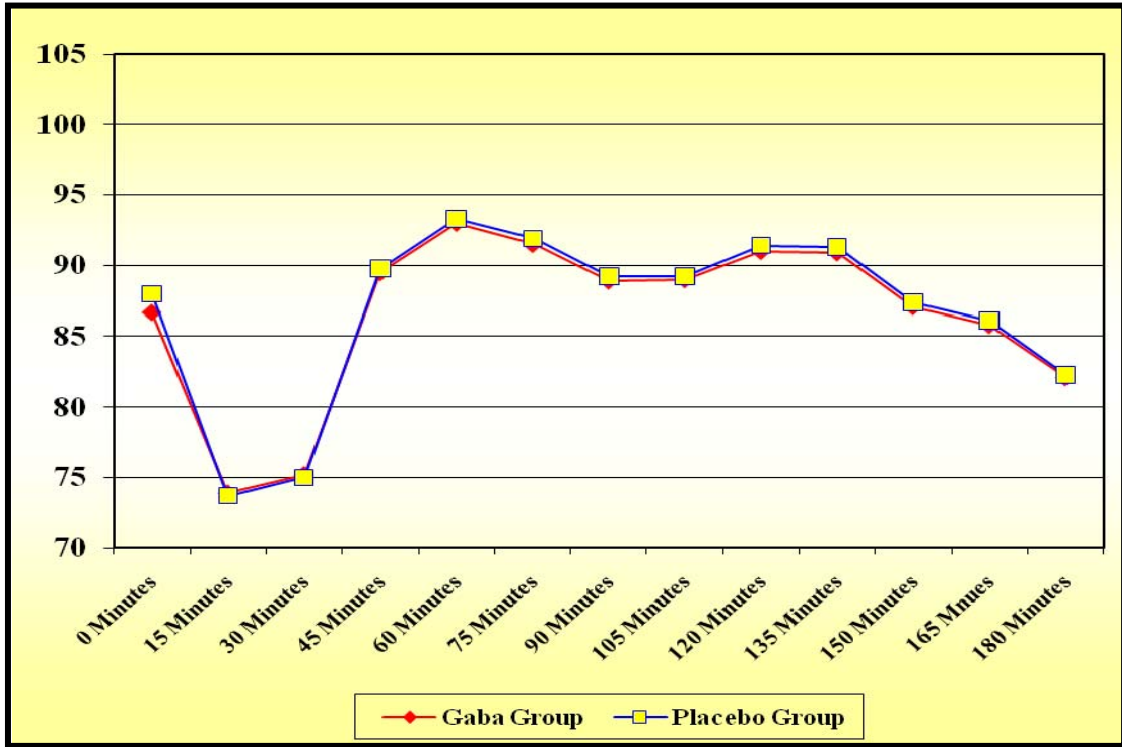


Table . 3. PULSE RATE AND BLOOD PRESSURE

Group	Pulse rate/min		Systolic BP (mmHg)		Diastolic BP(mmHg)	
	Mean ±SD	Percentage Changes Mean ±SD	Mean ±SD	Percentage changes Mean ±SD	Mean ±SD	Percentage Changes Mean ±SD
Group G	86.5 ±2.8	5.4 ±5.9	116.5 ±3.1	1.9 ±7.4	74.0 ±2.8	3.4 ±8.7
Group P	83.9 ±6.0	6.2 ±6.6	116.3 ±3.2	1.2 ±7.8	73.1 ±2.6	2.9 ±8.9
‘p’	0.2287	0.6711	0.8359	0.6623	0.8941	0.8881

Respiratory Rate and Saturation Of Hb (SpO₂)

The mean respiratory rate in Gabapentin group (group G) 14.9 ± 0.5 (SD) and that in placebo group was 15.3 ± 1.9 (SD). The mean saturation of Hb in Gabapentin group (group G) was 97.6 ± 1.4 (SD) and in placebo group (group P) was 98.3 ± 1.5 (SD).The changes in respiratory rate and saturation are statistically not significant(**‘p’** >**0.05**) (Table 4,**figure** 17,18,)

FIG.15.SYTOLIC BLOOD PRESSURE

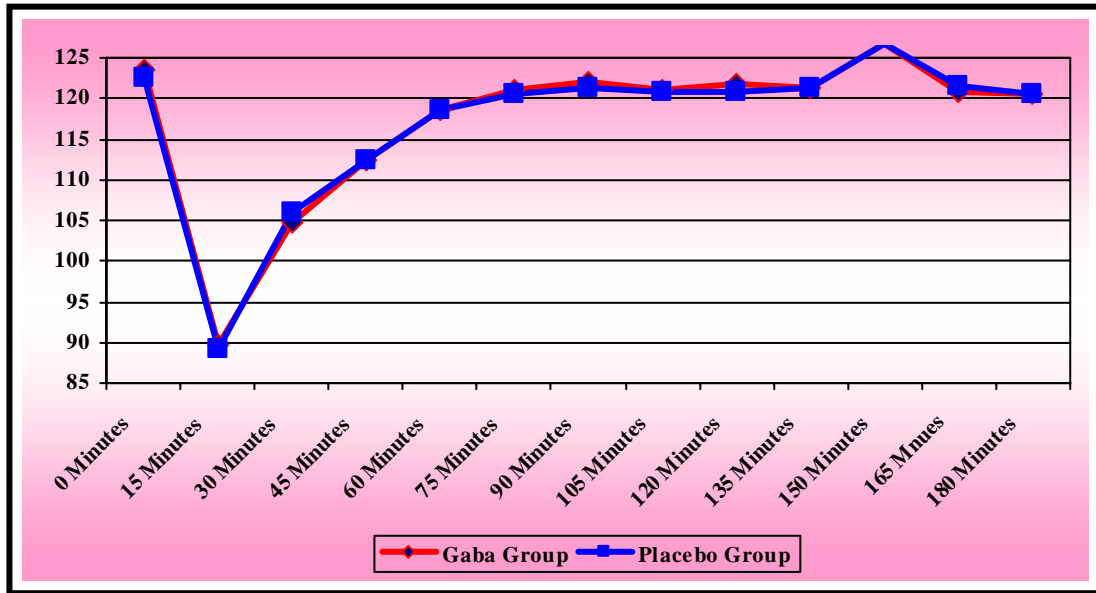


FIG.16.DIASTOLIC BLOOD PRESSURE

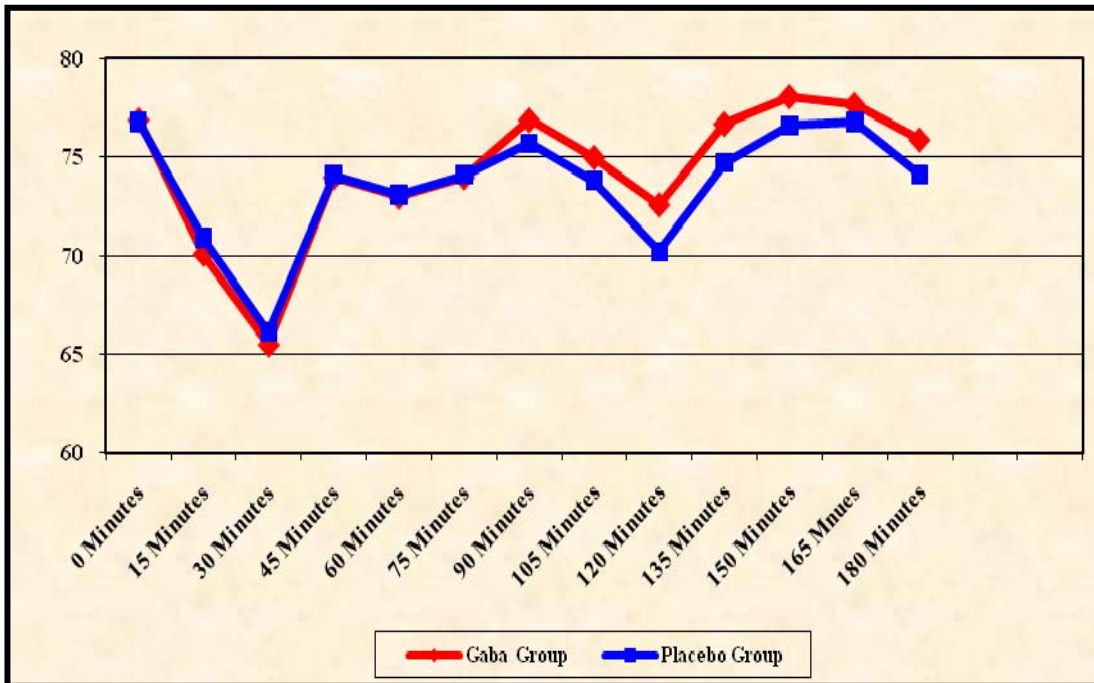


Table .4.RESPIRATORY RATE AND SATURATION

Group	Respiratory rate/min		Saturation of Hb
	Mean \pm SD	Percentage Changes Mean \pm SD	Mean \pm SD
Group G	14.9 \pm 05	-3.7 \pm 13.2	97.6 \pm 1.4
Group P	15.3 \pm 1.9	-1.3 \pm 10.0	98.3 \pm 1.5
'p'	0.6133	0.7079	0.0514

FIG.17.RESPIRATORY RATE

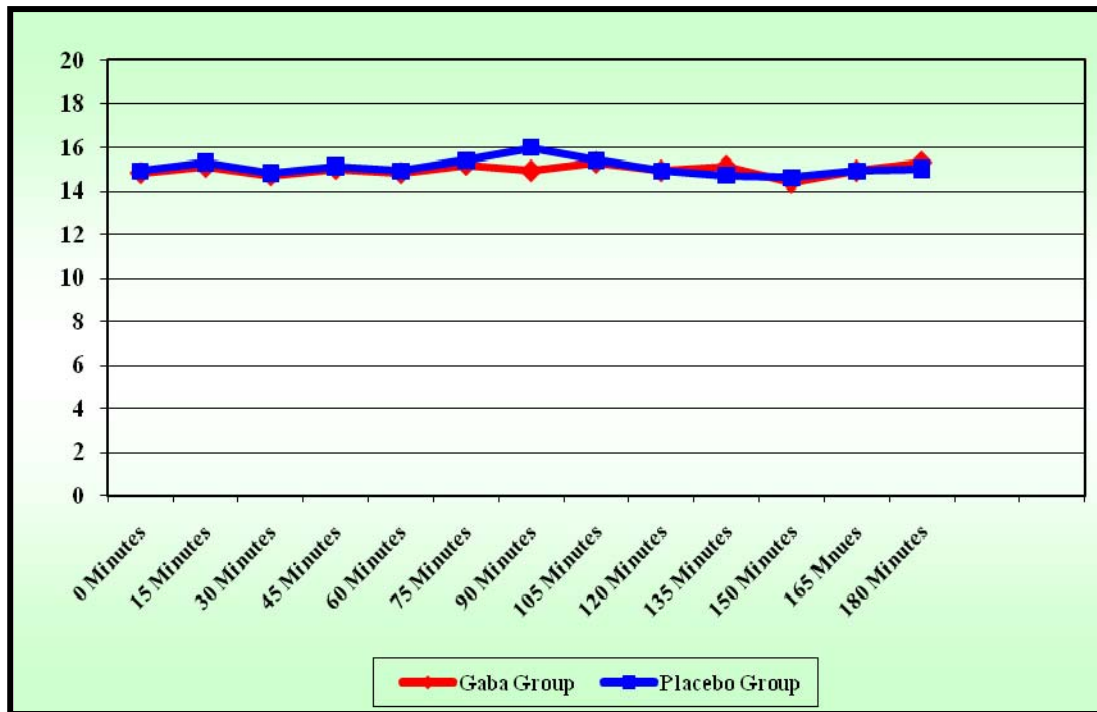
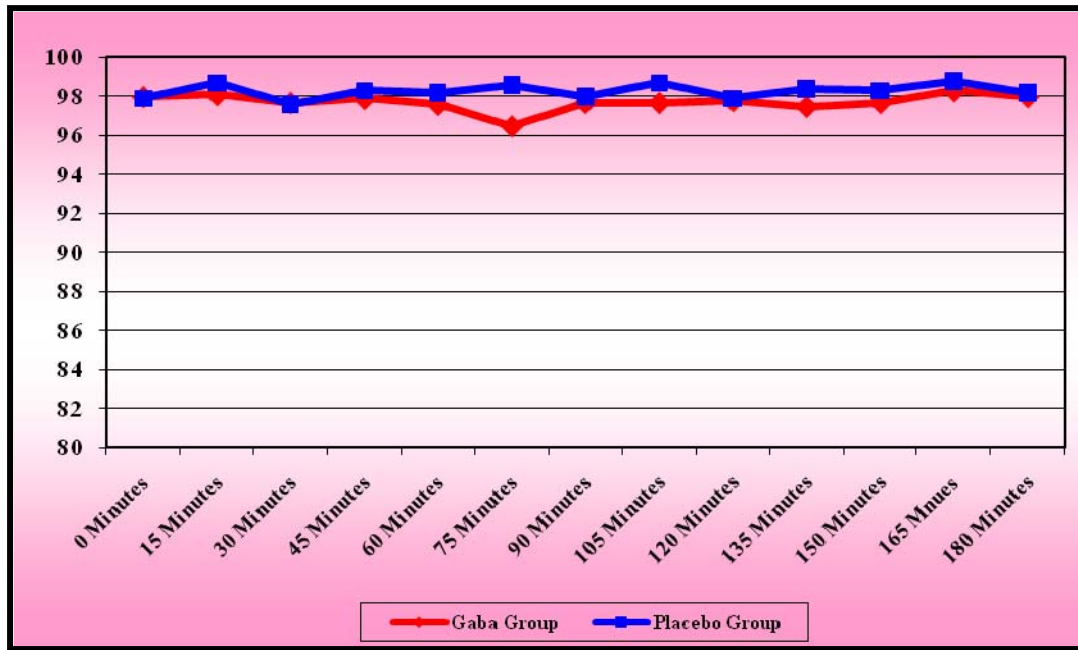


FIG.18.SATURATION OF HB



SEDATION SCORE

Ramsay sedation score was monitored every 4 hours since the oral capsules given up to 48 hours and compared in both groups.

The mean sedation score on day 1 in Gabapentin group (group G) was 2.33 ± 0.48 (SD) and that in placebo group was 1.83 ± 0.38 (SD). The mean sedation score on day 2 in group G was 2.17 ± 0.38 (SD) and that in group P was 1.4 ± 0.5 (SD). The observed difference between the two groups in sedation score is statistically significant ($'p' < 0.05$) (Table 5, **figure 19,20**.)

Table .5. SEDATION SCORE

Day	Group G	Group P	'p'
	Mean± SD	Mean± SD	
Day 1	2.33±0.48	1.83±0.38	0.0401
Day2	2.17±0.38	1.4±0.5	0.0001

FIG.19. RAMSAY SEDATION SCORE DAY 1

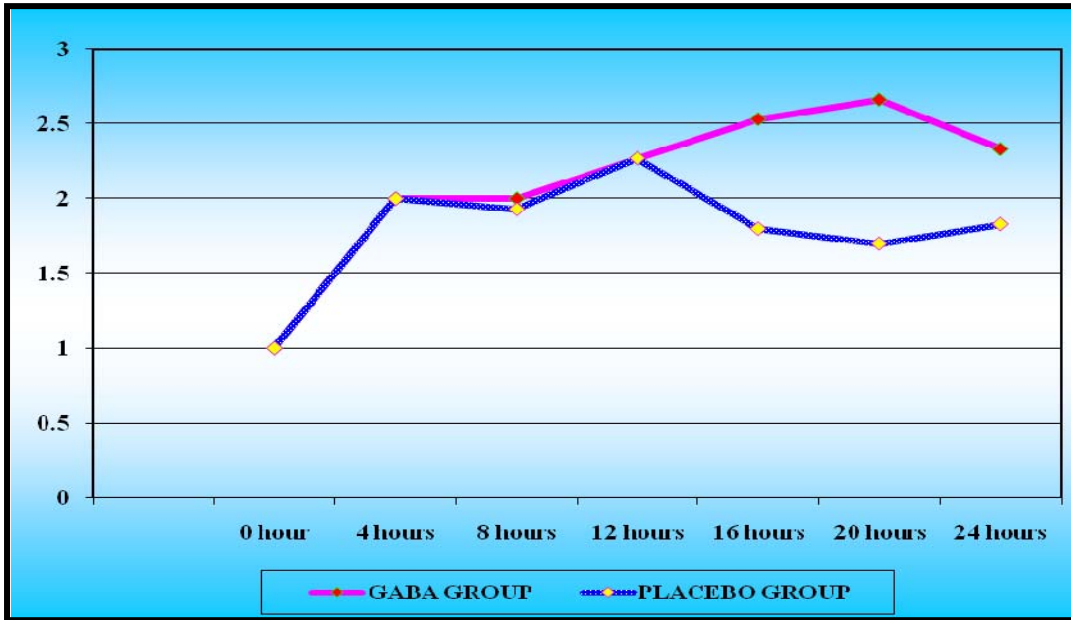
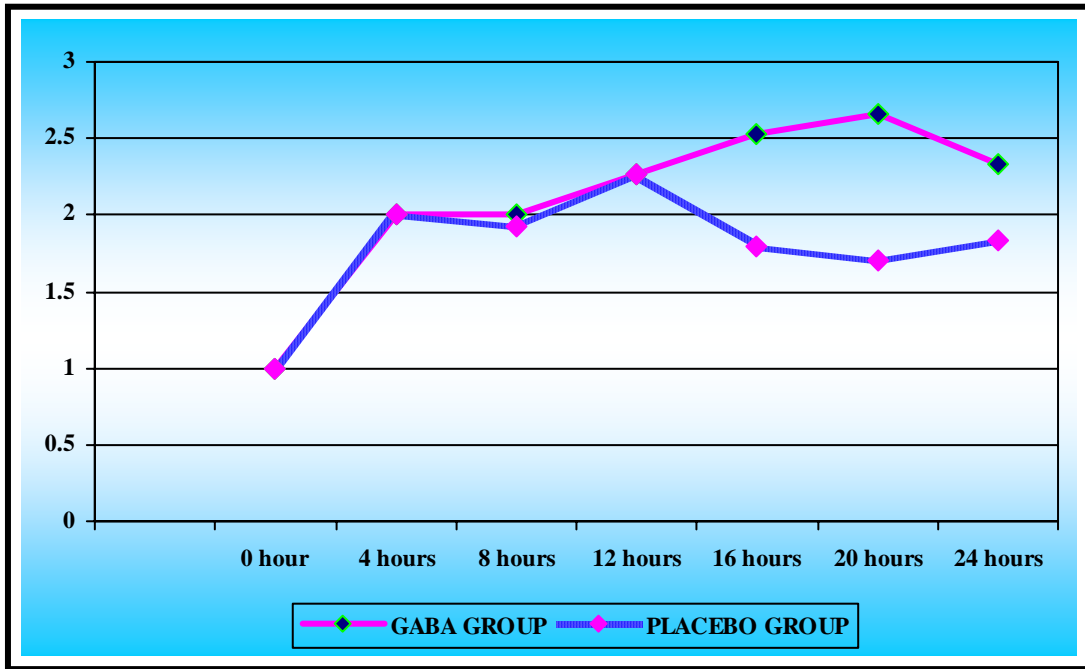


FIG.20. RAMSAY SEDATION SCORE DAY 2



SIDE EFFECTS

Most commonly noted side effects in this study were dizziness, and headache. Dizziness was reported in Gabapentin group (Group G) in 7 patients (23.3%) whereas in placebo group (Group P) it was not reported in any patients.

Headache was reported in Gabapentin Group (Group C) in 5 patients (16.7%) where as in placebo group(group P) it was reported in 8 patients (26.7%)

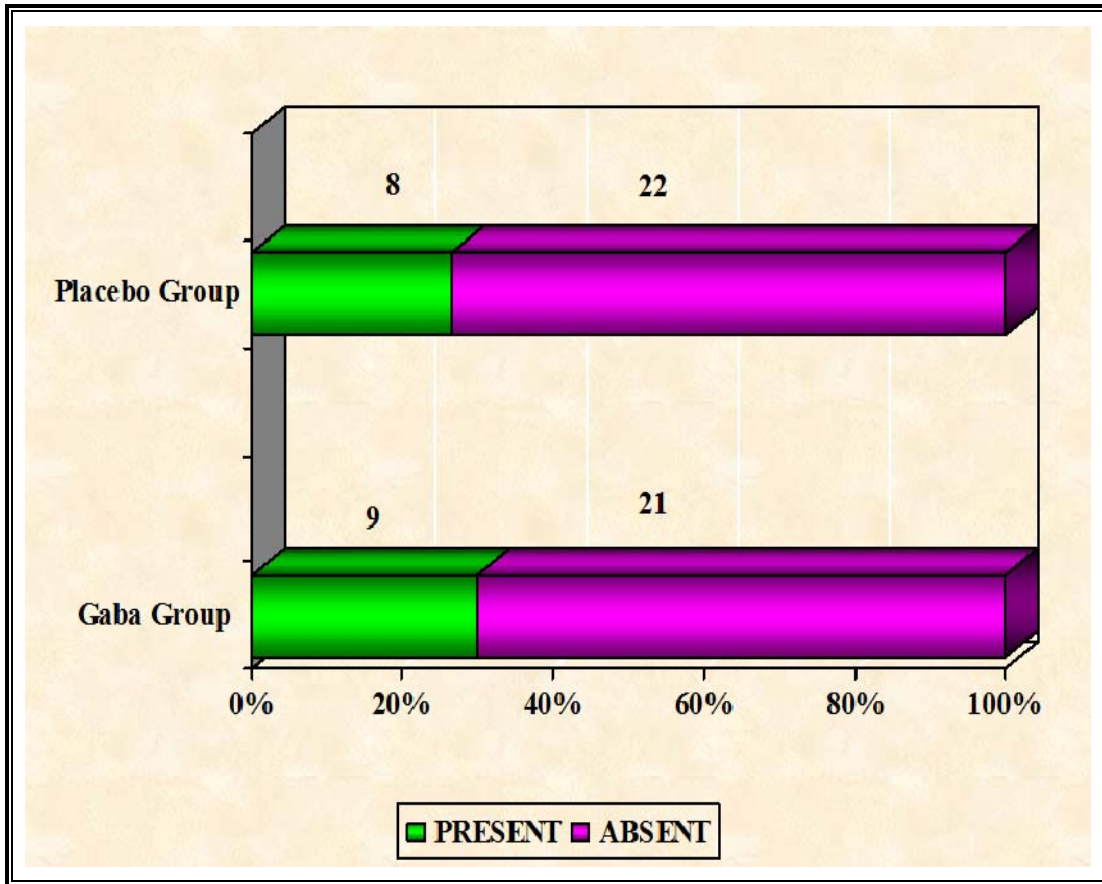
Totally 9 patients reported side effects in Gabapentin Group (Group G) where as 8 patients in placebo group (Group P) .On comparison of the incidence of side effects between the two groups are statistically not significant

('p'= 0.7763 , >0.05) (Table 6,figure 21)

6.SIDE EFFECTS

Side effects	Group G		Group P	
	No	%	No	%
Dizziness	7	23.3	-	-
Head ache	5	16.7	8	26.7
Nausea	-	-		
Vomiting	-			
Pruritus	-			
Ataxia	-			
Side effects present	9	30	8	26.7
Side effects absent	21	70	22	73.3
'p'	0.7763			

FIG .21.SIDE EFFECTS



TIME TO REACH T10 SEGMENT SENSORY BLOCK

Mean duration of time to reach T10 segment sensory blockade in Gabapentin group (group G) was 4.77 minutes \pm 0.97(SD) and that in placebo group (group P) was 4.53 minutes \pm 0.9(SD). The observed difference in time to

reach T10 segmental block between the two groups is statistically not significant ($p = 0.2499, >0.05$) (Table .7, figure 22)

FIG.22.MEAN TIME TO REACH T10 SEG BLOCK

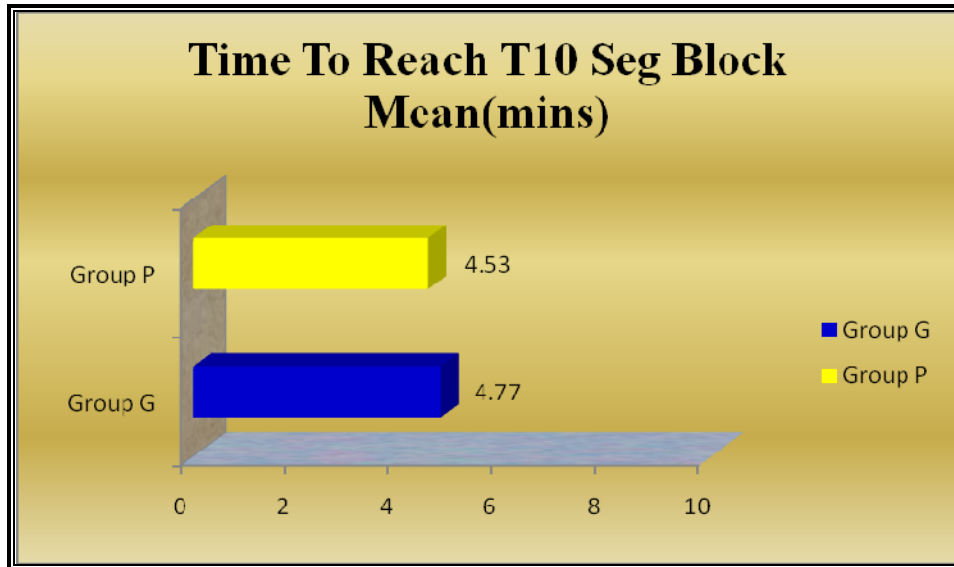


FIG.23.TWO SEGMENT REGRESSION TIME

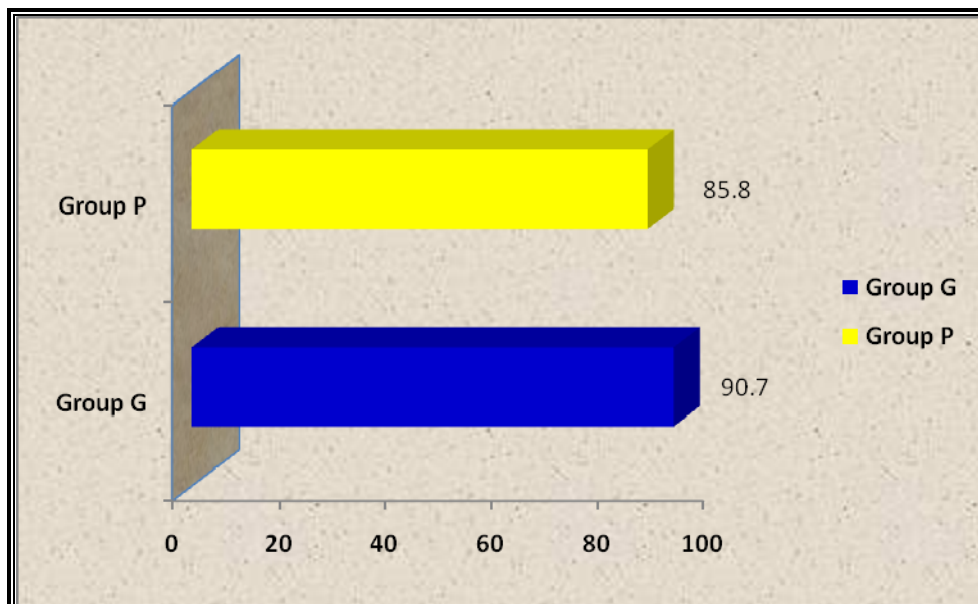


Table. 7.TIME TO REACH T10 SEGMENT SENSORY BLOCKADE

Group	Mean(minutes)±SD	'p'
Group G	4.77±0.97	0.2499
Group P	4.53±0.9	

TWO SEGMENT REGRESSION TIME

Mean time to regress by two segments from the higher level of blockade in group G was 90.7 mints ± 4.7 (SD) and that of in group P was 85.8 min ± 3.5(SD). The observed difference between the two groups in two segment regression time is statistically significant (**'p'**=**0.0001**,<**0.05**) (Table.8,**figure 23**)

Table.8. TWO SEGMENT REGRESSION TIME

Group	Two segment regression(minutes)	'p'
	(Mean) ±SD	
Group G	90.7±4.7	0.0001
Group P	85.8±3.5	

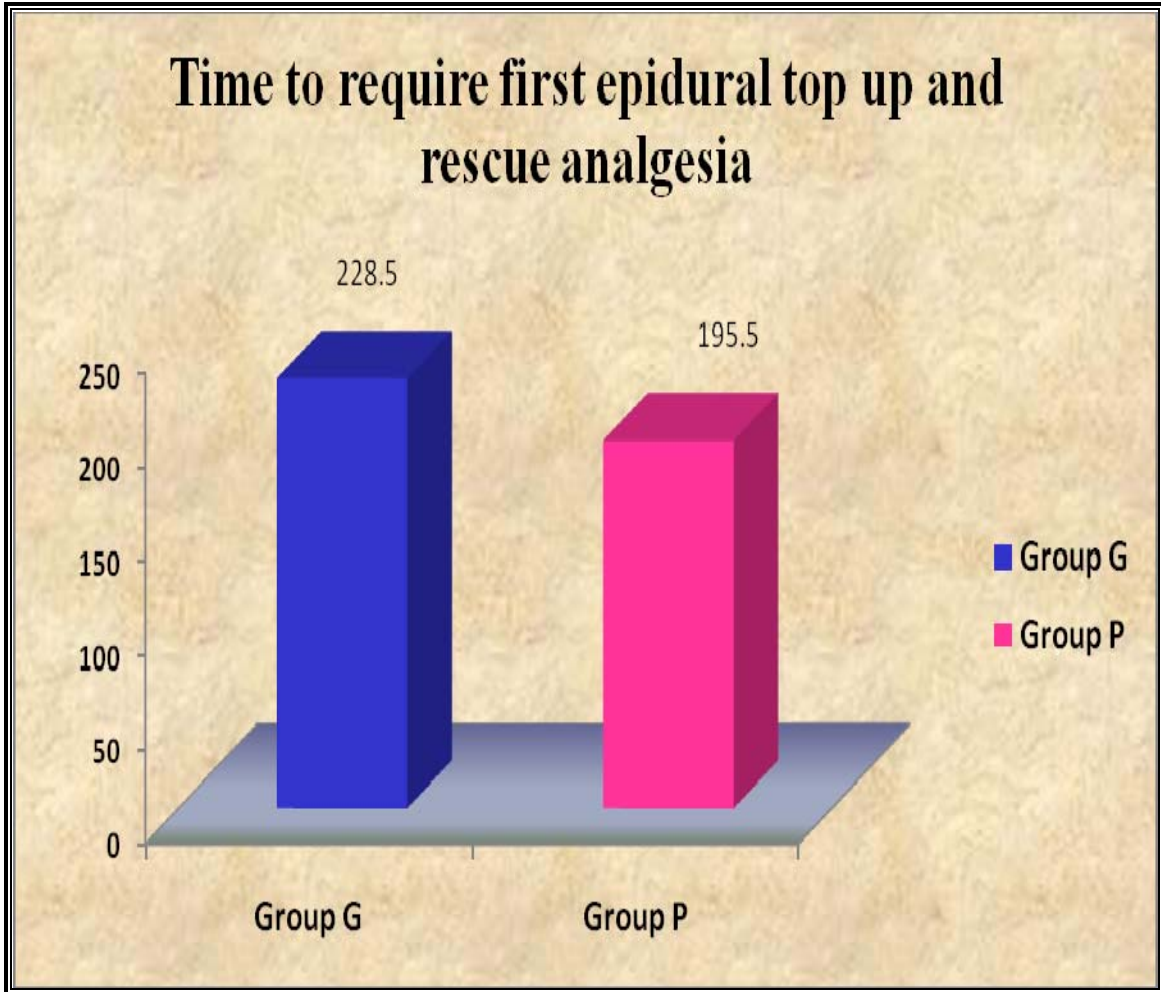
TIME TO REQUIRE FIRST EPIDURAL ANALGESIC SUPPLEMENTATION

The mean time duration to require first epidural supplementation in Gabapentin group (group G) was 228.5 minutes \pm 19.96(SD) and that in placebo group was 195.5 minutes \pm 13.3(SD). The observed difference between the two groups in time to require first epidural analgesic supplementation is statistically significant (‘p’=0.0001, <0.05) (Table 9,figure 24)

Table 9.TIME TO REQUIRE FIRST EPIDURAL SUPPLEMENTATION

Group	Time to require first epidural analgesic supplementation	‘p’
	Mean \pm SD	0.0001
Group G	228.5 \pm 19.96	
Group P	195.5 \pm 13.3	

FIG.24. TIME TO REQUIRE FIRST EPIDURAL SUPPLEMENTATION



TIME INTERVAL BETWEEN THE EPIDURAL ANALGESIC SUPPLEMENTS

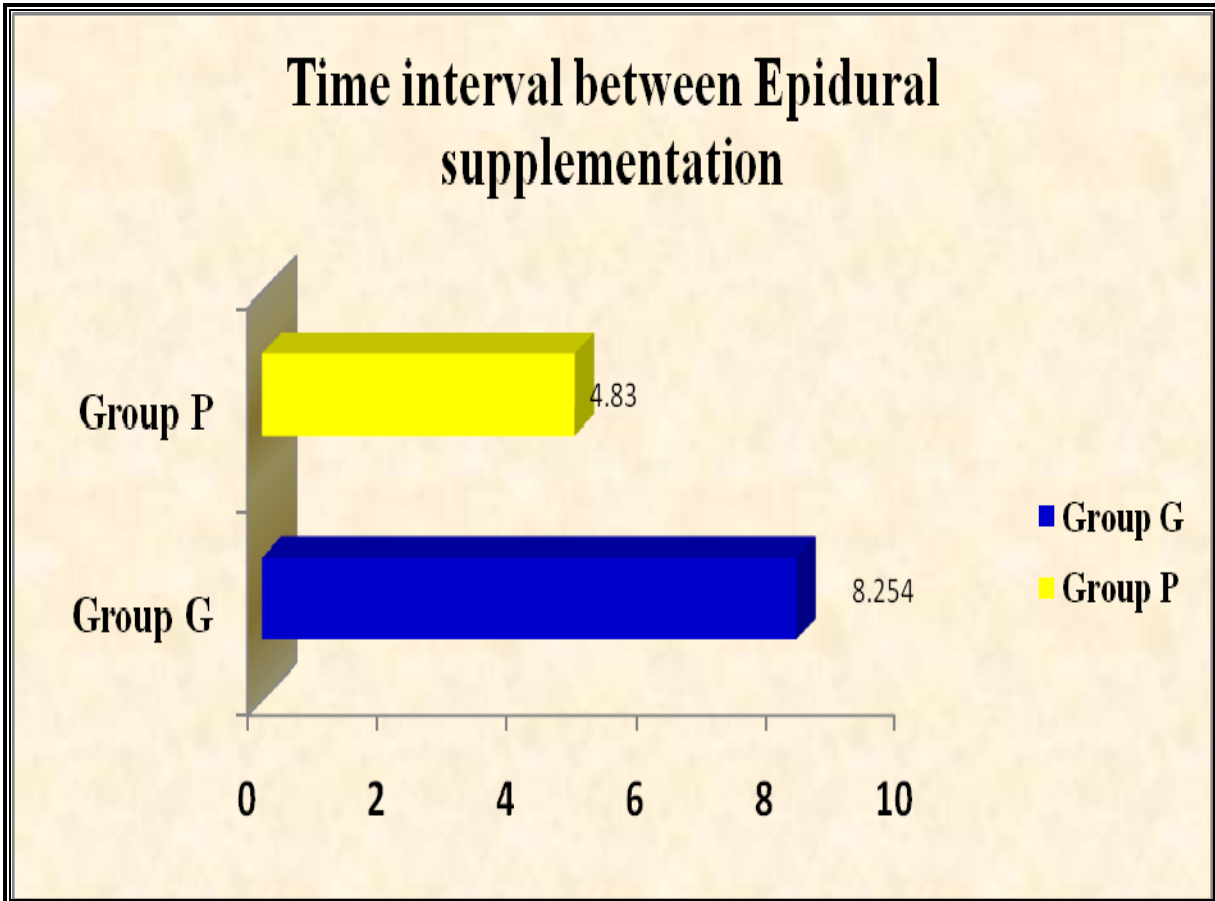
The time interval between the each epidural analgesic supplements in both groups were compared by using simple 't' test.

The mean time interval in Gabapentin group (group G) was 8.254hrs \pm 1.5276(SD) and the same in placebo group was 4.8 hours \pm 0.529(SD). The observed difference between the two groups in the time interval between the epidural analgesic supplements is statistically significant ('p'=0.0001, <0.05) (Table.10,figure 25)

Table.10. TIME INTERVAL BETWEEN THE EPIDURAL ANALGESIC SUPPLEMENTS

Group	Mean \pm SD	'p'
Group G	8.254 \pm 1.5276	0.0001
Group P	4.83 \pm 0.529	

FIG .25.TIME INTERVAL BETWEEN EPIDURAL ANALGESIC SUPPLEMENTS



TOTAL NUMBER OF EPIDURAL ANALGESIC REQUIREMENTS

DAY 1

Mean number of Epidural analgesic requirements in Gabapentin group (group G) was 2.07 ± 0.25 (SD) and the same in placebo group (group P) was 2.93 ± 0.25 (SD)

Day 2

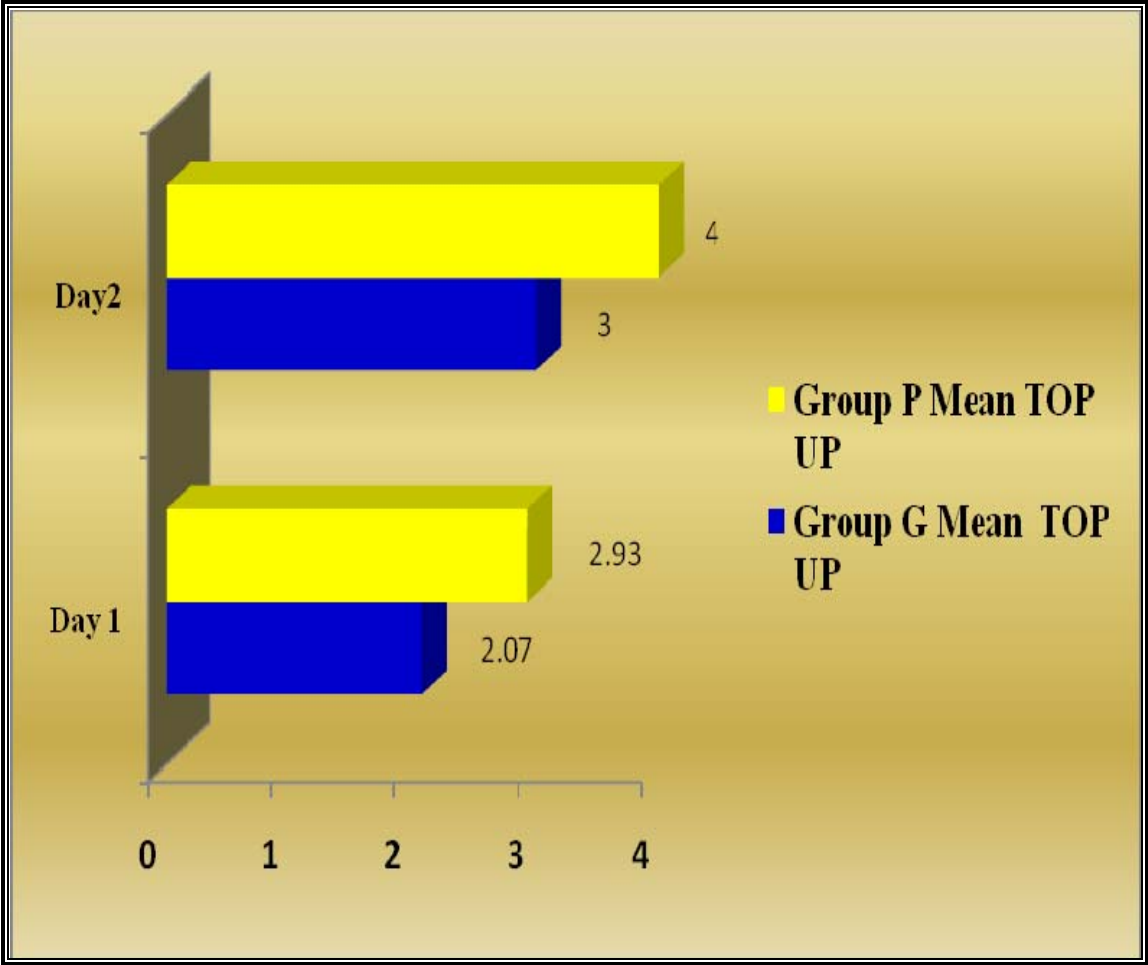
Mean number of Epidural analgesic requirements in Gabapentin group (group G) was 3 and is placebo group (group P) was 4.

The observed difference between the two groups in total number of epidural analgesic requirements for two days is statistically significant ($p=0.0001, <0.05$) (Table .11,figure 26)

Table.11.TOTAL NUMBER OF EPIDURAL ANALGESIC REQUIREMENTS

Day	Group G		Group P		'p'
	Mean	SD	Mean	SD	
Day 1	2.07	0.25	2.93	0.25	0.0001
Day2	3	-	4	-	

FIG.26. TOTAL NUMBER OF EPIDURAL ANALGESIC REQUIREMENT



DISCUSSION

NMDA receptor is a complex ligand gated ion channel that mediates influx of calcium ion when activated . Partial depolarisation of the neuron after glutamine activation causes release of a magnesium plug and allows calcium influx into the neuron. These receptors are known to be found in high concentrations in the hippocampus and have been attributed a key role in the process of central sensitisation of painful stimuli, commonly known as the wind-up phenomenon, leading to hyperalgesia. The alpha 2 delta subunit of the voltage-dependent calcium channel is a binding site for Gabapentin and antihyperalgesic action for Gabapentin is mediated by its binding to this site on the voltage-dependent calcium channel.

RAMSAY SEDATION SCORE

Gabapentin has high sedative property by acting on central nervous system , and that is the main side effect. Patient may have dizziness and sedation . various studies proved that it alters sleep pattern also

The mean sedation score in gabapention group (group G) on day 1 is 2.33 , on day 2 is 2.17 and that in placebo group on day 1 is 1.83, and on day 2 is 1.4.

Ramsay sedation score is significantly higher in Gabapentin group on day1 ($p=0.0401, <0.05$) and on day 2 ($p=0.0001, <0.05$) when compared to placebo group

EFFECT ON SUBARACHNOID BLOCK

Two segment regression time

Mean time to regress by two segments from the highest level of blockade in group G is 90.7 and that in group P is 85.8 minutes Two segment regression time prolonged in Gabapentin group than placebo group which is statistically significant ($p=0.0001, <0.05$)

Time to require first epidural supplementations

The mean time duration to require first epidural analgesic supplementation (When the patient's VAS score >5), in Gabapentin group (group G) is 228.5 minutes and that in placebo group is 195.5 minutes .The time to require first Epidural analgesic requirement is prolonged in Gabapentin group than placebo group which is statistically significant ($p=0.0001, <0.05$)

These two parameter showed that Gabapentin has effect on subarachnoid block which prolongs the two segment regression time and duration of Analgesia of subarachnoid block

EFFECT ON EPIDURAL ANALGESIC REQUIREMENTS

The total number of epidural analgesic requirements

The total number of epidural analgesic requirements on day 1, varied from 1-2 supplements in Gabapentin group ,in placebo group varied from 2-3 supplements. Total number of epidural analgesic requirements on day 2, varied from 2-3 supplements in Gabapentin group ,in placebo group varied from 3-4 supplements .Totally in Gabapentin group only one patient received 6 supplementations(others received 5 supplementations) and in placebo group two patients received 6 supplementations (others received 7 supplementations)

The total number of epidural analgesic requirements are significantly less in Gabapentin group than that in placebo group (**'p' = 0.0001, < 0.05**)

Time interval between the epidural supplements

The mean time interval in Gabapentin group (group G) is 8.254hrs \pm 1.5276(SD) and the same in placebo group is 4.8 hours \pm 0.529(SD)

The time interval between each epidural supplements is significantly prolonged in Gabapentin group (group G) than in placebo group (group P) and which is statistically significant (**'p'=0.0001,<0.05**)

In this study cap. Gabapentin which was given 1 hr before surgery had no effect on time to reach T10 segment sensory blockade

The two segment regression time and time to require first epidural analgesic supplementation are significantly prolonged in Gabapentin group than placebo group .

The total number of epidural analgesic requirements is significantly lower in Gabapentin group than placebo group. The time intervals between the epidural supplements are significantly prolonged in Gabapentin group than in placebo group. Patients in Gabapentin group have better sedation score but with side effect of dizziness.

The study was done by A.Turan, G. Kaya, B. Karamanlioglu, Z. Pamukcu and C. C. Apfel et al (British journal of anesthesia 2006) showed ,up to 72 hours by using PCA pump for epidural top up , the total usage was only 38 hours in Gabapentin (1200mg) group while comparing 57 hours in placebo group. The post operative VRS pain score was also lower in Gabapentin group than in placebo.

The study of Alparslan Tauran et al (anaesthesia analgesia 2007), gabapentin for intravenous regional anaesthesia, the study of Sen H,Sizlan A,Yanarateş O,Senol MG,Inangil G et al (European journal of anaesthesia 2009), The effects of gabapentin on acute and chronic pain after inguinal

herniorrhaphy showed that 1200 mg of gabapentin which was given orally , significantly reduced rescue analgesic requirements or opioids consumption in the post operative period.

Other studies (1,2,6,7,8,10,11 of review of literature) reported 300 to 800 mg of gabapentin is effective in reducing supplemental analgesia. The study of Anil Verma, Sangeeta Arya, Sandeep Sahu, Indu Lata, HD Pandey et al (Indian journal of anesthesia 2008) with 300mg of Gabapentin 2 hr before surgery for abdominal hysterectomy showed that reduction number of 2 supplementations of epidural analgesia than in placebo group.

Christophe Menigaux, M.D., Frederic Adam, M.D., Bruno Guignard, M.D., Daniel I. Sessler et al (**Anesthesia Analgesia . 2005 May ; 100(5): 1394** (bibliography 9) showed that 1200mg of gabapentin not only reducing postoperative opioid consumption , but also reducing anxiety score significantly.

As various studies showed that using 1200mg of Gabapentin is effective in reducing opioid demand and pain score, 1200mg of Gabapentin was chosen for this study . In this study 1200 mg Gabapentin significantly reduced number of post operative epidural analgesic supplementations ,it prolonged the two segment regression time and produced better sedation also than the placebo group.

SUMMARY

60 patients of ASA I , II undergoing lower limb surgeries were randomly assigned into two groups Group G, and Group P.

Surgery was done under combined spinal epidural anaesthesia.

The patients in group G received three Gabapentin capsules (1200mg)

In group P, three placebo capsules given.

Subarachnoid block was performed with 0.5% Bupivaccaine 3ml (Hyper baric).

Epidural analgesia was given by 0.125% bupivacaine + Fentanyl 2µg/ml (8 ml volume). The parameters observed were time to reach T10 segment sensory blockade, two segments regression time, time to receive first epidural analgesic requirement, total number of epidural analgesic requirements, time intervals between each epidural supplementations , Ramsay sedation score and side effects.

This study shows that

- 1) Gabapentin does not have effect on onset of sensory Blockade of subarachnoid Block
- 2) Gabapentin prolongs two segment regression time by 5minutes compared to placebo group
- 3) Gabapentin prolongs duration of sensory blockade of spinal analgesia by 33 minutes compared to placebo

- 4) Gabapentin significantly prolongs the time intervals between the epidural analgesic requirement by 4 hours compared to placebo (8hrs vs 4hrs)
- 5) Thus Gabapentin reduces the total requirements of epidural supplementation compared to placebo
- 6) Patients in Gabapentin group have higher Ramsay sedation score (2-3) compared to placebo group (1-2)
- 7) The commonly reported side effects in Gabapentin group are dizziness, and headache. In the placebo group head ache is the commonly reported side effects and no patients in placebo group reported dizziness.

This provides an evidence of the Gabapentin action on Acute pain relief by acting on NMDA receptor and voltage gated calcium channel by acting on central nervous system

CONCLUSION

Gabapentin before surgery significantly prolongs two segment regression time and duration of analgesia in subarachnoid blockade and it significantly reduces the post operative epidural analgesia requirements.

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