A Dissertation on

" COMPARISON OF POST OPERATIVE ANALGESIA FOLLOWING EPIDURAL BUPIVACAINE AND EPIDURAL BUPIVACAINE WITH VERAPAMIL IN ORTHOPAEDIC LOWER LIMB SURGERIES"

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In partial fulfillment of the regulations
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CERTIFICATE

This is to certify that the dissertation titled **"COMPARISON OF POST OPERATIVE ANALGESIA FOLLOWING EPIDURAL BUPIVACAINE AND EPIDURAL BUPIVACAINE WITH VERAPAMIL IN ORTHOPAEDIC LOWER LIMB SURGERIES"** is the bonafide original work of **Dr.K.Sureshkumar,** a Post Graduate in Anaesthesiology at Government Stanley Medical College, Chennai, during the Academic Year 2005-2008, which is to be submitted to the **"Tamil Nadu Dr. M.G.R. Medical University**, **Chennai",** towards the Partial fulfillment of the regulations for the award of **MD Degree in Anaesthesiology** in March 2008.

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DECLARATION

I, **DR.K. SURESHKUMAR** hereby declare that the Dissertation titled on **"COMPARISON OF POST OPERATIVE ANALGESIA FOLLOWING EPIDURAL BUPIVACAINE AND EPIDURAL BUPIVACAINE WITH VERAPAMIL IN ORTHOPAEDIC LOWER LIMB SURGERIES"** was entirely done by me, under the guidance of **PROF. Dr. R.MEENAKSHI, M.D. D.A., Prof. & HOD,** Department of Anaesthesiology, Government Stanley Medical College and Hospital, in partial fulfillment of regulations for MD (Anaesthesiology) Degree Examination of the Tamil Nadu Dr.M.G.R. Medical University to be held in March 2008.

Place: Chennai

Date: **DR.K. SURESHKUMAR**

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CONTENTS

INTRODUCTION

Recent advances in neurosciences have demonstrated that peripheral tissue injury may lead to long alterations in central processing with reduction in threshold, amplification of response, expanded receptive fields and after discharges of dorsal horn neurons [6, 25]. Experimental studies have revealed that the input which are innocuous may also begin to pain. Comparable alterations may also occur in humans following surgical trauma, resulting in amplification and prolongation of postoperative pain[6, 25, 26]. Nociceptive stimulation causes neurotransmitter release which is coupled with activation of voltage-dependent calcium conductance in synaptic terminal membranes of neurons. A disruption of calcium influx into cells interferes with normal sensory processing and contributes to antinociception.

Peripheral tissue injury provokes both peripheral and central sensitization. Peripheral sensitization is a reduction in the threshold of nociceptor - afferent peripheral terminals, and central sensitization is an activity - dependent increase in the excitability of spinal neurons. There is considerable evidence that excitatory amino acids and neuropeptides are involved in nociceptive transmission in the dorsal horn of the spinal cord[1, 5]. The actions of excitatory amino acids are mediated by the N-methyl D-aspartate (NMDA) receptor and non-NMDA receptors. Activation of NMDA receptors leads to Ca^{2+} entry into the cell and initiates a series of central

sensitization such as windup and long term potentiation in the spinal cord in the responses of cells to prolonged stimuli. This activation of NMDA receptors is responsible for the induction and the maintenance of enhanced responses for prolonged periods of time. This central sensitization may be prevented not only with NMDA antagonists such as ketamine and dextrometorphan, but also with calcium channel blockers that block Ca^{2+} entry into cells. This study was therefore designed to evaluate the analgesic efficacy of bupivacaine and verapamil mixture given through lumbar epidural route in patients undergoing elective orthopaedic lower limb surgeries and comparing the quality of analgesia with epidural plain bupivacaine.

AIMS AND OBJECTIVES

1. To evaluate the analgesic efficacy of bupivacaine and verapamil mixture given through lumbar epidural route for postoperative analgesia in patients undergoing elective orthopaedic lower limb surgeries.

2. To compare the quality of analgesia of epidural bupivacaine - verapamil mixture with epidural plain bupivacaine.

3. To evaluate the hemodynamic response of epidural verapamil.

PHYSIOLOGY OF PAIN

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage". This definition recognizes the interplay between the objective, physiological, sensory aspects of pain and its subjective, emotional and psychological components. The response to pain can be highly variable among persons as well as in the same person at different times.

They are of two types - physiological and pathological pain.

I. PHYSIOLOGICAL PAIN : has been defined by C.M. Woolf [24] as the pain which we experience in our everyday lives when exposed to noxious stimuli, it is characterised as being:

1. High threshold
2. Well localised and transient.
3. Has a stimulus response relationship similar to that of other somatosensations.
4. Operates as a protective system, warning of contact with potentially damaging stimuli

This is due to the highly specialised peripheral sensory pathways that subserve these different sensations.

II. CLINICAL PAIN : Clinical pain which arises as a consequence of either inflammation due to tissue injury or neuronal injury is pathological. It is divided into inflammatory (pain due to tissue damage) and neuropathic pain (damage to nervous system). Both inflammatory and neuropathic pain are characterised by changes in sensitivity as per Raja S et al [13].

ALLODYNIA : A stimulus that would never normally produce pain begin to do so.

HYPERALGESIA : Exaggerated response to painful stimuli. They are of 2 types - Primary Hyperalgesia,
Secondary Hyperalgesia

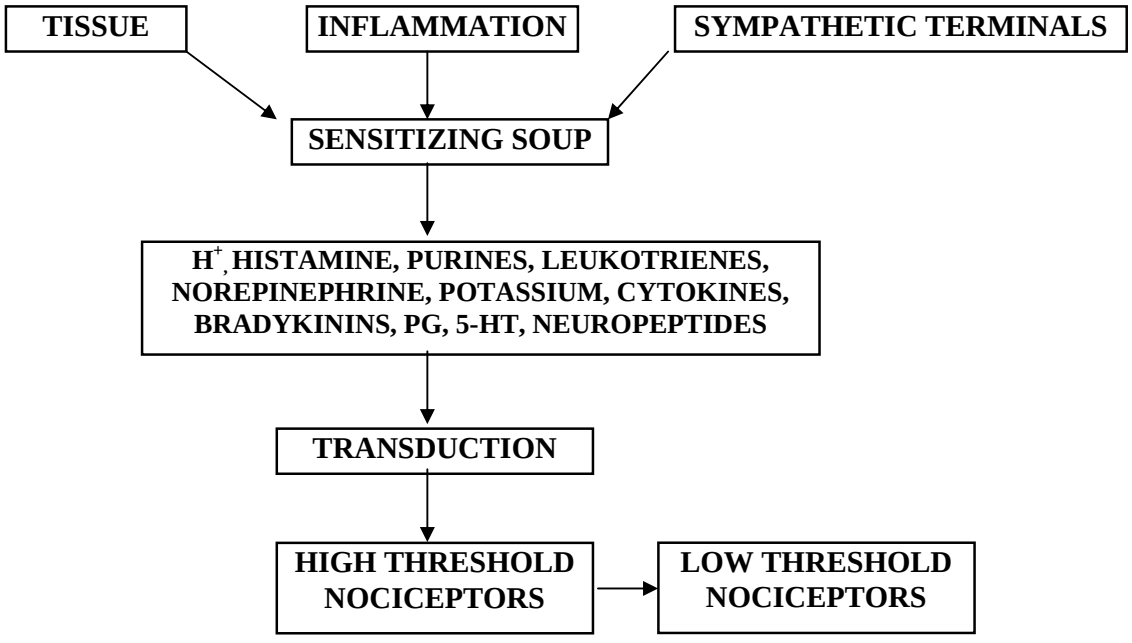
PRIMARY HYPERALGESIA : This refers to changes that occur within the site of injury. Within the site of injury, the nociceptors become sensitized and is characterised by a decrease in threshold, an augmented response to suprathreshold stimuli and occasionally by spontaneous activity.

SECONDARY HYPERALGESIA : This refers to the changes in the preinjured tissue surrounding the site of injury where again the pain threshold decreases. Both peripheral and central mechanisms have been suggested in the past to explain secondary hyperalgesia. Secondary hyperalgesia is due to

peripheral mechanism resulting from the spread of sensitization from adjoining nociceptors which were directly injured. In support of a central mechanism for secondary hyperalgesia sensitization of dorsal horn spinothalamic neurons to mechanical stimuli following cutaneous heat injury and C fibres stimulations has been demonstrated.

Two mechanisms operate to produce the changes in sensitivity found in inflammatory pain.

A. PERIPHERAL SENSITIZATION : This is due to increased transduction sensitivity of high threshold nociceptors, so that they behave like low threshold nociceptors as a result of exposure to sensitizing soup.



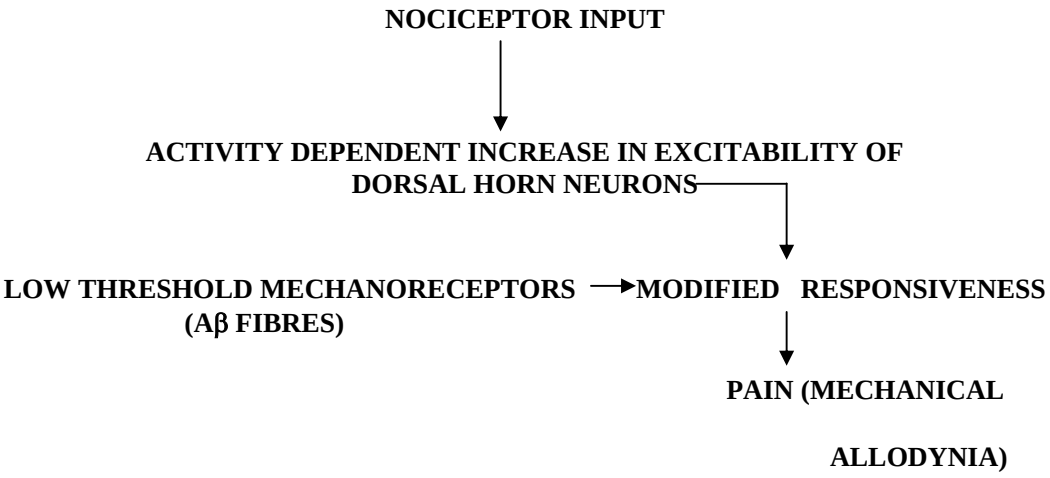
Raja et al[13] stated that nociceptors, both A δ and C are characterised by high thresholds and require intense stimuli to activate them. After peripheral tissue injury, the threshold for eliciting pain decreases both within the area of injury - primary hyperalgesia and in the surrounding uninjured tissue - secondary hyperalgesia. In the zone of injury, there is increased sensitivity to thermal and mechanical stimuli, while in the surrounding tissue, it is to mechanical stimuli. Changes in mechanical sensitivity have been more difficult to demonstrate, but occurs in joints. Therefore, peripheral sensitization enables low intensity stimuli to produce pain by activating A δ and C fibres.

B. CENTRAL SENSITIZATION : C.J. Woolf [24] describes that the change in the excitability of neurons in the spinal cord is triggered by outlasting nociceptive afferent inputs. This is characterised by.

1. Nociceptor input from low threshold mechanoreceptor (Aβ) causing hyperexcitability of the dorsal horn neurons in the spinal cord (allodynia).

2. It is responsible for all the changes in the mechanical sensitivity occurring in the zone of the secondary hyperalgesia, outside the site of injury. Therefore, central sensitization represents an input in normal low threshold A β fibres producing pain due to changes in the sensory processing in the spinal cord.

CENTRAL SENSITIZATION



To summarise, the major and fundamental difference between peripheral and central sensitization is as follows:

Peripheral sensitization enables low intensity stimuli to produce pain by activating sensitized Aδ and C nociceptors which normally have high thresholds and require intense stimuli to activate them. Central sensitization on the other hand represents an input in normal low threshold Aβ sensory fibres producing pain as a result of changes in sensory processing in the spinal cord. Sensory processing in the spinal cord can be monitored by studying the receptive field properties of the spinal neurons. These are patterns of neural activity generated by particular stimuli applied to the periphery and include (i) spatial (ii) threshold (iii) temporal element (iv) modality sensitivity as described by Willis WD et al[19]. Receptive field properties of spinal neurons are not fixed but can change. Therefore, sensory input is normally too low in amplitude to generate an action potential discharge and hence, an output signal

from the post synaptic cell. A summation of spatial and temporal elements is required to exceed the action potential threshold of the cell. The receptive field consists of :

CENTRAL PART : It is the firing zone where adequate stimuli will generate an action potential discharge.

THE SUBLIMINAL ZONE : This surrounds the centre where the response evoked in the cell by a peripheral input is subthreshold. This subliminal input provides an opportunity for change. Therefore an increase in the excitability of the neuron can convert a subthreshold input into a suprathreshold response - receptive field plasticity, which will lead to hypersensitivity to the subsequent stimuli. This in turn causes expansion of the size of the receptive field and increase in the magnitude and duration of response to suprathreshold stimuli.

CELLULAR MECHANISMS OF CENTRAL SENSITIZATION:

As described by Thompson et al[18] C fibre terminals release both excitatory amino acid glutamate and neuropeptides like tachykinins in the dorsal horn of the spinal cord. Glutamate can act on both alpha amino-3 hydroxy-5 methyl-4 isoxazole propionic acid (AMPA) and N-methyl-D aspartate (NMDA) receptors on post synaptic membranes of the dorsal horn neurons. Normally the ion channel linked to NMDA receptor is blocked by Mg++ but the block can be removed by a depolarisation of the cell leading to

an influx of Ca++ and Na+ ions causing further depolarisation. The tachykinins bind to neurokinin receptors NK and NK2, leading via GTP protein activation, to depolarisation and to changes in second messengers. The former will act on the NMDA ion channel where as the latter acts indirectly via protein kinase 'c' activation. Therefore NMDA receptor and tachykinins receptor blockers can prevent the central sensitization, as described by Woolf CJ[23] & Thompson SWN [18].

Evidence of neuroplasticity was shown by Woolf CJ et al[22] who proposed that the duration of central sensitization may outlast the duration of nociceptor input and alterations in central processing may be maintained for longer periods by structural and biochemical changes mediated by intracellular Ca++ or second messengers.

POST OPERATIVE PAIN

Effects of Postoperative Pain:

Postoperative pain can affect all organ systems and includes

- Respiratory - Reduced cough, atelectasis, sputum retention and hypoxemia.
- Cardiovascular - Increased myocardial oxygen consumption and ischemia.
- Gastrointestinal - Delayed gastric emptying, reduced gut motility and constipation.
- Genitourinary - Urinary retention.
- Neuroendocrine - Hyperglycemia, protein catabolism and sodium retention.
- Musculoskeletal - Reduced mobility pressure sores and increased risk of deep vein thrombosis.
- Psychological - Anxiety and fatigue.

Non-Pharmacological methods of pain relief:

Preoperative explanation and education, Relaxation therapy, Hypnosis, cold or heat, Splinting of wounds, Transcutaneous electrical nerve stimulation (TENS).

Pharmacological Methods of pain relief:

i. Simple Analgesia - Paracetamol (parenteral / oral)

Non - steroidal Anti - inflammatory agents - (parenteral / oral).

ii. Opioids - oral, subcutaneous, intramuscular, intravenous, Patient-controlled Analgesia (PCA), Epidural or intrathecal.

iii. **Local anaesthetic Agents -** Wound infiltration, nerve (or) nerve plexus blockade, epidural, intrathecal.

BENEFITS OF EPIDURAL ANALGESIA

Use of perioperative epidural anaesthesia and analgesia especially with a local anaesthetic - based analgesic solution can attenuate the pathophysiologic response to surgery and may be associated with a reduction in mortality and morbidity compared with analgesia with systemic opioids.

Rodgers et al[14] demonstrated through a meta - analysis of randomized data (141 trials enrolling 9559 subjects) that perioperative use of neuraxial anaesthesia and analgesia versus general anaesthesia and systemic opioids reduced overall mortality by approximately 30%. Use of epidural analgesia can decrease the incidence of postoperative gastrointestinal, pulmonary and cardiac complications.

Christopherson et al[3] demonstrated that use of intra operative regional anaesthesia decreases the incidence of postoperative hypercoagulable - related events (e.g. Deep vein thrombosis, pulmonary embolism. vascular graft failure).

POSTOPERATIVE ANALGESIA IN ORTHOPAEDICS

Postoperative pain is of major concern after orthopaedic lower limb surgery. Moderate to severe at rest, it is exacerbated on movement and particularly after hip and knee surgery and by severe reflex muscular spasms. This not only causes patient discomfort but also compromises the early physical therapy, the most influential factor on rapid postoperative rehabilitation and ambulation.

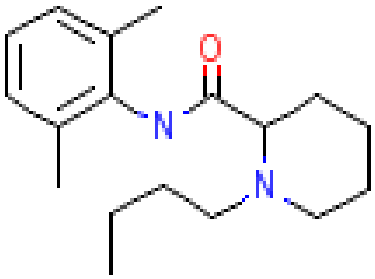
Postoperative pain relief can be achieved by a number of techniques such as intravenous patient controlled analgesia (PCA) with morphine or non-steroidal anti - inflammatory drugs or epidural analgesia. Effective analgesia with epidural or peripheral blockade reduces narcotic requirements, provides better analgesia, reduces catabolism and results in improved rates of rehabilitation after orthopaedic lower limb surgeries.

The benefits of effective postoperative analgesia in orthopaedic surgeries was made evident by the fact that it facilitates early ambulation which is beneficial in the prophylaxis of deep vein thrombosis, which is a common problem encountered in orthopaedics[15]. Postoperative modalities like pneumatic compression boots, foot pumps, foot exercises, aspirin and low dose warfarin (started the day after surgery) can be safely used in conjunction with epidural anaesthesia to reduce the incidence of deep vein thrombosis.

BUPIVACAINE

Bupivacaine was introduced by Boaf Ekenstam in 1963.

Chemical Structure : Bupivacaine hydrochloride is 2- piperidinecarboxamide 1-butyl-N-(2,6 dimethylphenyl) monohydrochloride, a monohydrate a white crystalline powder that is freely soluble in 95% ethanol, soluble in water and slightly soluble in chloroform or acetone.



Bupivacaine is related chemically and pharmacologically to the amide group of local anaesthetics. It is a structural homologue of mepivacaine.

Presentation : Bupivacaine hydrochloride is available in sterile isotonic solution with and without epinephrine 1:2,00,000 for injection. 0.25%, 0.5%, 0.75% concentration containing 2.5mg/ml 5mg/ml, 7.5mg/ml of bupivacaine hydrochloride respectively. Sodium chloride, sodium hydroxide $\pm$ hydrochloric acid for pH adjustment. Methylparaben 1mg/ml added as preservative. 0.5% (Hyperbaric) solution containing 80mg/ml of glucose (with a specific gravity of 1.026) - for intrathecal use.

Mechanism of Action:

Local anaesthetics diffuse in their nonionized form through neural sheaths and the axonal membrane to the internal surface of cell membrane sodium ion channels where they combine with hydrogen ions to form a cationic species which enters the internal opening of the sodium ion channel and combines with a receptor. This produces blockade of the sodium ion channel thereby decreasing sodium conductance and preventing depolarisation of the cell membrane.

Pharmacological actions:

a) Central Nervous System (CNS) : The principal effect of bupivacaine is reversible neural blockade, this leads to a characteristically biphasic effect on the CNS.

   - Initially excitation : Lightheadedness, dizziness, visual and auditory disturbances and seizures occurs due to blockade of inhibitory pathways in the cortex.

   - With increasing doses : CNS depression occurs. Depression of both facilitatory and inhibitory pathways leading to drowsiness, disorientation and coma.

   - Local anaesthetic agents block neuromuscular transmission when administered intra-arterially (formation of

neurotransmitter, receptor and local anaesthetic complex which has negligible conductance)

b) Cardiovascular System (CVS) **:** It binds specifically to myocardial proteins. In toxic concentrations, the drug decreases the peripheral vascular resistance and myocardial contractility producing hypotension and possibly cardiavascular collapse. (Cardiotoxic only in high doses).

Routes of Administration: Topical, Infiltration, Intrathecal, Epidural.

Doses : 2mg/ kg (with or without adrenaline)

Pharmacokinetics :

Absorption : The absorption of local anaesthetic agents is related to

1. The site of injection (intercostal > epidural > brachial plexus > subcutaneous).
2. The dose-linear relationship exists between the total dose and the peak blood concentration achieved.
3. Addition of adrenaline to bupivacaine solutions doesn't influence the rate of systemic absorption as:

- the drug is highly lipid soluble and therefore uptake into fat is rapid.
- the drug has a direct vasodilatory effect.

Distribution : 95% protein bound in plasma. The volume of distribution is 41-103 litres.

Metabolism : Occurs in Liver by N-dealkylation primarily to pipcolyloxylidine. N-desbutyl bupivacaine and 4-hydroxy bupivacaine are also formed.

Excretion : 16% - unchanged form
5% - pipcolyloxylidine in Urine
Clearance rate - 0.47 litres/ min
Elimination half life - 0.31- 0.61 hours.

Pharmacodynamics : pKa of bupivacaine is 8.1, Heptane : Buffer partition coefficient is 27.5.

The onset and duration of conduction blockade is related to the pKa, lipid solubility and the extent of protein binding of the drug.

- A low pKa and high lipid solubility are associated with a rapid onset time.
- High degree of protein binding is associated with a long duration of action.

Toxicity / side effects:

i) Allergic reactions to amide - type local anaesthetics.

ii) No longer recommended for intravenous regional blockade - as refractory cardiac depression leading to death has been reported.

Contra-indications:

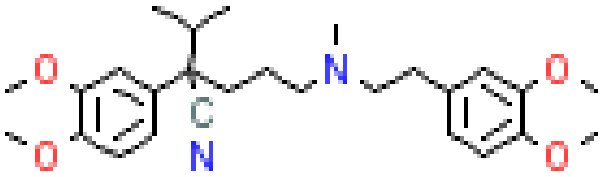
i) Obstetrical paracervical block - Resulted in fetal bradycardia & death.

ii) Known hypersensitivity to any amide group of local anaesthetics.

VERAPAMIL

Verapamil is an L-type calcium channel blocker approved by FDA in 1981.

Chemical Structure : A synthetic papaverine derivative.



Systemic (IUPAC) name -

2-(3,4-dimethoxyphenyl)-5[2-(3, 4-dimethoxyphenyl) ethyl-methyl-amino] -2-(1-methylethyl)pentanenitrile

Formula - C_{27} H_{38} N_2 O_4

Molecular mass - 454.602g/mol

Preparations : Oral - 40/80/120/160/180/240 mg tablets Intravenous injection - Racemic mixture of verapamil hydrochloride (2.5 mg / ml).

Mechanism of Action:

Competitive blockade of cell membrane slow calcium ion channels (L-type) leading to a decreased influx of Ca^{2+} ions into vascular smooth muscle and myocardial cells and cells of intracardiac conduction system. This results

in electromechanical decoupling, inhibition of contraction and relaxation of cardiac and smooth muscle fibres.

Pharmacological actions:

Cardiovascular System (CVS): Verapamil is a class IV anti-arrhythmic agent; it decreases automaticity and conduction velocity and increases refractory period. Atrio-ventricular conduction is slowed; the drug appears to be taken up and bound specifically by atrioventricular nodal tissue. The drug causes a decrease in the systemic vascular resistance and a potent coronary artery vasodilator. It has a negative dromotropic and inotropic effect which are enhanced by acidosis.

Central Nervous System (CNS) : It causes cerebral vasodilation

- **Verapamil has a local anaesthetic action that is 1.6 times that of procaine on an equimolar basis.**

Genitourinary - Verapamil decreases renovascular resistance.

Routes of Administration / Doses:

- Adult oral dose - 240- 480 mg daily in 2- 3 divided doses.
- Intravenous dose - 5 - 10 mg administered over 30 seconds

Peak effect after IV injection occurs at 3-5 minutes and the duration of action is 10-20 minutes.

Pharmacokinetics:

Absorption : Oral bioavailability - 35.1% due to significant first pass metabolism.

Distribution: 90% protein bound in the plasma.

volume of distribution - 3.1 - 4.9 L/kg

Metabolism : By demethylation and dealkylation in liver.

Twelve inactive metabolites [though one metabolite - norverapamil has 20% of vasodilating activity of parent drug.]

Half - Life : 2.8 - 7.4 hours

Excretion : 70% dose is excreted in urine, 16% in faeces

Clearance is 6.8 - 16.8 ml / min / kg.

Adverse Effects: Constipation, dizziness, headache, nausea, edema, hypotension, AV block, bradycardia and heart failure.

Contra-indications:

1. Acute myocardial infarction
2. Severe congestive cardiac failure
3. Severe left ventricular dysfunction
4. Cardiogenic shock
5. Severe hypotension

6. Second or third degree AV block
7. Sick sinus syndrome
8. Accessory bypass tract (WPW syndrome & LGL syndrome)

Therapeutic uses:

i. Anti-anginal - chronic stable angina
vasospastic angina.

ii. Antiarrhythmic - paroxysmal supraventricular tachycardia, atrial fibrillation & atrial flutter with rapid ventricular response (refractory to digitalis).

iii. Mild to moderate hypertension.

Anaesthetic considerations:

i. Effects of volatile anaesthetic agents and β- blockers on myocardial contractility and conduction are synergistic with those of verapamil - caution should be exercised when these combinations are used.

ii. Verapamil increases the serum concentrations of co-administered digoxin.

iii. Chronic exposure to the drug may potentiate the actions of both depolarising and non depolarising muscle relaxants.

iv. Verapamil attenuates the pressor response to laryngoscopy and intubation.

v. Verapamil and dantrolene administered concurrently in animals cause hyperkalemia leading to ventricular fibrillation.

vi. Verapamil is not removed by hemodialysis.

Research Studies:

i. Antinociceptive effect of verapamil[8,10,11,12,16].

ii. Anti-manic effect especially in pregnant mothers (with no teratogenecity).

iii. Uses in cell biology[27] - an inhibitor of drug efflux pump proteins such as P-glycoprotein which will be useful as many tumour cell lines overexpress drug efflux pumps, limiting the effectiveness also used in fluorescent cell sorting for DNA content as it blocks efflux of a variety of DNA binding fluorochromes such as Hoechst 33342.

REVIEW OF LITERATURE

Antinociceptive effects of Ca2+ channel blockers:

Miranda, et al [12] in 1992, demonstrated the antinociceptive action of four Ca2+ channel blockers, Nifedipine, Nimodipine, Verapamil and Diltiazem. He evaluated and compared to that of morphine using three algesiometric tests in mice and rats, namely, formalin, writhing and modified hot-plate test. Dose-response curves for all the drugs tested were similar and a significant dose-dependent antinociceptive action was evident in the formalin and writhing tests. However, in the hot-plate test, only nimodipine exhibited a significant analgesic effect, confirming the misleading results previously reported for this test. The findings suggest a pharmacological role of Ca2+ channel blockers in the modulation of antinociception under acute conditions.

The analgesic action of Ca2+ channel blockers could be mediated by an increase in the nociceptive threshold resulting from interference with Ca2+ influx at opioid receptors, because Ca2+ influx is critical for the release of neurotransmitters and other substances implicated in nociception and inflammation. He suggested that if a substance has a Ca2+ channel blocking effect, it should probably have some antinociceptive properties.

Effects of verapamil on Spinal Anesthesia with Local Anesthetics:

Keiichi Omote, et al[10] in 1995, demonstrated to investigate the effects of the intrathecal calcium channel blocker, verapamil, on the spinal anesthesia from lidocaine and tetracaine. Male Sprague-Dawley rats were chronically implanted with lumbar intrathecal catheters. Tail-flick (TF) and mechanical paw pressure (MPP) tests were used to assess thermal and mechanical nociceptive threshold, respectively. Motor function was assessed using a modified Langerman's scale. Intrathecal lidocaine or tetracaine alone showed the prolongation of TF latency, the increase of MPP threshold, and the increase in motor function scale in a time - and dose - dependent manner.

Although intrathecal verapamil alone demonstrated neither sensory nor motor block at the doses used (50-200μg), the combination of lidocaine (20, 50, 100, or 200 μg) or tetracaine (10, 20, 50, or 100 μg) and verapamil (50 μg) produced the more potent and prolonged antinociception and motor block when compared with local anesthetics alone. He interpreted these results to indicate that the intrathecal calcium channel blocker, verapamil, potentiates spinal anesthesia with local anesthetics.

Local Anesthetic Effects of Calcium Antagonists on Extracted Rabbit Vagus Nerve:

Kokubu Masahiro et al[11] in 1999, demonstrated the local anesthetic effects of calcium antagonists (diltiazem, verapamil, and nicardipine) on extracted rabbit vagus nerve and their binding ability to the phospholipid membrane model were examined by 1H-NMR spectroscopy. Effective concentrations of these drugs for vagus nerve blockade were examined with 12-14V electrical stimuli. The minimum effective concentration of calcium antagonist which completely blocked the compound action potential was 0.5mM for diltiazem, and 0.2mM for verapamil. Nicardipine did not show any conduction blocking effect at 1.0mM.

Local anesthetic effects of ditiazem and verapamil were characterized by a slower onset (over 20min) and longer duration (over 30 min) compared with lidocaine. The local anesthetic effects of diltiazem and verapamil may be due to the SA and AV nodal blocking effect and reductions in the ventricular rate by these drugs. However, in the SA and AV nodes, depolarization is largely dependent on the movement of Ca2+ through the slow channel. The results of 1 H-NMR spectroscopy indicated that poor electrostatic binding with the phospholipid membrane occured only with diltiazem. Local anesthetic effects of calcium antagonists may not be based on electrostatic binding with the nerve membrane as in the case of local anesthetics.

Epidural Verapamil Reduces Analgesic consumption After Lower Abdominal Surgery:

Huhn Choe, et al[8] in 1998, demonstrated the possible role of the calcium channel blocker, verapamil, in postoperative pain in a double-blind study. One hundred patients (ASA physical class I or II) scheduled for lower abdominal surgery were randomly assigned to one of four groups. Group-1 received 10mL of 0.5% epidural bupivacaine injected 15 min before incision, followed by 10 mL of epidural normal saline 30 min after incision. Group-2 received 10 mL of epidural normal saline injected before incision, followed by 10 mL of 0.5% epidural bupivacaine 30 min after incision. Group 3 received 10 mL of 0.5% epidural bupivacaine plus 5 mg of verapamil injected before incision, followed by 10 mL of epidural normal saline 30 min after incision. Group-4 received the same drugs as Group 3, in the reverse order.

Pain and mood numeric rating scores, sedation scores, Prince Henry scores, patient-controlled cumulative postoperative analgesic consumption, and the incidence of side effects were assessed 2, 6, 12, 24, and 48h after the operation in each group. Cumulative postoperative analgesic consumption in Groups 3 and 4 was significantly lower ($P<0.05$) than that in Groups 1 and 2, 24 and 48 h after surgery. There were no differences in the pain, mood, and sedation scores and the incidence of side effects among the four groups. He concluded that epidural verapamil decreases postoperative pain, possibly by interfering with normal sensory processing and by preventing the establishment

of central sensitization and the combination, verapamil and bupivacaine administered epidurally, resulted in less postoperative analgesic consumption than bupivacaine alone.

Brachial Plexus Anesthesia with Verapamil and / or Morphine:

Scott S. Reuben, et al[16] in 2000, demonstrated the analgesic effects of administering morphine, verapamil, or its combination into the brachial plexus sheath with lidocaine in 75 patients undergoing upper extremity orthopedic surgery. All patients received brachial plexus anesthesia with 40 mL of 1.5% lidocaine and epinephrine 5 μg/ mL. In addition, patients were randomized to 1 of 5 groups: Group 1 received IV saline, Group 2 received IV verapamil 2.5 mg and morphine 5 mg; Group 3 received IV verapamil 2.5 mg and morphine 5 mg was added to the lidocaine solution; Group 4 received IV morphine 5 mg and verapamil 2.5 mg was added to the lidocaine solution; and Group 5 received verapamil 2.5 mg and morphine 5 mg were added to the lidocaine solution.

Postoperatively, patients were rated their pain scores (0 -10) at 1, 6, 12, and 24 h. Patients were instructed to take 1 acetaminophen 325 mg/ oxycodone 5 mg tablet every 3 h whenever the pain score exceeded 3. Analgesic duration was significantly increased in those patients receiving brachial plexus blocks with morphine (Groups 3 and 5) ($P < 0.005$). The total 24h acetaminophen /oxycodone use was also less in Groups 3 and 5 ($P < 0.03$). Duration of anesthesia (time of abolition of pinprick response) was significantly increased

in those patients receiving brachial plexus blocks with verapamil (Groups 4 and 5) (P = 0.002). He concluded that the addition of verapamil to brachial plexus block with lidocaine can prolong the duration of sensory anesthesia, but it had no effect on analgesic duration of 24 h analgesic use.

The effects of verapamil and nimodipine on bupivacaine-induced cardiotoxicity in rats: an in vivo and in vitro study:

H Adsan, et al[9] in 1998, compared the effects of verapamil or nimodipine pretreatment on bupivacaine-induced cardiotoxicity. In the in vivo study, the dose-response curve for the 50% lethal dose (LD50) of bupivacaine was determined for rats. Two separate groups of rats were pretreated with i.v. verapamil 150 μg/kg (n=35) or i.v. nimodipine 200 μg/kg (n=35). Each pretreatment group was then subdivided into four groups of at least four rats each. Three minutes after pretreatment, bupivacaine was administered to each of four groups in doses of 2.5, 3.0, 3.25, and 3.5 mg/kg, respectively, both verapamil and nimodipine pretreatment increased the LD50 and 95% confidence intervals for bupivacaine and increased survival.

In the in vitro study, the effects of verapamil or nimodipine perfusion on bupivacaine cardiotoxicity (negative chronotropic, negative inotropic, and arrhythmogenic effects) and coronary perfusion pressure (CPP) were investigated in isolated, perfused rat heart preparations. Depression of heart rate, contractile force, and CPP, and the incidence of arrhythmias caused by

bupivacaine alone were similar to those caused by bupivacaine after verapamil pretreatment. In contrast, bupivacaine induced less negative chronotropic effects ($P < 0.05$, paired t- test) and arrhythmias ($P<0.05$, chi2 analysis) after nimodipine pretreatment. The results of this study demonstrated that both verapamil and nimodipine pretreatment decrease bupivacaine-induced cardiotoxicity in vivo, whereas only nimodipine pretreatment decreased bupivacaine- induced cardiotoxicity and arrhythmias in vitro. Implications : In this experimental study consisting of two stages (in vivo and in vitro), he compared the effects of two calcium channel-blocking drugs (verapamil and nimodipine) on bupivacaine toxicity. **Bupivacaine is a local anesthetic frequently used in clinical practice, and cardiotoxicity is one of its severe side effects. Verapamil and nimodipine were both effective in decreasing bupivacaine cardiotoxicity in this rat model.**

MATERIALS AND METHODS

The study population consisted of 40 ASA I & II patients in the age group of 18 years to 65 years admitted to undergo elective orthopaedic lower limb surgeries at Govt. Stanley Hospital, Chennai. After getting approval by the institutional ethics committee and after obtaining written informed consent from each patient the study was conducted.

Exclusion Criteria:

1. Age more than 65 yrs.
2. Systemic Hypertension
3. Ischemic heart disease / Rheumatic heart diseases
4. Sinus bradycardia / heart blocks/ conduction defects
5. Patients on Digitalis, calcium channel blockers and β- blockers.
6. Preoperative hypotension
7. Local infection at lumbar area
8. Pre-existing neurological disorders
9. Coagulation defects & patients on anticoagulants
10. Patient refusal.

Preoperative Assessment:

All the patients were examined prior to surgery. Routine clinical examination, Biochemical investigations, Electrocardiogram (12 leads) and chest X-ray were examined thoroughly for the conduct of anaesthesia.

Conduct of Anaesthesia:

Patients were allocated randomly in a double binded fashion into two equal groups (20 in each group). Group P (placebo) received 2 ml of Normal Saline along with the first dose of epidural 0.5% bupivacaine. Group V (Verapamil) received 5 mg (2ml) of injection Verapamil epidurally along with the first dose of 0.5% bupivacaine.

No premedication was given. On arrival in the operating room, baseline cardiorespiratory parameters viz., Heart rate (HR), Systolic blood pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP) and Respiratory rate (RR) were recorded.

A good intravenous access was established at the non-operative side forearm of the patient using 18 G IV cannula. Preloading was done with crystalloids (10 ml/kg).

With the patient in sitting posture, after informing the procedure to the patient & under strict aseptic precautions, epidural space was identified at L3-L4 or L2 - L3 interspace using 17G Tuohy needle by Loss of Resistance technique. 19G epidural catheter was threaded in a cephalad direction & 3-4 cm catheter length was kept inside the epidural space. A test dose of 3 cc of 1.5% lignocaine with adrenaline (5μg/ml) was given. Epidural catheter was fixed and secured with tapes. Patient turned into decubitus position.

A standard anaesthetic technique was followed in all patients.

Epidural 1st dose - 14 ml of 0.5% bupivacaine + 2 ml of placebo or injection verapamil.

Epidural 2nd dose- 6 ml of 0.5% bupivacaine.

Epidural 3rd dose - 6 ml of 0.25% bupivacaine.

Epidural 2nd dose was given exactly 60 minutes after the first dose and epidural 3rd dose was given exactly 60 minutes after the epidural 2nd dose for all patients according to the duration of surgery.

Patients with duration of surgery between 2 - 2:30 hours requiring standard 3 doses of epidural local anaesthetics were only taken up for study. Unanticipated prolonged duration of surgery (requiring more than 3 doses) were excluded from the study.

Intra-operatively the patient was monitored with Electro cardiogram (ECG), Non-invasive blood pressure (NIBP), Pulseoximetry (SPO_2) and urine output. During the entire operative procedure. Heart rate (HR). Systolic Blood pressure (SBP), Diastolic Blood pressure (DBP), mean arterial pressure (MAP), respiratory rate (RR) were continuously monitored & recorded every 5 minutes. All patients were given oxygen supplementation (4-5 L/min) through hudson's face mask. All the patients were given a dose of anxiolytic with

Injection Midazolam 0.05 mg/kg IV. No intravenous opioid analgesics were supplemented during the study.

Intravenous fluid management was done based on mean arterial blood pressure and surgical blood loss.

Post-operative Monitoring:

Postoperatively the patient was transferred to the recovery room and observed continuously for 60 minutes. Patient was then shifted to the postoperative ward where pulse rate, systolic blood pressure, diastolic blood pressure and respiratory rate were recorded at 2, 6, 12, 24, 48 hour intervals. The patients were assessed by the same observer in the postoperative period who was blinded for the group assignment. The intensity of pain was measured by using the verbal rating pain scale at 2, 6, 12, 24, 48 hour intervals.

Pain Score (Verbal Rating Scale)

Grade0	**-**	**No complaint of pain**
Grade 1	**-**	**Patient complaints of pain but tolerable (Mild pain)**
Grade 2	**-**	**Patient complaining of severe pain and demands relief. (Moderate pain)**
Grade 3	**-**	**Patient restless and sreaming with pain. (Severe pain)**

When the patient complained of pain i.e., the pain intensity was assessed based on Verbal Rating Scale and if the pain score reached 1, patient was given injection. Diclofenac sodium 75 mg intramuscularly. The time of first rescue analgesia (TFA) was calculated from the time of injection of the study drug in the epidural space to the time when the verbal rating pain score reached 1 in the postoperative period.

Number of supplementary analgesics (Injection Diclofenac sodium 75 mg IM) required by each patient for a period of 48 hours was noted in both the groups. Occurrence of significant side effects like hypotension, bradycardia were noted down.

OBSERVATIONS

STATISTICS AND ANALYSIS:

Forty patients posted for orthopaedic lower limb surgeries of ASA I & II were taken up for the study. They were allocated randomly in a double - blinded fashion into two groups in equal number of 20 each. Group P recieved 2 ml of placebo along with the first dose of epidural 0.5% bupivacaine and group V received 2 ml (5mg) of injection verapamil along with the first dose of epidural 0.5% bupivacaine. A standard anaesthetic technique was followed in all patients. The patients were assessed by the same observer in the postoperative period who was blinded for the group assignment.

All the datas were expressed as mean $\pm$ standard deviation (SD). Qualitative variables were compared with 'chisquare test'. Quantitative variables were compared with the 'student 't' test'.

The level of statistical significance was set at

** $P < 0.01$ - Significance at 1% level.

* $P < 0.05$ - Significance at 5% level.

$P > 0.05$ - Not Significant at 5% level.

Demographic Profile:

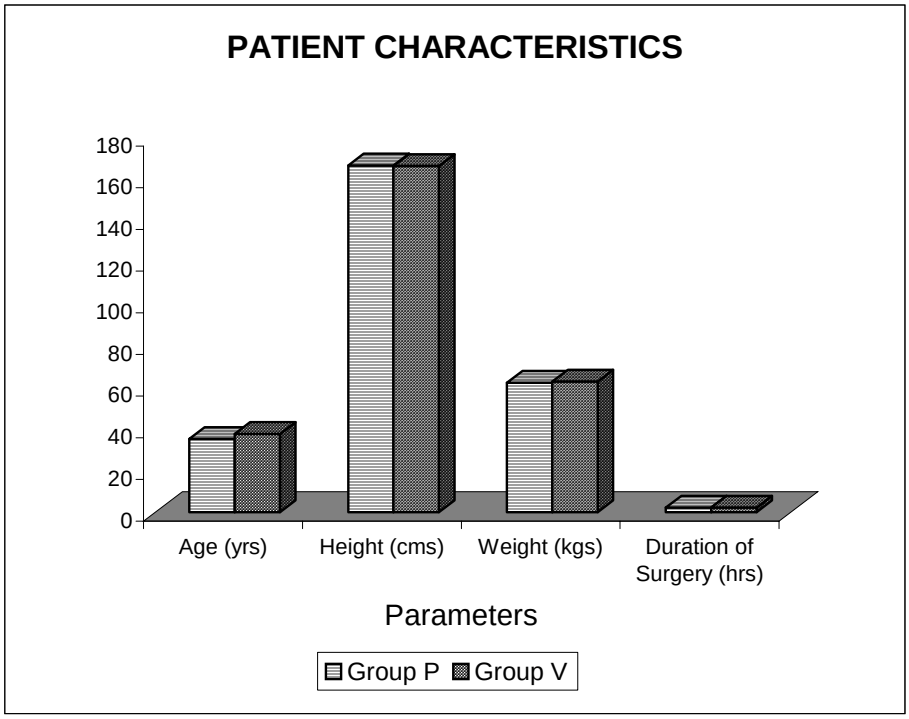
TABLE 1

PATIENT CHARACTERISTICS

S. No.	Parameters	Group		p value
		Group P	Group V	
		Mean ± SD	Mean ± SD	
1.	Age (yrs)	35.10 ± 9.26	37.65 ± 11.60	0.447
2.	Height (cms)	166.50 ± 4.72	166.30 ± 4.66	0.893
3.	Weight (kgs)	62.25 ± 6.41	62.80 ± 8.46	0.818
4.	Duration of Surgery (hrs)	2.15 ± 0.09	2.15 ± 0.08	0.913

Thus the demographic profile and duration of Surgery (hrs) were comparable between the two groups. P value was not significant.

FIGURE - 1



LIST OF ORTHOPAEDIC LOWER LIMB SURGERIES

S. No.	DIAGNOSIS AND SURGICAL PROCEDURES	NO. OF CASES	
		GROUP P	GROUP V
1.	Fracture shaft of femur - ORIF with interlocking nailing	11	9
2.	Fracture both bones leg - ORIF with intramedullary nailing	3	4
3.	Fracture neck of femur - Hemiarthroplasty	3	4
4.	Supracondylar fracture femur - ORIF with dynamic condylar screw (DCS)	2	3
5.	Fracture Patella - ORIF with Tension band wiring	1	-
	TOTAL CASES	**20**	**20**

(ORIF - Open Reduction and Internal Fixation)

TABLE 2

HEART RATE

S. No.	Parameters (Minutes)	Group		p value
		Group P	Group V	
		Mean ± SD	Mean ± SD	
1.	HR PRE - OP	101.70 ± 7.83	100.70 ± 8.54	0.702
2.	HR10	96.05 ± 5.98	94.60 ± 6.59	0.471
3.	HR20	90.80 ± 7.09	97.20 ± 6.60	0.465
4.	HR30	87.55 ± 4.77	86.15 ± 4.11	0.326
5.	HR40	86.45 ± 5.71	85.95 ± 5.31	0.776
6.	HR50	85.10 ± 6.16	84.85 ± 6.71	0.903
7.	HR60	85.05 ± 7.42	83.75 ± 7.44	0.583
8.	HR70	83.90 ± 7.78	81.35 ± 7.24	0.290
9.	HR80	82.95 ± 7.16	82.10 ± 6.88	0.704
10.	HR90	82.95 ± 7.16	82.70 ± 7.98	0.917
11.	HR100	84.25 ± 6.58	85.90 ± 6.98	0.447
12.	HR110	88.40 ± 5.08	88.80 ± 4.96	0.802
13.	HR120	92.00 ± 4.84	89.00 ± 4.59	0.052
14.	HR130	90.85 ± 4.53	88.50 ± 3.09	0.063
15.	HR140	91.50 ± 5.25	91.10 ± 5.28	0.811
16.	HR150	96.40 ± 5.04	98.35 ± 6.23	0.283

P value is not significant among both the groups at any point of time during intraperative heart rate monitoring.

TABLE 3

SYSTOLIC BLOOD PRESSURE

S. No.	Parameters (Minutes)	Group		p value
		Group P	Group V	
		Mean ± SD	Mean ± SD	
1.	SBP PRE-OP	129.25 ± 4.67	127.60 ± 4.52	0.263
2.	SBP10	119.60 ± 3.91	116.20 ± 3.41	0.006**
3.	SBP20	105.40 ± 6.24	102.30 ± 5.35	0.095
4.	SBP30	108.45 ± 6.75	106.95 ± 6.38	0.474
5.	SBP40	110.45 ± 6.56	113.10 ± 4.53	0.145
6.	SBP50	112.85 ± 7.25	112.70 ± 6.10	0.944
7.	SBP60	114.35 ± 4.86	114.20 ± 4.40	0.919
8.	SBP70	113.25 ± 5.06	112.25 ± 4.92	0.530
9.	SBP80	113.60 ± 5.39	115.50 ± 4.36	0.228
10.	SBP90	112.65 ± 4.75	114.10 ± 3.84	0.295
11.	SBP100	112.70 ± 6.58	108.35 ± 23.43	0.429
12.	SBP110	118.15 ± 3.45	116.05 ± 4.65	0.113
13.	SBP120	120.75 ± 4.69	119.75 ± 4.71	0.505
14.	SBP130	116.60 ± 3.19	117.60 ± 3.22	0.330
15.	SBP140	118.40 ± 5.47	119.40 ± 4.16	0.519
16.	SBP150	124.80 ± 2.17	125.15 ± 2.48	0.637

(** P < 0.01 - Significant)

Systolic blood pressure (SBP) monitoring between two groups were found to be insignificant except during 10 mins. interval (with a significant P value P< 0.01)

FIGURE - 2

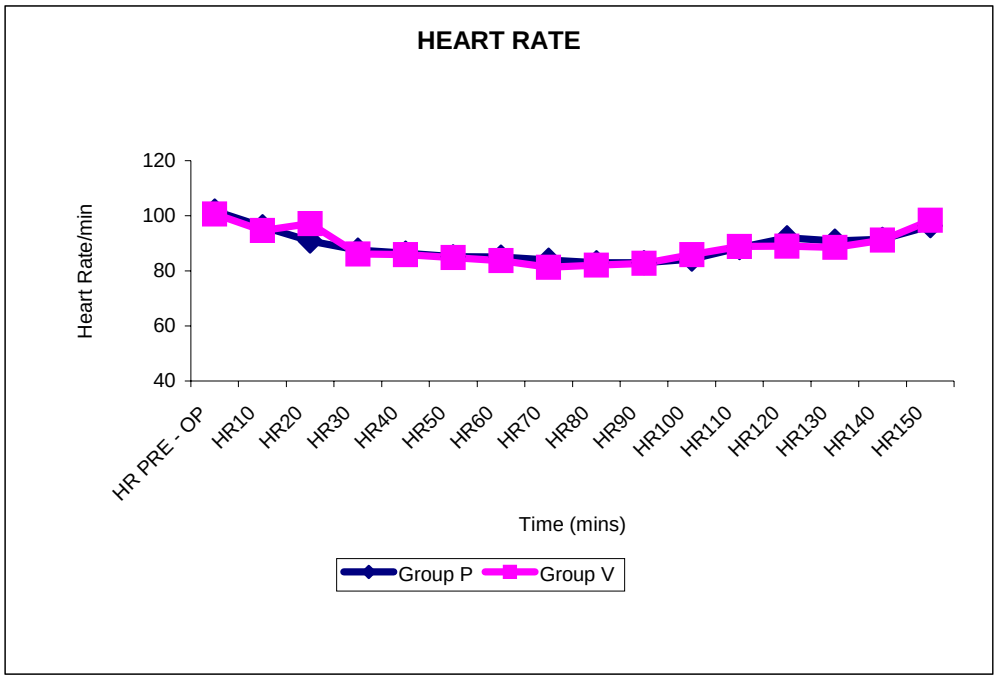


FIGURE - 3

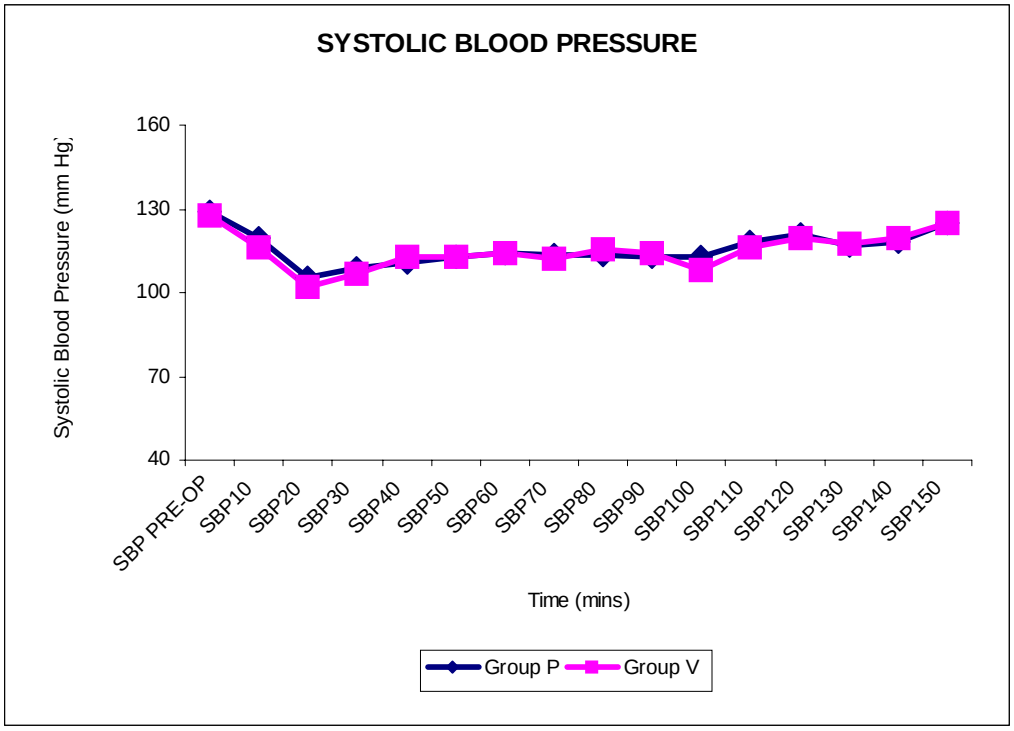


TABLE 4

DIASTOLIC BLOOD PRESSURE

S. No.	Parameters (Minutes)	Group		p value
		Group P	Group V	
		Mean ± SD	Mean ± SD	
1.	DBP PRE-OP	83.15 ± 3.00	81.45 ± 2.96	0.079
2.	DBP10	74.05 ± 4.65	70.25 ± 3.42	0.005**
3.	DBP20	62.75 ± 6.62	58.80 ± 4.86	0.038*
4.	DBP30	64.95 ± 6.69	63.70 ± 6.22	0.544
5.	DBP40	67.60 ± 4.16	68.35 ± 4.89	0.604
6.	DBP50	68.05 ± 5.09	67.70 ± 5.62	0.838
7.	DBP60	70.45 ± 4.35	69.65 ± 4.31	0.562
8.	DBP70	68.85 ± 5.35	67.40 ± 4.64	0.366
9.	DBP80	69.45 ± 4.73	69.90 ± 4.39	0.757
10.	DBP90	69.10 ± 3.71	69.15 ± 4.21	0.968
11.	DBP100	69.35 ± 5.31	69.20 ± 6.35	0.936
12.	DBP110	73.30 ± 3.63	70.95 ± 3.68	0.049*
13.	DBP120	74.40 ± 5.17	73.65 ± 4.80	0.638
14.	DBP130	72.05 ± 3.82	71.25 ± 3.96	0.519
15.	DBP140	73.60 ± 5.83	73.70 ± 4.52	0.952
16.	DBP150	79.15 ± 2.48	78.95 ± 3.72	0.342

(* $P < 0.05$, ** $P < 0.01$ - significant)

Intraoperative Diastolic Blood Pressure (DBP), monitoring between the two groups were found to be insignificant except during 10 mins, 20 mins and 110 minutes, which were only found to have a significant P Value.

TABLE 5

MEAN ARTERIAL BLOOD PRESSURE

S. No.	Parameters (Minutes)	Group		p value
		Group P	Group V	
		Mean ± SD	Mean ± SD	
1.	MAP PRE-OP	98.50 ± 3.33	96.35 ± 4.06	0.075
2.	MAP10	89.10 ± 4.14	85.65 ± 2.91	0.004**
3.	MAP20	77.00 ± 6.18	73.05 ± 5.04	0.033*
4.	MAP30	79.35 ± 6.47	78.20 ± 6.08	0.566
5.	MAP40	82.00 ± 4.50	83.30 ± 4.11	0.346
6.	MAP50	82.95 ± 5.59	82.65 ± 5.52	0.865
7.	MAP60	85.55 ± 5.09	84.65 ± 4.09	0.542
8.	MAP70	83.60 ± 4.90	82.40 ± 4.48	0.424
9.	MAP80	84.25 ± 4.63	85.15 ± 3.92	0.511
10.	MAP90	84.55 ± 4.71	84.10 ± 3.73	0.739
11.	MAP100	83.85 ± 5.47	84.35 ± 5.42	0.773
12.	MAP110	88.50 ± 3.82	86.00 ± 3.68	0.042*
13.	MAP120	89.70 ± 5.06	88.95 ± 4.45	0.622
14.	MAP130	87.25 ± 3.01	86.90 ± 3.40	0.732
15.	MAP140	88.10 ± 5.61	89.20 ± 3.89	0.475
16.	MAP150	94.30 ± 2.36	94.30 ± 3.11	1.000

(* $P < 0.05$, ** $P < 0.01$ - Significant)

Intra operative Mean Arterial pressure (MAP) recordings between the two groups were found to be insignificant except during 10 mins, 20 mins and 110 minutes.

FIGURE - 4

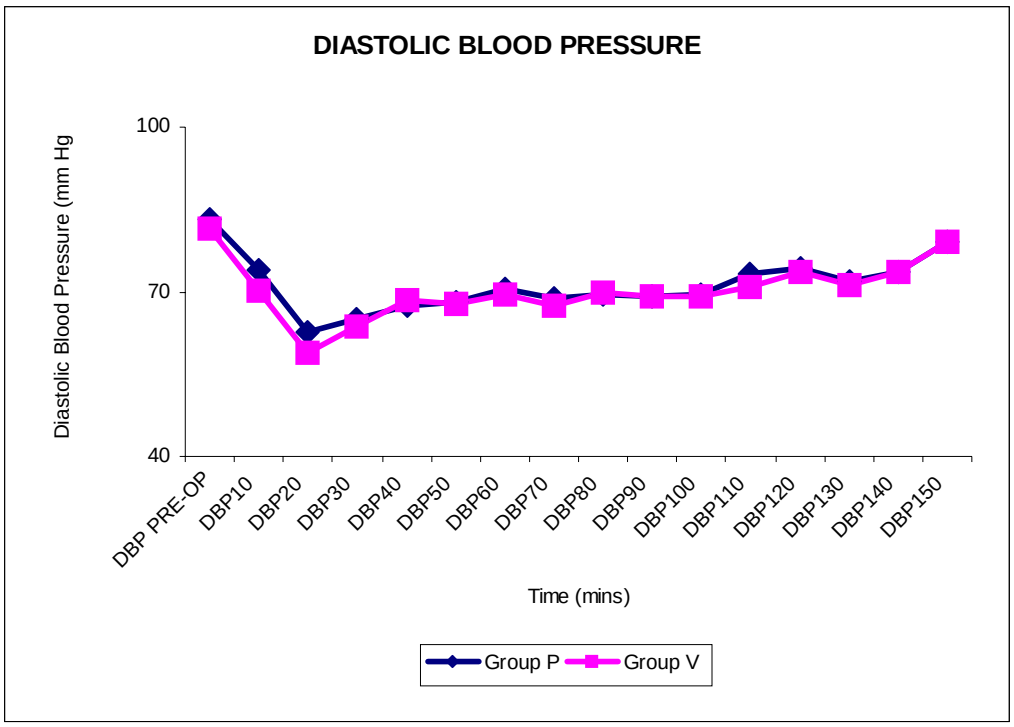
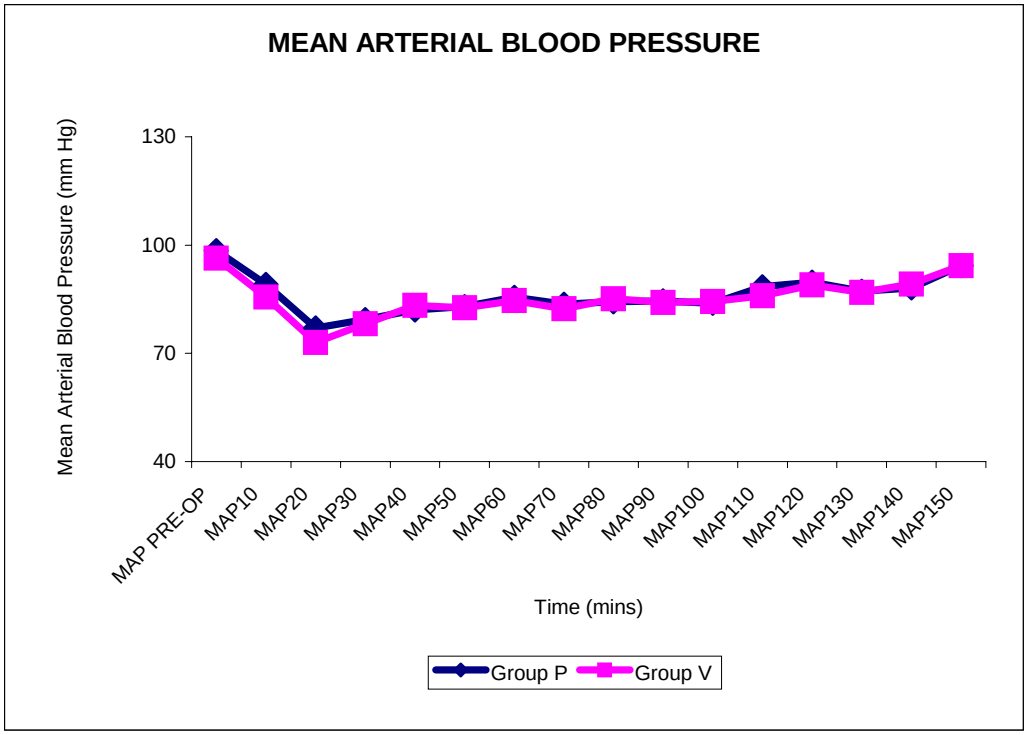


FIGURE - 5



Intraoperative monitoring of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) between the two groups (Group P & Group V) were found to be insignificant at most of the time intervals except at 10, 20, 110 mins. intervals which were only found to be significant. This demonstrates that the hemodynamic stability maintained in verapamil group is comparable to that of the hemodynamic stability maintained in placebo group throughout the intraoperative period.

TABLE 6

RESPIRATORY RATE

S. No.	Parameters (Minutes)	Group		p value
		Group P	Group V	
		Mean ± SD	Mean ± SD	
1.	RR PRE-OP	15.30 ± 1.13	15.15 ± 1.09	0.671
2.	RR10	13.30 ± 1.22	14.15 ± 0.93	0.018*
3.	RR20	13.90 ± 0.97	14.10 ± 1.12	0.549
4.	RR30	12.75 ± 0.97	13.10 ± 0.97	0.260
5.	RR40	12.45 ± 0.69	12.60 ± 0.75	0.515
6.	RR50	12.65 ± 1.09	12.55 ± 0.76	0.738
7.	RR60	13.00 ± 0.79	12.95 ± 0.69	0.833
8.	RR70	13.45 ± 0.94	13.25 ± 0.85	0.486
9.	RR80	12.80 ± 1.15	12.95 ± 1.05	0.669
10.	RR90	12.95 ± 0.94	12.95 ± 0.89	1.000
11.	RR100	13.10 ± 1.12	13.15 ± 1.09	0.887
12.	RR110	13.20 ± 1.15	13.05 ± 1.15	0.682
13.	RR120	13.15 ± 1.39	12.55 ± 0.83	0.105
14.	RR130	13.05 ± 1.32	12.50 ± 1.00	0.145
15.	RR140	13.90 ± 1.07	13.35 ± 0.93	0.092
16.	RR150	14.95 ± 1.15	14.75 ± 1.22	0.508

(* P < 0.05 - Significant)

Comparison of respiratory rate among the two groups were found to be insignificant except during 10 mins. interval (*P value at RR 10 minutes < 0.05)

FIGURE - 6

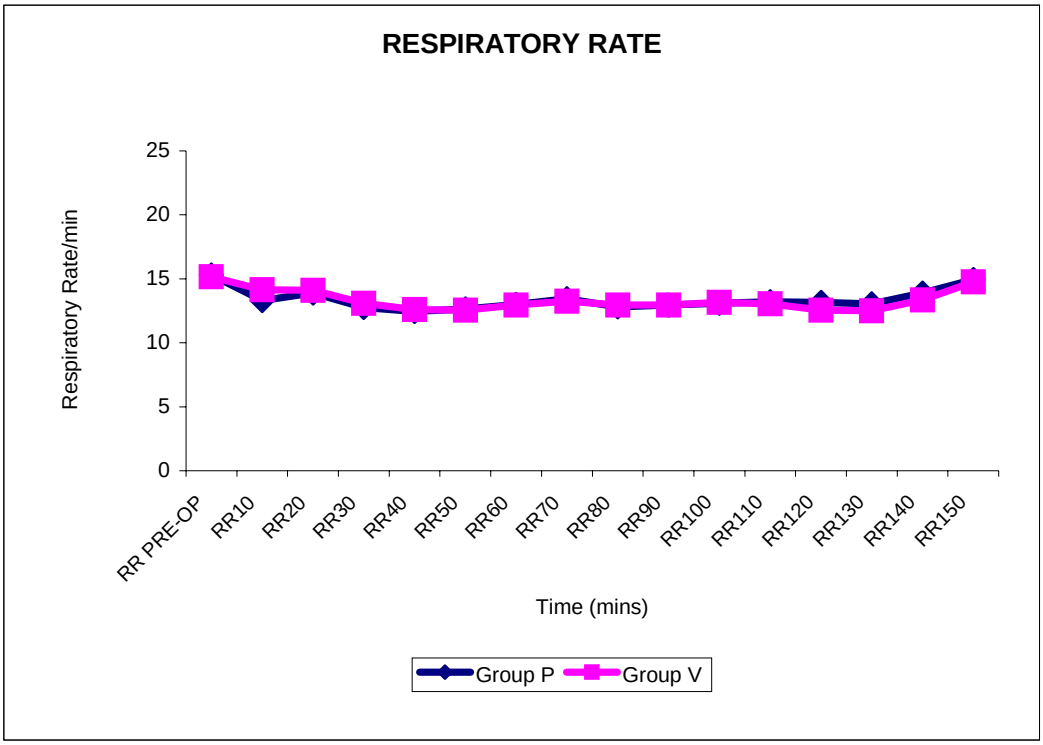


FIGURE - 7

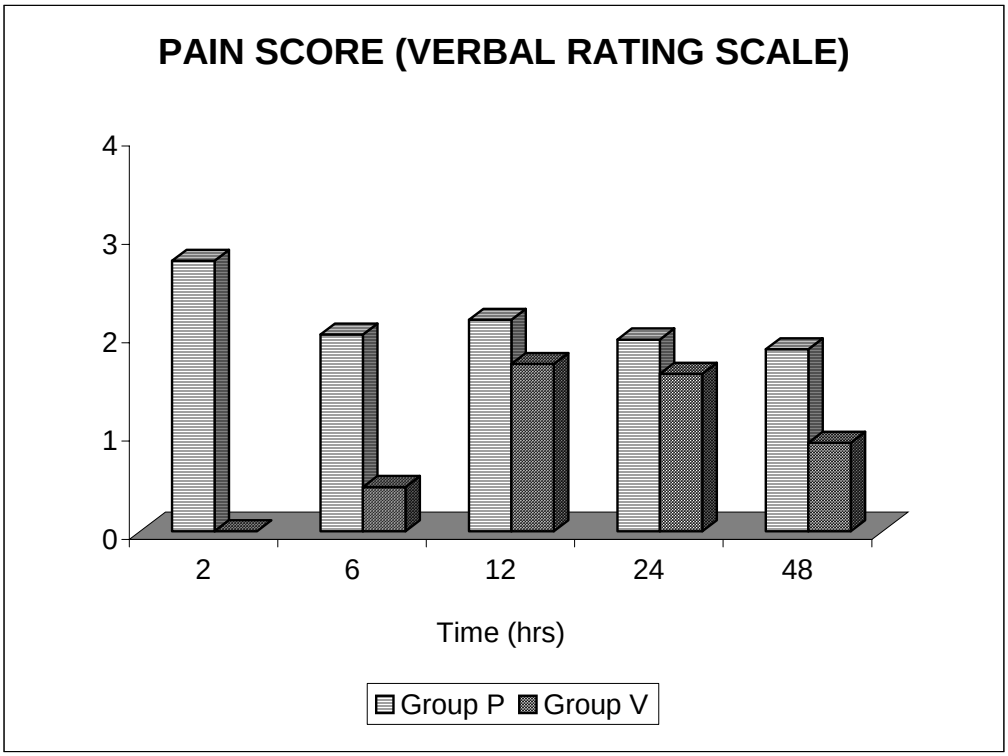


TABLE 7

PAIN SCORE (VERBAL RATING SCALE)

S. No.	Parameters (Hours)	Group		p value
		Group P	Group V	
		Mean ± SD	Mean ± SD	
1.	PS2 (hrs)	2.75± 0.44	0.00± 0.00	0.001**
2.	PS6 (hrs)	2.00± 0.46	0.45 ± 0.69	0.001**
3.	PS12 (hrs)	2.15± 0.49	1.70 ± 0.57	0.011*
4.	PS24 (hrs)	1.95± 0.69	1.60 ± 0.60	0.094
5.	PS48 (hrs)	1.85± 0.49	0.90 ± 0.31	0.001**

(* $P < 0.05$, ** $P < 0.01$ - Significant)

The postoperative pain score (verbal rating scale) was found to be low at all time intervals (2, 6, 12, 24, and 48 hrs) in Group V when compared to group P. Significantly low pain scores were observed at 2, 6, 12 and 48 hours intervals in patients belonging to group V ($P < 0.01$ at 2, 6, & 48 hours intervals & $P < 0.05$ at 12 hours interval) than group P as shown in figure 7. The study demonstrated that pain relief was significantly better ($P<0.05$) in patients who received epidural bupivacaine with verapamil mixture than the patients who received epidural bupivacaine with placebo.

TABLE 8
TFA & TOTAL POST - OPERATIVE
ANALGESIC REQUIREMENTS

S. No.	Parameters	Group		p value
		Group P	Group V	
		Mean ± SD	Mean ± SD	
1.	Time of First rescue analgesic (hrs)	3.84 ± 0.46	6.42 ± 0.63	0.001**
2.	No. of supplementary analgesic doses (Doses for 48 hrs)	6.35± 0.49	4.25± 0.44	0.001**

(* P < 0.05, ** P < 0.01 - Significant)

The mean time of first rescue analgesic (TFA in hours) was found to be 6.42 ± 0.63 hours in Group V than the 3.84 ± 0.46 hours observed in Group P which is statistically significant. ($p<0.01$).

Mean supplementary analgesic doses required in group V for 48 hours - 4.25 ± 0.44 doses. Mean supplementary analgesic dose required in group P for 48 hours - 6.35 ± 0.49 doses. The demand for supplementary analgesia over 48 hours was low in group V than group P with significant statistical difference ($P<0.01$).

Chi-square test demonstrated no significant difference among both the groups regarding the incidence of side effects. (2 patients in Group P and 1 patient in Group V developed hypotension). No bradycardia was reported in either of the two groups.

FIGURE - 8 (a)

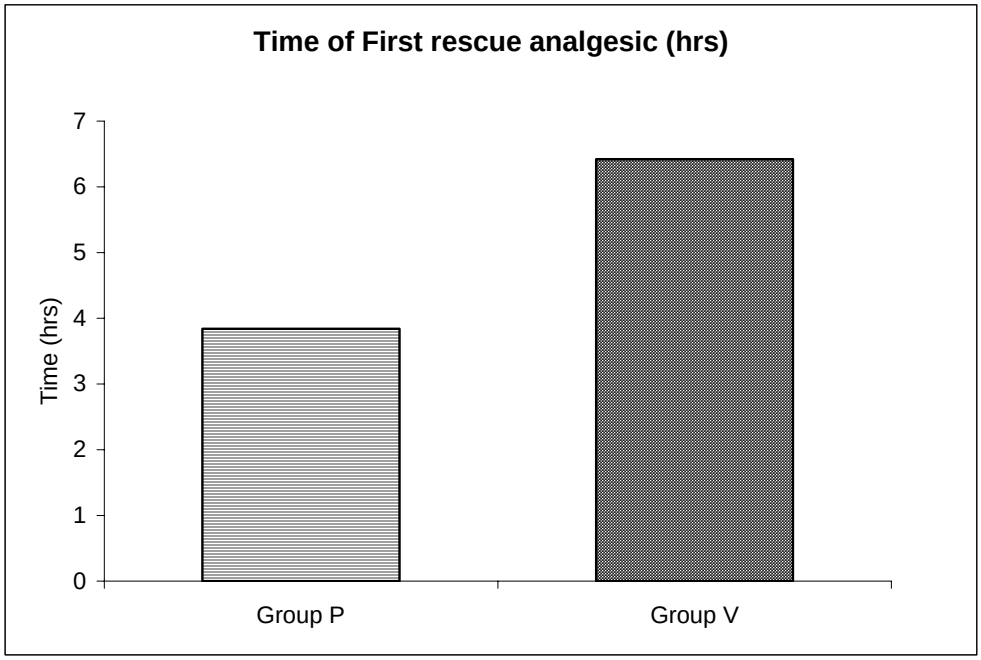
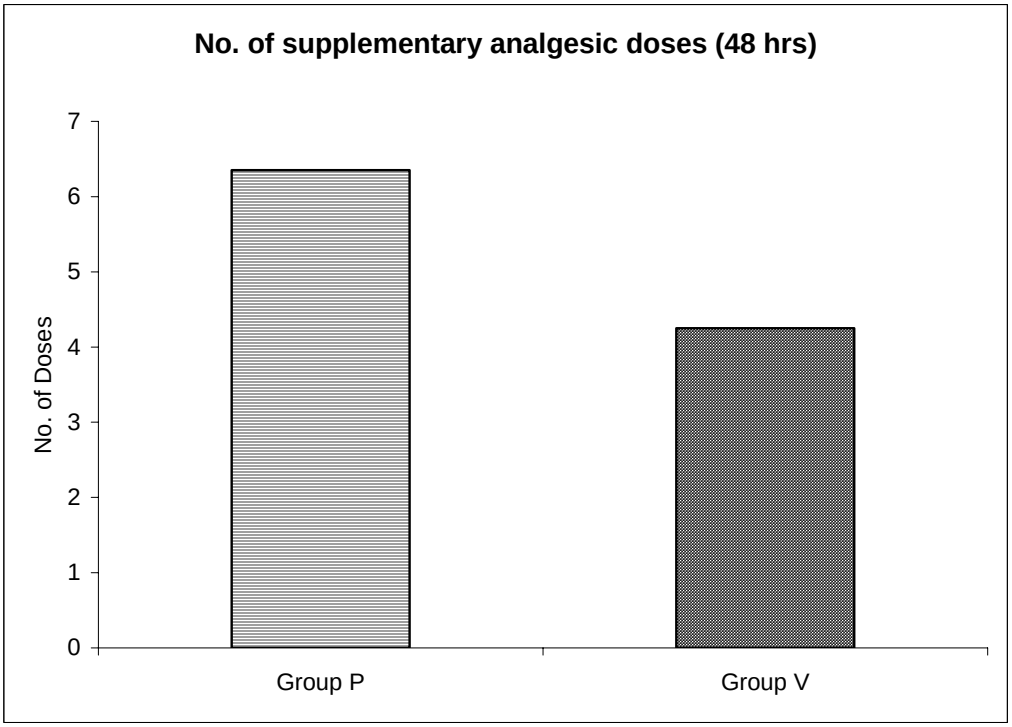


FIGURE - 8 (b)



DISCUSSION

Our knowledge of acute pain mechanisms has advanced sufficiently over the past decade so that rational rather than empirically derived therapy can be used by aiming specifically at interrupting the mechanisms responsible for the generation of clinical pain. Breakthrough pain after surgical procedures is now beginning to be recognised as constituting suboptimal management. This is an active research area. A number of clinical trials have been conducted to prove the efficacy of anti-nociceptive effect of Ca^{2+} channel blockers using different techniques and different types of drugs with conflicting results. The use of epidural techniques also offer the advantage of allowing single shot injection of local anaesthetics and additives offering effective prolonged postoperative analgesia as compared to nerve blocks and local infiltrations[21].

The altered sensory processing caused by high-intensity noxious stimuli has several possible mechanisms, including an expansion of receptive fields and a decrease in thresholds of dorsal horn neurons; an enhancement of responses of dorsal horn neurons elicited by repetitive C fiber stimuli, which is known as wind-up phenomenon; and an increase in dynorphine gene expression[24, 4, 6]. Repetitive fast - transmitter activity of aspartate and glutamate at α-amino-3-hydroxy- 5-methyl-4-isoxazolepropionic acid (AMPA)/ kinate receptors produces a membrane depolarization that counters a voltage-dependent blockade of the NMDA receptor by Mg^{2+}. Activation of

neurokinin-1 receptors by substance P produces a slow, prolonged depolarization and enhances the influx of extracellular Ca^{2+} through voltage - operated Ca^{2+} channels. A further action of asparatate and glutamate on NMDA and metabotropic receptors produces an influx of Ca^{2+} through NMDA receptor-operated Ca^{2+} channels and activates phospholipase C.

Phospholipase C catalyzes the formation of intracellular second messengers, which causes the release of Ca^{2+} from the endoplasmic reticulum. The increase in intracellular Ca^{2+} produced by these reactions results in increased gene expression and central sensitization, including wind-up and long-term potentiation[4]. Thus, calcium channel conductance is required for the nervous system to signal a painful situation. A disruption of calcium ion movement interferes with sensory processing and contributes to antinociception

This series of reactions may be prevented or attenuated either presynaptically by reducing the release of neurotransmitters or postsynaptically by blocking specific receptors, such as NMDA receptor, or by both mechanisms. Opioids and local anesthetics reduce the presynaptic release of the neurotransmitters.

Calcium channel blockers have antinociceptive effects in animals[12, 19] and show morphine potentiation in patients with chronic pain[17]. Substances with calcium channel-blocking effects and NMDA receptor antagonists may prevent pain and facilitate treatment of established pain

states [23]. In this study, we found that bupivacaine and verapamil administered epidurally, reduced the amount of analgesic that patients required postoperatively suggesting that verapamil may prevent central sensitization by surgical trauma.

In this double blind study, we have evaluated the analgesic efficacy of bupivacaine with verapamil mixture given through lumbar epidural route in patient undergoing elective orthopaedic lower limb surgeries.

Pain intensity was assessed using the verbal rating scale (VRS). Significant lower VRS scores after 2, 6, 12,24 & 48 hours has demonstrated the clinical advantage of administering a mixture of bupivacaine and verapamil through lumbar epidural route for effective postoperative analgesia.

Duration of analgesia was significantly more in group V patients receiving bupivacaine and verapamil mixture (6.42 ± 0.63 hours) as compared to group P (3.84 ± 0.46 hours). The demand for supplementary analgesic doses over 48 hours postoperatively was significantly low in group V (4.25 ± 0.44 doses) than group P (6.35 ± 0.49 doses).

Bradycardia with a heart rate < 60/ min was not encountered in any of the patient in both the groups.

Two patients of placebo group (10% of Group P) and one patient of verapamil group (5% of Group V) had episodes of hypotension with a MAP

<65 mm Hg during intraoperative period who were managed with a single dose of ephedrine 6 mg IV and crystalloids probably as a result of epidural anaesthesia as such.

Postoperatively two patients of placebo group (10% of Group P) and one patient of verapamil group (5% of Group V) had episodes of hypotension with a MAP <65 mm Hg. These patients were found to have an excessive blood loss seen in the operative site wound drain, who were managed with compatible whole blood transfusion. No incidence of any bradycardia was noted in both the groups during postoperative period.

SUMMARY

This randomised double blind study was designed to evaluate the analgesic efficacy of bupivacaine with verapamil mixture given through lumbar epidural route for postoperative analgesia in patients undergoing elective orthopaedic lower limb surgeries and the quality of analgesia was compared with epidural plain bupivacaine.

Forty ASA I & II patients undergoing elective orthopaedic lower limb surgical procedure under epidural anaesthesia were randomly allocated in a double blinded fashion to one of the two groups. Group P received 2 ml of normal saline along with first dose of 14 ml 0.5% bupivacaine. Group V received 2 ml (5 mg) of injection verapamil along with the first dose of 14 ml 0.5 % bupivacaine.

Pain in the postoperative period was assessed using a verbal rating scale (VRS). Pain score were significantly less in group V at 2, 6, 12, 48 hours ($P < 0.05$) than in group P. Overall pain score over 48 hours period also revealed better pain relief in group V ($P<0.05$) as compared to Group P. Time of first rescue analgesic (TFA) and the supplementary analgesic doses required for 48 hours were noted for the two groups.

Time of first rescue analgesic (TFA) in group V (6. 42 ±0.63 hours) was significantly prolonged compared with group P (3.84 ± 0.46 hours). The

postoperative analgesic consumption was also significantly less in Group V (4.25 doses for 48 hours) than in Group P (6.35 doses for 48 hours). The incidence of hypotension did not differ significantly between the two groups & there was no bradycardia in both the groups.

So this study demonstrates that addition of verapamil to bupivacaine definitely improves the quality of analgesia by reducing the over all pain score, prolonging the duration of the time of first rescue analgesia (TFA) and causing reduction of total analgesic consumption in the post operative period without any hemodynamic instability.

CONCLUSION

1. Single dose administration of verapamil and bupivacaine mixture given through lumbar epidural route provides effective postoperative analgesia in patients undergoing elective orthopaedic lower limb surgeries, without any hemodynamic instability.

2. Epidural verapamil significantly reduces the postoperative analgesic consumption.

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PROFORMA

Name : Height :

Age : Sex : Weight :

I.P.No. : Diagnosis :

ASA Status : Surgery :

Group : Duration of Surgery :

Time of Injection of drugs: Epidural 1st dose-

Dose of Verapamil or Placebo-

Epidural 2nd dose-

Epidural 3rd dose-

Time of incision

INTRA – OPERATIVE VITALS MONITORING																	
Time interval (minutes)																	
Sl. No	Parameter	Pre-op	10	20	30	40	50	60	70	80	90	100	110	120	130	140	150
1.	HR																
2.	SBP																
3.	DBP																
4.	MAP																
5.	RR																

Intra – operative events:

POST –OPERATIVE MONITORING					
Parameter	Time interval (hours)				
	2 hrs	6 hrs	12 hrs	24 hrs	48 hrs
1. **Pain Score :** (Verbal Rating Scale) 0 - No Pain 1 – Mild Pain 2 – Moderate Pain 3 - Severe Pain 2. **Adverse Effects**: Hypotension Bradycardia					

POST –OPERATIVE ANALGESICS CONSUMPTION	
1. **Time of First Rescue analgesic :** (TFA in hours)	
2. **No.of Supplementary analgesic doses required** (for 48 hours)	