**DISSERTATION ON EVALUATION OF THE PREEMPTIVE ANALGESIC EFFICACY OF ORAL GABAPENTIN FOR POSTOPERATIVE EPIDURAL ANALGESIA REQUIREMENT IN PATIENTS UNDERGOING ELECTIVE ORTHOPAEDIC LOWER LIMB SURGERIES.**

*Dissertation submitted to*

***THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY***
Chennai

***for***

***MD (ANAESTHESIOLOGY) Branch – X***
March 2010

***GOVT. STANLEY MEDICAL COLLEGE***
Chennai

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY
CHENNAI – TAMILNADU

# ACKNOWLEDGEMENT

I wish to express my sincere thanks to **Prof. Dr.S.CHITRA, MD.,** Dean, Government Stanley Medical College and Hospital for having permitted me to utilize the facilities of the hospital for the conduct of study.

My heartfelt thanks to **Prof. Dr. SUBRAMANIYA BHARATHIAR M.D.,D.A.,** Professor and Head, Department of Anaesthesiology, Govt. Stanley Medical College and Hospital for his motivation, valuable suggestions, constant supervision and for all necessary arrangements for conducting the study.

I am greatly indebted to **Prof. Dr. P.CHANDRASEKAR M.D., D.A., Prof.Dr.LAKSHMI M.D.,D.A,** and **Prof. Dr. PONNAMABALA NAMASIVAYAM M.D., D.A.,** for their guidance throughout the study. I thank **Dr.V.J.KARTHIK M.D., Dr.SATHISH LOGIDASAN M.D,D.N.B., Dr.NARASIMMAN M.D** and other assistant professors who evinced keen interest and gave support without which this study would not have been possible.I thank **Mr. Padmanaban,** Statistician, for helping me in the stastical analysis.

# *CONTENTS*

## *Annexure*

# *INTRODUCTION*

Emotion, perception and past experience all affect an individual's response to noxious stimuli. Patient's attitudes and concerns about postoperative pain need to be addressed preoperatively. Early interventions influence long-term outcomes. Because of the multiplicity of mechanisms involved in post operative pain, a multimodal analgesia regimen, with a combination of opioid and non-opioid analgesic drugs is often used to enhance analgesic efficacy and reduce opioid requirements and side effects. Preemptive analgesia was assumed to reduce risk of developing persistent postoperative pain[1].

Peripheral tissue injury provokes peripheral sensitization and central sensitization[1,2]. These changes contribute to the post injury pain hypersensitivity state which manifests as an increase in the responsiveness to noxious stimuli and a decrease in the pain threshold, both at the site of injury and in the surrounding uninjured tissue[2,3]. The preemptive treatment could be directed at the periphery, at inputs along sensory axons and at central neurons. Different treatment regimen could be used at different levels of sensory inputs[2,3].

Gabapentin, a structural analogue of gamma-amino butyric acid, has been used as an anticonvulsant and antinociceptive drug but its mode of action is not well understood[4]. In addition it has been effective in neuropathic pain, diabetic neuropathy, post herpetic neuralgia and reflex sympathetic dystrophy. Pretreatment with gabapentin can block the development of hyperalgesia. Studies have demonstrated that mechanical hyperalgesia surrounding the wound in post operative patients and experimentally, heat-induced secondary hyperalgesia share a common mechanism and the central neuronal sensitization contributes to postoperative pain. Gabapentin has a selective effect on the nociceptive process involving central sensitization.

In our institution we chose to study the efficacy of oral Gabapentin administered preoperatively on the postoperative pain relief and it's influence on the postoperative Epidural analgesic requirement in patients undergoing elective lower limb orthopaedic procedures undercombinedspinalepidural anaesthesia

# AIMS AND OBJECTIVES

1. To evaluate the preemptive analgesic efficacy of gabapentin given orally for postoperative epidural analgesia requirement in patients undergoing elective orthopaedic lower limb surgeries.

2. To evaluate the hemodynamic response of oral gabapentin

3. To evaluate the side effect profile of oral gabapentin

## DEFINITION 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"

## PHYSIOLOGY OF PAIN

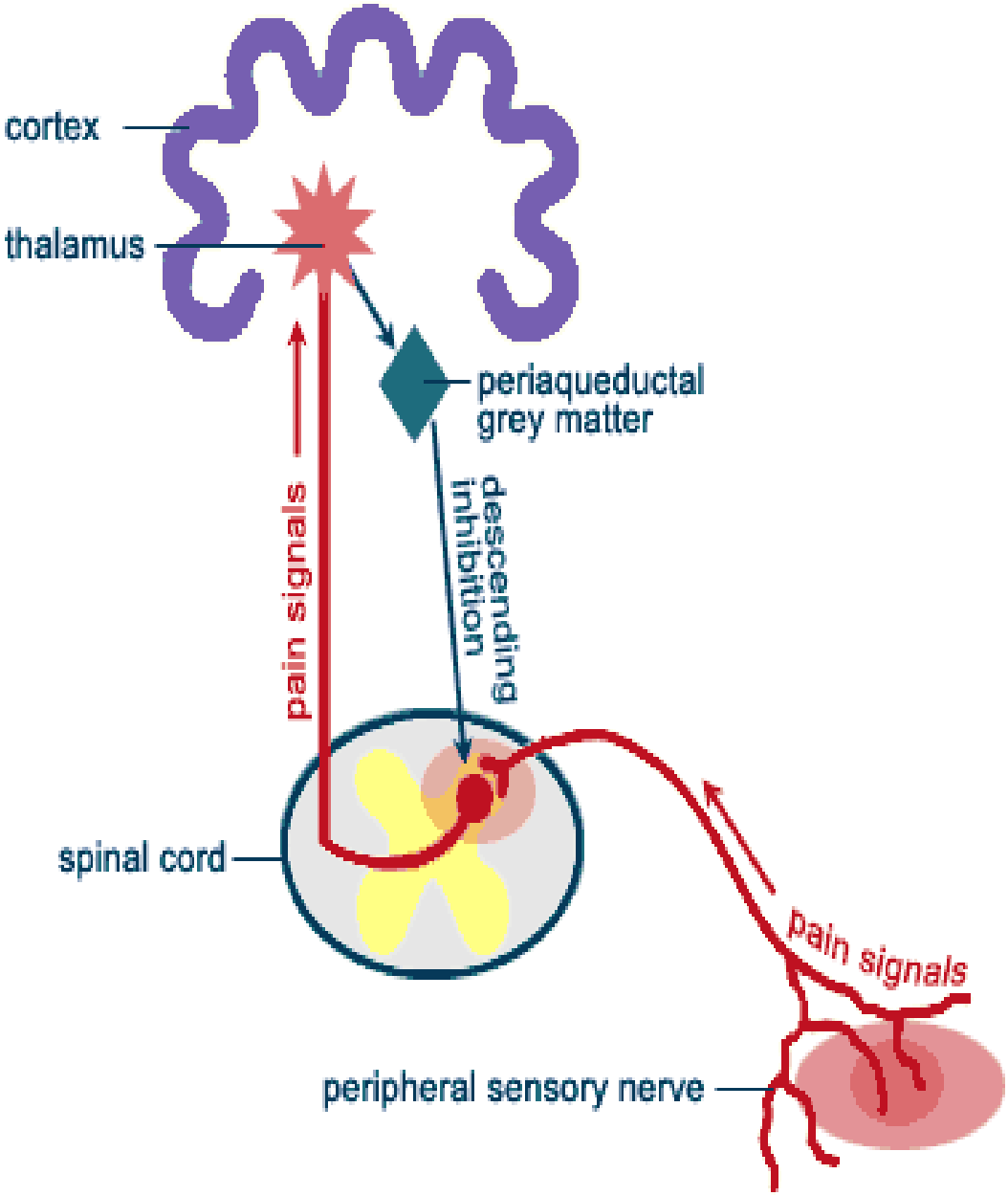
Nociception is conveyed from periphery to the brain at three levels:the peripheral nociceptor, the spinal cord and the supra- spinal levels.

They are of two types - physiological and pathological pain.

**I. PHYSIOLOGICAL PAIN :**is produced by stimulation of high threshold thermo/chemical nociceptors, which transmit via fast conducting A delta fibres. They enter the dorsal horn of the spinal cord and synapse at laminae I & V.

**II. PATHOLOGICAL PAIN :** originates from stimulation of the high threshold polymodal nociceptors to mechanical,chemical and thermal stimuli and are transmitted via slow conducting unmyelinated C fibres. These synapse at laminae II& III (substantia gelatinosa) of the dorsal horn. The second order neurons are either nociceptive (substantia gelatinosa) or wide dynamic range (WDN) neurons( in laminae V &VI) that respond to a wide range of noxious and non – noxious input. Both

pathways ascend up the spinal cord via the spinothalamic tracts to the thalamus, which synapse and project on to the somatosensory cortex. Inhibitory inter-neurons in the substantia gelatinosa prevent activation of the dorsal root ganglia. Inter-neurons can be activated by A Delta and inhibited by the A beta and C fibre activity. Pain can be gated out by stimulating large A beta fibres in the painful area. This is the working mechanism behind the transcutaneous electrical nerve stimulation. The descending inhibitory pathways originate at the level of the cortex and thalamus, and descend via the brainstem (periaqueductal grey) and the dorsal columns to terminate at the dorsal horn of the spinal cord. Neurotransmitters noradrenaline, serotonin and the endogenous opiods are released to provide antinociception.




**NEURAL PAIN PATHWAYS**

# PREEMPTIVE ANALGESIA

Definition : “what is administered before surgical incision, what prevents establishment of central sensitization resulting from incisional injury (only intraoperative) or what prevents central sensitization resulting from incisional and inflammatory injuries (intra-operative and postoperative period)”.

Surgical tissue injury is known to produce neuroplastic changes leading to spinal sensitization and the expression of stimulus-evoked hyperalgesia and allodynia. Poorly controlled acute postoperative pain may be an important factor in the development of pathologic long-term chronic pain. Prevention of central sensitization and control of postoperative pain may decrease the incidence of chronic pain. In case of inflammatory pain there is release of inflammatory and pro-inflammatory cytokines from the cells that sensitize or stimulate free nerve endings, initiate the coagulation cascade and activate the immune system. The ensuing lowering of the activation of the receptors for pain at the site of injury results in the bombardment of the spinal cord with continuous noxious input via A-delta and c-fiber. Additionally, under the stress of intense inflammatory pain, A-alpha and A-beta fibers are induced to participate in the

transmission of pain signals. This is significant, given that their input is not filtered in the spinal cord in the same way as A-delta and c-fibers, nor can it be dampened or modified as effectively with classic analgesic medications such as opioids. It is believed that the continuous nature of the input provokes changes in the chemical milieu in the spinal cord and triggers structural reorganization that raises the potential for establishing naturopathic pain. Thus, whenever there is enhanced noxious input, there is an induction of decreased central inhibition that would ordinarily modify the input and the subsequent central nervous system response.

This is where preemptive analgesia plays an important role. Confining the definition of preemptive analgesia to only the intra operative period may not be clinically relevant or appropriate because the inflammatory response may last well into the postoperative period and continue to maintain central sensitization. Maximal clinical benefit is observed when there is complete blockade of noxious stimuli with extension of this block into the postoperative period.

# POST OPERATIVE PAIN

## Effects of Post operative Pain:

Post operative pain can affect all organ system and includes

- Respiratory -reduced cough, atelectasis, sputum retention and hypoxemia.
- Cardiovascular - increased myocardial oxygen consumption and ischemia
- Gastrointestinal - decreased 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:**

Simple Analgesia - paracetomol (parenteral / oral)

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

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

**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 opoids.

Rodgers et al (38) 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 opiods reduced overall mortality by approximately 30%. Use of epidural analgesia can decrease the incidence of postoperative gastrointestinal, pulmonary and cardiac complications.

The 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 a 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 factors are 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 benefit 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. 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

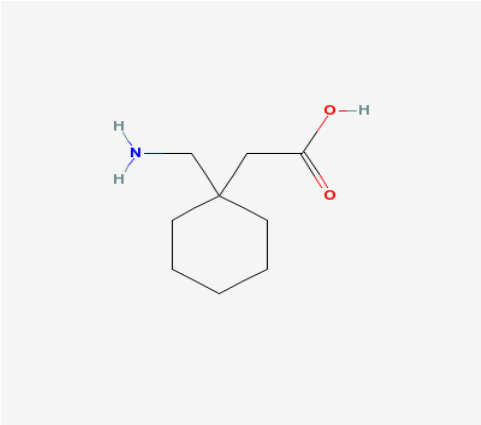
conjunction with epidural anaesthesia to reduce the incidence of deep vein thrombosis.

# GABAPENTIN

Initially introduced in 1994 as an antiepileptic drug (AED).

**CHEMICAL STRUCTURE:**

Gabapentin [l-aminomethyl cyclohexane acetic acid] is a structural analogue of gamma-aminobutyricacid (GABA).




Has a GABA molecule covalently bound to a lipophilic cyclohexane ring. Gabapentin, with its centrally active GABA agonist property and lipid solubility crosses the blood-brain barrier

**MECHANISM OF ACTION**:

Gabapentin was developed as a direct agonist but does not have high affinity for GABA-A or GABA-B receptors The mechanism of anticonvulsant action of gabapentin is unknown. Despite its design as a GABA agonist, gabapentin does not mimic GABA when iontophoreticaly applied to neurons in primary culture. Gabapentin may influence the synthesis and release of GABA[9], but it does not affect the uptake and metabolism of endogenous GABA[10].

The gabapentin specific binding site was identified as the $\alpha_2$-theta subunit of voltage dependent calcium channels[11] has high affinity for the alpha 2 delta one subtype[12]. Gabapentin can inhibit high threshold calcium currents in cultured sensory neurons[13]. It inhibits excitatory amino acid release through its interaction with the calcium channels and reduces hyperalgesia[14]. Gabapentin does not affect calcium currents of T,N and L type calcium channels in the dorsal root ganglion cells[15].

Gabapentin has not been found to reduce sustained repetitive firing of action potentials[16]. The exact mechanism by which gabapentin exerts its analgesic effect is not yet known.

**PHARMACOKINETICS:**

Oral administration of gabapentin is well absorbed and is not metabolized in the humans. It is not bound to plasma proteins. It is excreted unchanged by kidneys in the urine. Half-life of gabapentin, when used as mono therapy is 4-6 hours. It has no known interactions with other antiseizure drugs.

In renal failure gabapentin should be titrated according to the creatinine clearance and can be given with hemodialysis.

**PREPARATIONS:**

They are available only in the oral form

(1) Tablet

(2) Capsule

(3) Oral solutions

**DOSAGE:** 5-20 mg/kg

**USES:**

1. Partial seizures

2.Post herpetic neuralgia[17]

3. Painful diabetic neuropathy[18]

4. Gullain-Barre syndrome[19]

5. Complex regional pain syndrome [20]

6. Phantom limb pain[21]

7. Postoperative pain

8. Mixed neuropathic pain

**ADVERSE EFFECTS:**

Gabapentin is usually well tolerated. The most common side effects are:

(1) Somnolescence

(2) Dizziness

(3) Ataxia

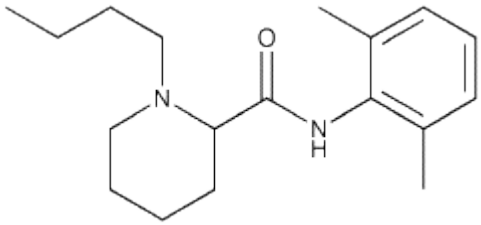
(4) Fatigue

These effects are usually mild to moderate in severity but resolve within two weeks of onset during continued treatment. The contraindications in using gabapentin are hypersensitivity and lactation.

## BUPIVACAINE

Bupivacaine was introduced by Boaf Ekenstam in 1963.

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




C18 H28 N2 O

Bupivacaine is related chemically and pharmacologically to the amide 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 ± 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) - intrathecal use.

**Mechanism of Action:**

Local anaesthesics 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) 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 o inhibitory pathways in the cortex.

- With increasing doses CNS depression : Depression of both facilitatory and inhibitory pathways occur leading to central nervous system depression (drowsiness, disorientation and coma)

- Local anaesthetic agent block neuromuscular transmission when administered intra-arterially (fomation of neurotransmitter, receptor and local anaesthetic complex which has negligible conductance)

b ) **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 volume of distribution - 41-103 litres.

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

**Excretion :** 16% - unchanged form

5% - Urine as pipcolyloxylidine

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 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.

# REVIEW OF LITERATURE

**Role of gabapentin as preemptive Analgesic in Patients Undergoing Total Abdominal Hysterectomy in combined spinal epidural anaesthesia.IJA 2008 52(4) 428-431**

**Anil Verma,Sangeeta Arya et al** conducted a study to evaluate the role of gabapentin as preemptive analgesic in patients undergoing total abdominal hysterectomy under combined spinal epidural anaesthesia and the epidural bolus requirements for pain relief in the postoperative period was noted.Total numbers of epidural boluses were significantly less in gabapentin group They concluded that preemptive use of gabapentin 300mg orally significantly reduces the number of postoperative epidural bolus requirement and postoperative pain in patients undergoing total abdominal hysterectomy under combined spinal epidural anaesthesia.

**Effect of oral gabapentin on postoperative epidural Analgesia in patients undergoing elective lower extremity procedures:**British Journal of Anaesthesia 96 (2): 242–6 (2006)

**Turan a et al 2006** hypothesized that gabapentin might be a useful adjuvant for postoperative analgesia provided with patient-controlled epidural analgesia (PCEA) in patients undergoing lower extremity surgery procedures. Postoperative assessments included verbal rating scale scoring for pain and sedation, PCEA usage, quality of

recovery assessment, times of GI function recovery, and patient satisfaction scoring for pain management. Pain scores, PCEA bolus requirements and paracetamol (mg) consumption were significantly lower in the gabapentin-treated patients than in the control group. Patient satisfaction with postoperative pain management at 24 h was better in gabapentin-treated patients .He concluded that Oral gabapentin (1.2 g / day) as an adjunct to epidural analgesia decreased pain and analgesic consumption.

**MONTAZERI ET AL** (25)

Singapore journal of anaesthesia 07 demonstrated the pre-emptive use of gabapentin could reduce postoperative pain and morphine consumption in patients after lower extremity orthopaedic surgery . He concluded that the Pre-emptive use of gabapentin 300 mg orally significantly decreases postoperative pain and rescue analgesic requirements in patients who undergo lower extremity orthopaedic surgery.

**Dirks et al 2002**[33] Anaesthesiology 2002 concluded that a single dose of 1,200 mg oral gabapentin resulted in a substantial reduction in postoperative morphine consumption and movement-related pain after radical mastectomy, without significant side effects.

**Pandey et al 2004**[22] CJA compared the effects of gabapentin, tramadol and placebo on postoperative pain scores and opioid requirement.

Postoperatively the three groups were evaluated for pain scores through Visual Analogue Score (VAS) and then total consumption of fentanyl by all the three groups were compared. There was significantly less consumption of fentanyl in the Gabapentin group than tramadol and placebo group

**Pandey et al 2004** [23] Canadian Journal of Anaesthesia 2004; 52: 986 -989. He studied the effects of preemptive gabapentin on postoperative pain and total amount of fentanyl consumption. The postoperative pain score evaluated using pain scale and total amount of fentanyl consumption was recorded. He concluded that fentanyl consumption is significantly lesser in gabapentin group compared to the placebo group.

**Turan et al 2004**[24] Anaesthesia and analgesia, conducted a Study to compare the effect of oral gabapentin and placebo and the requirement of rescue analgesia in patients undergoing elective total abdominal hysterectomy.Pain was evaluated by VAS and the total amount of rescue medication needed was statistically evaluated in both the groups. There was significant reduction in VAS and requirement of rescue medication

with $p<0.05$.

**Dierking G et al 2004**[29] Acta Anaesthesiologica scandinavica, 2004; 48: 322-327. Conducted a study in which eighty patients were given gabapentin 1200mg or placebo. Analysis of VAS at rest and mobilization was done. Postoperative opioid requirement in the gabapentin group was significantly low with $p<0.001$.

**Menigaux C et al 2005**[27] Anaesthesia and analgesia 2005; 100:1394-1399 studied the effects of preoperative gabapentin on preoperative anxiety and postoperative analgesia with early knee mobilization. Forty patients were studied under gabapentin and placebo group. VAS, postoperative opioid requirement and maximal effect achieved was observed in the postoperative period. Gabapentin was found to have anxiolysis, postoperative analgesia and early knee mobilization.

**Mikkelsen S et al 2006**[30] Acta Anesthesiologica Scandinavia,2006; 50: 809-815. Conducted a study to evaluate the effects of single dose gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy Postoperative pain score evaluated using four point verbal rating scale. There was significant reduction in requirement of morphine during the postoperative period in the gabapentin group with a $p<0.003$.

# 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 during the period of January 2009 to june 2009. After getting approval by the institutional ethics committee and after obtaining written informed consent from each patient the study was conducted.

**Inclusion Criteria:**

1.Age group 18-65 yrs

2.ASA I &ASA II

3.Elective lower limb orthopaedic surgeries

4.Duration of surgery between 2:00 to 2:30 hours

**Exclusion Criteria:**

1. Emergency surgery
2. Pre existing neurologic disorders
3. Liver & Renal disorders
4. Psychiatric illness
5. Local infection at lumbar area

6. Coagulation defects & patients on anticoagulation

**Preoperative Assessment:**

All the patients were examined prior to surgery. Routine clinical examination, Biochemical investigations, Electrocardiogram 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 a tablet of alike looking placebo(Vitamin C), Group G(Gabapentin) received 300mg tablet of gabapentin 90 minutes prior to anaesthesia with sips of water.

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

With the patient in sitting posture, after informing the procedure to the patient & under strict aseptic precautions, epidural space was identified at L2-L3 or L1- L2 interspace using 16 G Tuohy needle by Loss of Resistance technique. 18 G epidural catheter was threaded in a cephalad direction & 3-4 cm catheter length was kept inside the epidural space. Test dose of 3 cc of 1.5% lignocaine with adrenaline (5µg/ml) was given. spinal anaesthesia was performed in L3-L4 space and 3 c.c of 0.5% bupivacaine hyperbaric was injected. Epidural catheter was fixed & secured with tapes.

A standard anaesthetic technique was followed in all patients. Any surgery prolonging more than 150 minutes or those requiring intra op requirement of activation of epidural was 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) was 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 anxiolytic - Injection Midazolam 0.05 mg/kg. IV. No. intravenous opiod analgesics were supplemented during the study.

Intravenous fluid management was done based on mean arterial Blood pressure & 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, occurance of headache, dizziness were recorded at 2, 4, 8, 12, 24 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, 4, 8, 12, 24hour intervals.

**Pain Score (Verbal Rating Scale)**

**Grade 0 - 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 screaming with pain. (Severe pain)**

When the patient complained of pain i.e., the pain intensity was assessed based on Verbal Rating Scale, if the pain score reaches 1, patient was given an epidural top up of 6c.c of 0.125% bupivacaine and vitals were monitored.

Number of supplementary analgesic doses (6c.c of 0.125% bupivacaine) required by each patient for period of 24 hours was noted in both the groups. Occurrence of significant side effects hypotension, bradycardia were noted.

# 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 - blind fashion into two groups in equal number of 20 each. Group P (placebo) received a tablet of alike looking placebo(Vitamin C), Group G (Gabapentin) received 300mg tablet of gabapentin 90 minutes prior to anaesthesia .A standard anaesthetic technique was followed in all patients. The patients were assessed by an observer in the postoperative period who was blinded for the group assignment.

Data was expressed as mean $\pm$ standard deviation (SD). Qualitative data were compared with chisquare test. Quantitative variables were compared with the student 't' test. the level of statistical significance was set at * $P < 0.05$ and ** $P < 0.01$.

**Demographic Profile:**

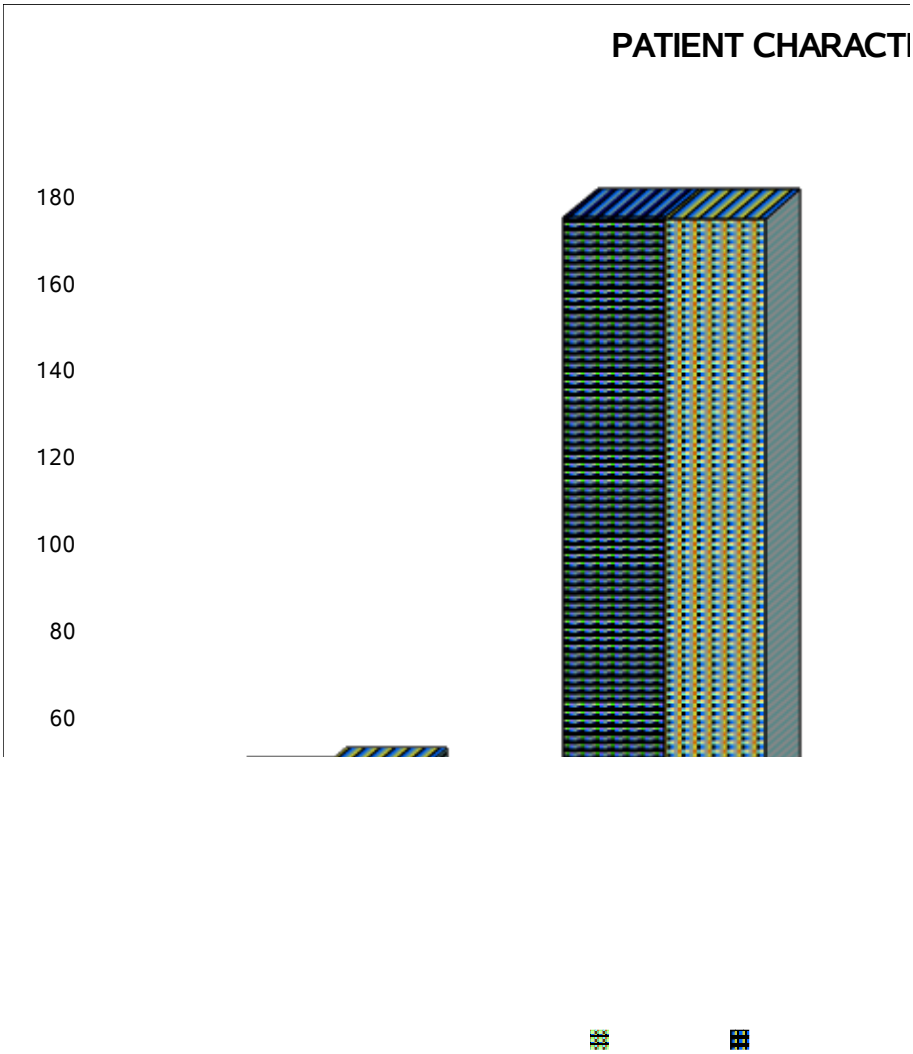
**TABLE 1**

**PATIENT CHARACTERISTICS**

| S. No. | Parameters | Group | | p value |
|---|---|---|---|---|
| | | Group P | Group G | |
| | | 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) was comparable between the two groups. P value is not significant.

**FIGURE - 1**



## LIST OF ORTHOPAEDIC LOWER LIMB SURGERIES

| S. NO | DIAGNOSIS AND SURGICAL PROCEDURES | NO.OF CASES | |
|---|---|---|---|
| | | GROUP P | GROUP G |
| 1 | Fracture shaft of femur –ORIF with interlocking nailing | 9 | 11 |
| 2 | Fracture neck of femur -- Hemiarthroplasty | 4 | 5 |
| 3 | Total hip replacement | 2 | 1 |
| 4 | Supracondylar fracture femur- ORIF with dynamic condylar screw(DCS) | 7 | 3 |
| | TOTAL CASES | 20 | 20 |

**(ORIF - Open Reduction and Internal Fixation)**

**TABLE 2**

**HEART RATE**

| S. No. | Parameters (Minutes) | Group | | p value |
|---|---|---|---|---|
| | | Group P | Group G | |
| | | 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 |

**TABLE 3**

**SYSTOLIC BLOOD PRESSURE**

| S. No. | Parameters (minutes) | Group | | p value |
|---|---|---|---|---|
| | | Group P | Group G | |
| | | Mean ± SD | Mean ± SD | |
| 1. | SBP PRE-OP | 129.25 ± 4.67 | 127.60 ± 4.52 | 0.263 |
| 2. | SBP10 | 119.60 ± 3.91 | 118.35±4.79 | 0.372 |
| 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 |

**FIGURE - 2**


**FIGURE - 3**

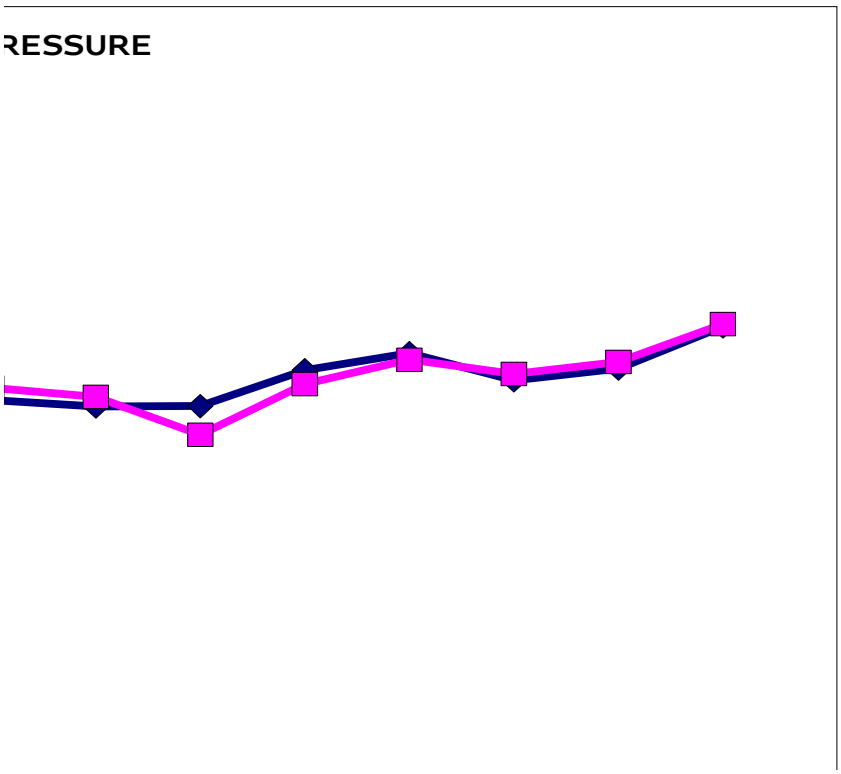


**TABLE 4**

**DIASTOLIC BLOOD PRESSURE**

| S. No. | Parameters (minutes) | Group | | p value |
|---|---|---|---|---|
| | | Group P | Group G | |
| | | Mean ± SD | Mean ± SD | |
| 1. | DBP PRE-OP | 83.15 ± 3.00 | 81.45 ± 2.96 | 0.079 |
| 2. | DBP10 | 74.05 ± 4.65 | 72.9±4.33 | 0.423 |
| 3. | DBP20 | 62.75 ± 6.62 | 61.7±5.72 | 0.600 |
| 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 | 72.45±4.55 | 0.213 |
| 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 |

**TABLE 5**

**MEAN ARTERIAL BLOOD PRESSURE**

| S. No. | Parameters (minutes) | Group | | p value |
|---|---|---|---|---|
| | | Group P | Group G | |
| | | Mean ± SD | Mean ± SD | |
| 1. | MAP PRE-OP | 98.50 ± 3.33 | 96.35 ± 4.06 | 0.075 |
| 2. | MAP10 | 89.10 ± 4.14 | 88.45±5.34 | 0.545 |
| 3. | MAP20 | 77.00 ± 6.18 | 76.7±5.66 | 0.432 |
| 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 | 87.6±6.43 | 0.782 |
| 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 |

**FIGURE - 4**

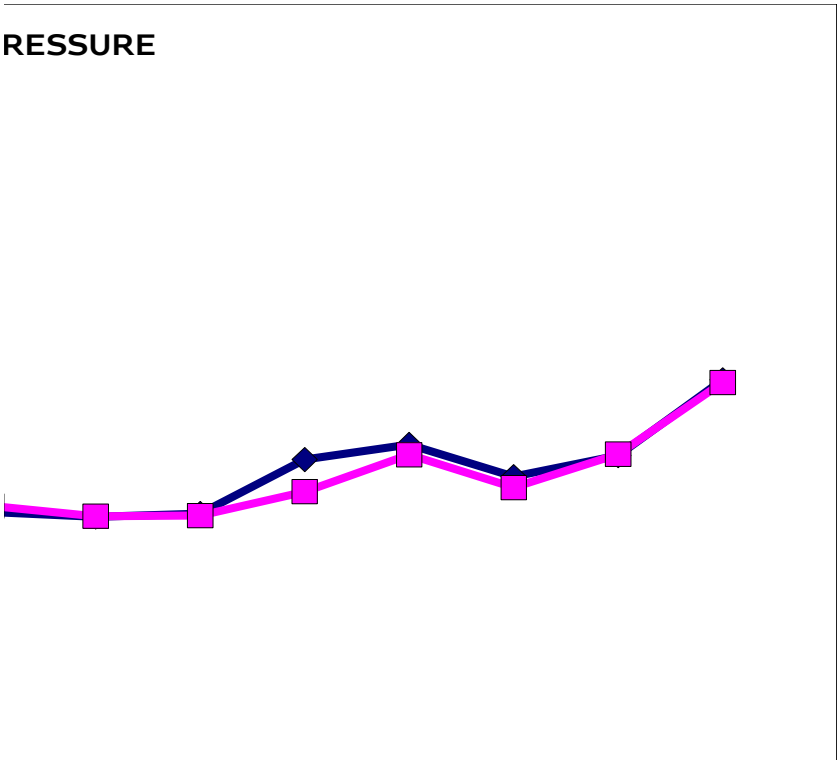
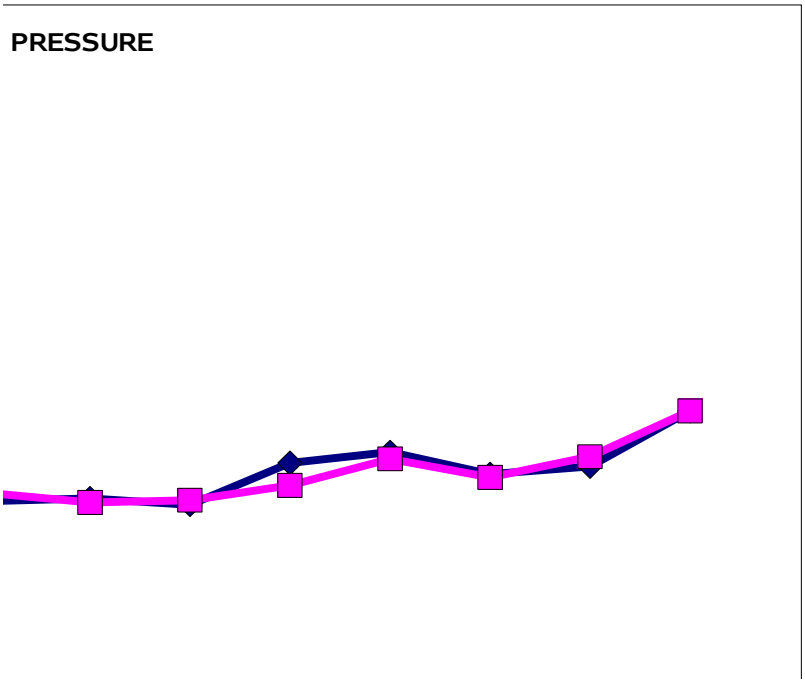



**FIGURE - 5**



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 G) were found to be insignificant in all of the time intervals.. This demonstrates that the hemodynamic stability maintained in gabapentin group is as 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 G | |
| | | 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 |

* $P < 0.05$

**FIGURE - 6**

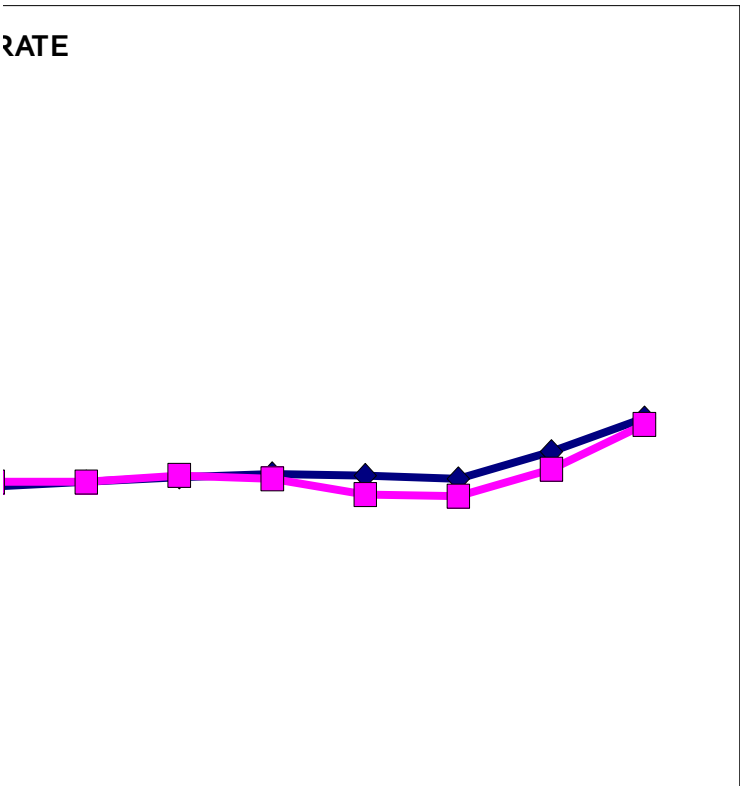



**FIGURE - 7**

**TABLE 7**

**PAIN SCORE (VERBAL RATING SCALE)**

| S. No. | Parameters | Group | | p value |
|---|---|---|---|---|
| | | Group P | Group G | |
| | | Mean ± SD | Mean ± SD | |
| 1. | PS2 (hrs) | 2.75± 0.44 | 0.00± 0.00 | 0.001** |
| 2. | PS4(hrs) | 2.00± 0.46 | 0.45 ± 0.69 | 0.001** |
| 3. | PS8 (hrs) | 2.15± 0.49 | 1.70 ± 0.57 | 0.011* |
| 4. | PS12 (hrs) | 1.95± 0.69 | 1.50 ± 0.51 | 0.020* |
| 5. | PS24 (hrs) | 1.85± 0.49 | 0.90 ± 0.31 | 0.001** |

* $P < 0.05$ ** $P < 0.01$

The postoperative pain score (verbal rating scale) was found to be low at all time intervals (2,4, 8, 12, 24 Hrs ) in Group G when compared to group P. Significantly low pain scores were observed at 2, 4, 8, 12 and 24 hours intervals in patients belonging to group G ($P < 0.01$ at 2, 4, 8, & 24 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 gabapentin pre emptively than the patients who received placebo.

**TABLE 8**
**TOTAL POST - OPERATIVE**
**EPIDURAL TOP UP REQUIREMENTS**

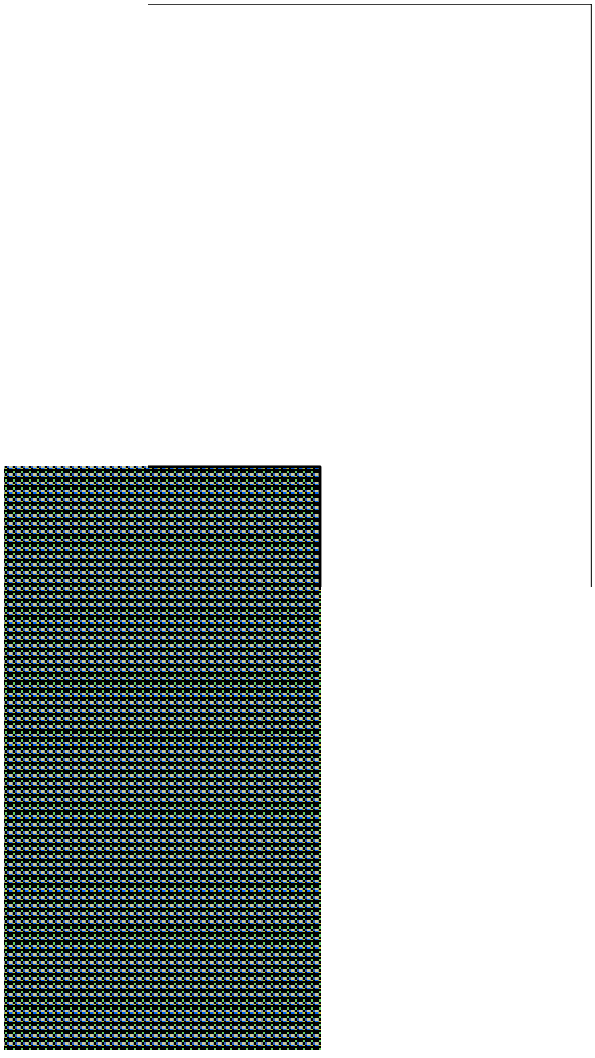
| S. No. | Parameters | Group | | p value |
|---|---|---|---|---|
| | | Group P | Group G | |
| | | Mean ± SD | Mean ± SD | |
| 1 | No. of supplementary analgesic doses (24 hrs) | 6.35± 0.49 | 4.25± 0.44 | 0.001** |

** P < 0.01

Mean supplementary analgesic dose required in group G for 24 hours - 4.25 ± 0.44 doses. Mean supplementary analgesic dose required in group P for 24 hours - 6.35 ± 0.49 doses. The demand for supplementary analgesia over 24 hours was low in group G than group P with significant statistical difference (P<0.01).

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

**FIGURE - 8**



## DISCUSSION

The present study was designed to evaluate the effectiveness of gabapentin as a preemptive analgesic in patients undergoing elective lower limb orthopaedic procedures under combined spinal epidural anaesthesia and evaluated the total number of epidural top up requirements for 24 hours and the occurance of any side effects to oral gabapentin A total of forty patients were randomized into two groups (A & B) of 20 each. Group A received gabapentin while group B received vitamin C tablet. Both the groups were monitored for postoperative VRS, requirement of epidural top ups , heart rate, blood pressure , headache and dizziness

Both the groups were comparable with respect to demographic details like age, sex,and height of the patient.

In our study VRS and Epidural analgesic requirement in the postoperative period was found to be significantly lesser in gabapentin group compared to placebo group. Gabapentin with prolonged incubation in vitro decreases sustained firing of sodium dependent action potentials and suppresses discharges after nerve injury. Gabapentin also interacts with NMDA receptor complexes at the glycine site. Gabapentin has been found to decrease pain and prevent acute nociceptive and inflammatory

pain, when given before trauma[34]. Gabapentin has also been found to have anxiolytic property without amnestic effect[27]. The decrease in perioperative anxiety has been found to have a positive effect in decreasing postoperative pain and reduces postoperative opioid requirement. In our study gabapentin was given approximately 90 minutes prior to surgery. Hussain (34) et al observed gabapentin given approximately one and half hours prior to surgery orally acquired a maximal plasma concentration level during the period of surgical stimuli, as it crosses the blood brain barrier rapidly and the concentration in the brain reaches that of the plasma.

In our study the mean VRS at "2" hour after surgery was 0(ZERO) in gabapentin group, while 2.4 (±0.44) in placebo group, the difference being highly significant ($p<0.01$). Similarly, the VRS were significantly higher in the placebo group at $4^{TH}$, $8^{th}$ $12^{th}$ and 24 hours with the mean at $24^{th}$ hour being 0.9(±0.31) in the gabapentin group and 1.85 (±0.49) in the placebo group. The differences being highly significant ($p<0.01$) at all hours.

**Anil Verma et al (37)** had demonstrated the efficacy of oral gabapentin on post operative pain scores. His study showed that the patients who received Gabapentin had significantly lower VAS scores compared to

those who received a placebo

**Pandey C K et al** [22,23] had demonstrated the efficacy of gabapentin on Post operative pain scores. Their study showed that patients who received gabapentin preemptively had lesser pain scores compared to the placebo group. **Turan et al**[24, 32] had also demonstrated that preoperative oral gabapentin decreased postoperative pain scores and requirement of analgesics in patients undergoing abdominal hysterectomy. **Dirks et al**[33] found that even single dose of preoperative gabapentin resulted in substantial reduction in postoperative pain after radical mastectomy. **Mengaux et al**[27] recorded the postoperative pain scores for 48 hours in knee surgeries and found that the VAS was significantly low and mobilization of limbs were better in gabapentin group compared to placebo. **Rosarius et al**[35] demonstrated that a single dose of gabapentin given two and a half hours before induction of anesthesia reduced the need for postoperative pain medication by 40% during the first 20 postoperative hours in patients undergoing vaginal hysterectomy.

**Jorgean B Dhal et al**[36] in his publication has analyzed about preemptive analgesia and its efficacy in decreasing postoperative pain. He has also showed that by blocking the sensitization of the nociceptive signal preemptively by preoperative medications like gabapentin, NMDA

receptor antagonist and non-steroidal anti-inflammatory drugs reduces the development of the postoperative pain into chronic pain.

A number of hypotheses have been proposed in regard to the gabapentin opioid interaction, including those of inhibition of glutamate release, nitric oxide or postsynaptic calcium entry. In our study we observed that there was decreased requirement of postoperative rescue medication in the gabapentin group compared to the placebo group. The amount of the total epidural top up required by the gabapentin group was 4.25 (±0.44) compared to 6.35(±0.49) used by the placebo group, with a significant p value.

**Anil Verma et al (36)** showed that the total epidural top up requirements for the first 24 hours in gabapentin group was 3.4±1.6 compared to the placebo group which required 5.6 ± 2.1.

**The results of our study correlate well with the above.**

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 gabapentin group (5% of Group G) 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.

Postoperatively two patients of placebo group (10% of Group P) and one patient of gabapentin 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 wound drain, who are managed with compatible whole blood transfusion. No incidence of any bradycardia was noted in both the groups during postoperative period. No incidence of headache and dizziness which are common with prolonged intake of gabapentin was noted in any of the patients.

# SUMMARY

This double blind study was designed to evaluate the preemptive analgesic efficacy of gabapentin given 90 minutes prior to elective lower limb orthopaedic procedures under combined spinal epidural anaesthesia

Forty ASA I & II patients undergoing elective orthopaedic lower limb surgical procedure under epidural anaesthesia were randomly allocated in a double blinded fashion of one of the two groups. Group P received a similar looking placebo .Pain was assessed using a verbal rating scale (VRS). The number of supplementary analgesic doses required for 24 hours were noted for the two groups. Pain score were significantly less in group G at 2, 4, 8, 12, 24 hours ($P < 0.05$) than in group P, after surgery. Overall pain score over 24 hour period also revealed better pain relief in group G ($P<0.05$) as compared to Group P.

The postoperative analgesic consumption was also significantly less in Group G (4.25 doses for 24 hours) than in Group P (6.35 doses for 24 hours). The incidence of hypotension did not differ significantly between the two groups & with no reported case of any bradycardia in both the groups. The study demonstrates that oral gabapentin given 90 minutes before surgery would improve analgesic quality and reduce postoperative analgesic consumption without any

hemodynamic instability. There was no headache or dizziness in any of the patients who received oral gabapentin which shows the pre emptive analgesic efficacy is with out any major side effects.

# CONCLUSION

1. Single dose oral administration of gabapentin as pre emptive analgesic effectively reduces the post operative epidural analgesia requirements in patients undergoing elective orthopaedic lower limb surgeries.

2. Oral gabapentin has no effect on the hemodynamics of the patient

3. No side effects were noted with a single dose of oral gabapentin

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