"THE EFFECT OF ORAL GABAPENTIN AS AN ADJUVANT TO POST OPERATIVE EPIDURAL ANALGESIA FOR LOWER ABDOMINAL SURGERIES. A RANDOMIZED PLACEBO CONTROLLED DOUBLE BLIND TRIAL"

By

DR. SUJAY J. N.

DISSERTATION

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Under the Guidance of

Dr. V. K. DHULKHED M.D., D.A.

Professor and Head

DEPARTMENT OF ANAESTHESIOLOGY,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
BELGAUM – 10, KARNATAKA

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I hereby declare that this dissertation entitled **"THE EFFECT OF ORAL GABAPENTIN AS AN ADJUVANT TO POST OPERATIVE EPIDURAL ANALGESIA FOR LOWER ABDOMINAL SURGERIES – A RANDOMIZED PLACEBO CONTROLLED DOUBLE BLIND TRIAL"** *is a bonafide and genuine research work carried out by me under the guidance of* **Dr. V. K. DHULKHED** **M.D.,D.A.,** *Professor & Head, Department of Anaesthesiology, Jawaharlal Nehru Medical College, Nehru Nagar, Belgaum-590010.*

Date :

Place : Belgaum **Dr. Sujay J. N.**

KLE UNIVERSITY, BELGAUM, KARNATAKA

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled **"THE EFFECT OF ORAL GABAPENTIN AS AN ADJUVANT TO POST OPERATIVE EPIDURAL ANALGESIA FOR LOWER ABDOMINAL SURGERIES – A RANDOMIZED PLACEBO CONTROLLED DOUBLE BLIND TRIAL"** *is a bonafide research work done by* **Dr. SUJAY J. N.** *in partial fulfillment of the requirement for* the award of the degree of **M.D. (Anaesthesiology)**, *examination to be held in May 2009.*

Guide
Dr. V. K. Dhulkhed M. D. , D.A.
Professor & Head,
Department of Anaesthesiology,
J. N. Medical College, Belgaum

Date :
Place : Belgaum

KLE UNIVERSITY, BELGAUM, KARNATAKA

ENDORSEMENT BY THE HOD, PRINCIPAL/HEAD OF THE INSTITUTION

This is to certify that the dissertation entitled **"THE EFFECT OF ORAL GABAPENTIN AS AN ADJUVANT TO POST OPERATIVE EPIDURAL ANALGESIA FOR LOWER ABDOMINAL SURGERIES – A RANDOMIZED PLACEBO CONTROLLED DOUBLE BLIND TRIAL"** *is a bonafide research work done by* **Dr. SUJAY J. N.** *under the guidance of* **Dr. V. K. DHULKHED** **M.D., D.A.**, *Professor & Head, Department of Anaesthesiology, Jawaharlal Nehru Medical College, Nehru Nagar, Belgaum-590010.*

Dr. V. K. Dhulkhed **M.D., D.A.**
Professor & Head,
Department of Anaesthesiology,
J. N. Medical College,
Nehru Nagar, Belgaum-590010.

Date :
Place : Belgaum

Dr. V. D. Patil **M.D. D.C.H**
Principal,
J. N. Medical College,
Nehru Nagar, Belgaum-590010.

Date :
Place : Belgaum

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Date :

Place : Belgaum **Dr. Sujay J. N.**

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Date:

Place: Belgaum

Dr. Sujay J. N

ABBREVIATIONS

α2 agonist	Alpha 2 – Agonist
ASA	American society of Anaesthesiologists
Cap	Capsule
Cms	Centimeters
CSF	Cerebrospinal fluid
GI	Gastrointestinal
Hr	Hour
IASP	International association for the study of pain
Kg	Kilograms
M/sec	Meter / second
µg	Micrograms
mg	Milligrams
min	Minute
NSAIDs	Non steroidal anti inflammatory drugs
OAS PCA	Oral Analogue Scale. Patient Controlled Analgesia.
Tab	Tablet
T cells	Transmitting cells
TENS	Trancutaneous electrical nerve stimulation
VAS	Visual analogue scale
Yrs	Years

ABSTRACT

Background and objectives:

To determine whether adjuvanting epidural analgesia with gabapentin can alter first analgesic requirement time, Postoperative epidural fentanyl consumption, and Postoperative pain scores in the first 24 hrs after surgery.

Methodology:

66 ASA grade I and II patients, of either sex, aged 18 to 65 yrs, scheduled for lower abdominal surgery under epidural anaesthesia were included in the study. All were allocated randomly by computer generated randomization sheet into two groups of 33 each. Participants in the study were administered 2 capsules (either gabapentin or placebo) one hour before surgery with sips of water. A compound solution containing 0.5% bupivacaine and 2% lignocaine was prepared and administered into epidural space through 20 gauge epidural catheter. The volume of the drug was calculated based on the patient's body weight and age. Pain was assessed postoperatively using visual analogue scale. Inj. Fentanyl 20 μg was administered as rescue analgesic. The data were analyzed using Mann-Whitney 'U' test and unpaired student 't' test.

Results:

The time at which rescue analgesic was administered in the control group was 2.62±0.82 hrs and in the study group 4.27±1.24 hrs. The time at which rescue analgesics were required in the study group was significantly prolonged ($p<0.0001$). The amount of Inj. fentanyl required as rescue analgesic in the control group (103.03 ± 15.91μg) and in study group (69.09 ± 12.34 μg). This was statistically significant ($p<0.0001$).

Conclusion and interpretation:

We conclude that the preemptive administration of 800mg oral gabapentin as an adjuvant to postoperative epidural analgesia for lower abdominal surgeries significantly prolongs the time at which patient requires rescue analgesic and the amount of rescue analgesic needed was also significantly reduced in the study group as compared to control.

Keywords:

Gabapentin; Visual Analogue Scale; postoperative pain.

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INTRODUCTION

Pain has been a major concern of mankind since time immemorial and it has been the subject of ubiquitous efforts to understand and treat it.

The postoperative period is an integral part of the surgical experience of a patient. If the surgery is an injury, then allowing the patient to suffer postoperative pain is like adding insult to injury. Postoperative pain affects recovery from anaesthesia and surgery.[1]

Peripheral tissue injury provokes peripheral sensitization (a reduction in the threshold of nociceptor afferent peripheral terminals) and central sensitization (an activity dependent increase in excitability of spinal neurons.[2,3] 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 regimens could be used at different times relative to surgery to maximize the prevention of pain in response to different levels of sensory inputs.[2,3]

Preemptive analgesia has been defined as treatment that:

1. Starts before surgery.

2. Prevents the establishment of central sensitization caused by incisional injury (covers only the period of surgery);

3. Prevents the establishment of central sensitization caused by incisional and inflammatory injuries (covers the period of surgery and the initial post operative period).[4]

Many types of analgesics have been used alone or in combination for post-operative pain treatment. Postoperative pain is typically regarded as a type of nociceptive pain involving peripheral mechanoreceptor stimulation, inflammatory and neurogenic and visceral mechanisms, with a transient, reversible type of neuropathic pain.[5]

Consistent delivery of first class postoperative pain control is still a major challenge. So to meet this challenge there are various methods to counteract acute post-operative pain. They can be divided broadly into 2 groups.

1. Non pharmacological method
2. Pharmacological method

1. Non-pharmacological method: Though pharmacotherapy forms an integral part of management of acute pain, one has to look at various other methodologies to relieve post-operative pain.

The non-pharmacological methods can be used as adjuvants to the pharmacological methods of pain relief.

They are;

1. Herbal medicine 2. Hypnosis 3. Homeopathy
4. Meditation 5. Trans-cutaneous nerve stimulation
6. Acupuncture 7. Heat application

B. Pharmacological methods include

a. Opioids

b. Non steroidal anti-inflammatory drugs

c. Infiltration of local anaesthetic at the incisional site.

d. Epidural analgesia

e. Adjuvant to epidural anesthesia like gabapentin, clonidine

Despite all available methods, postoperative pain control has been a major challenge. Opioids are inevitably associated with emesis and risk of respiratory depression. Local anaesthetic techniques are often short lived or require interventional procedures, and the use of NSAIDS and COX-2 inhibitors are limited by renal, gastrointestinal and heamostatic effects. On contrary gabapentin significantly improves the quality of opioid analgesia, reduces opioid requirements, possibly prevents or reduces opioid tolerance and relieves anxiety. Furthermore, it doesn't depress respiration and has no effect on the gastric mucosa, platelets and renal function.[6]

Surgical injury can lead to chronic pain is well established. The estimated incidence of chronic pain after various procedures are; leg amputation about 60%, thoracotomy 50%, breast surgery about 30%, cholecystectomy 10-20%, and inguinal herniorrhaphy about 10%. Predictive risk factors for chronic postoperative pain are: preoperative pain, repeat surgery, psychological vulnerability, a surgical approach with risk of nerve damage, moderate or severe intensity of acute postoperative pain, radiation therapy and anxiety.[7, 8] So it is important to tackle postoperative pain at the earliest.

The rationale behind preoperative use of gabapentin is, the gabapentin has a substantial inhibitory effect on the development and establishment of allodynia and hyperalgesia. Hence this clinical study was undertaken to know whether preoperative use of gabapentin alters, first analgesic requirement time, and post-operative epidural fentanyl consumption and has any effect on postoperative pain scores in the first 24hrs after surgery.

OBJECTIVES

To determine whether adjuvanting epidural analgesia with gabapentin can alter:

- First analgesic requirement time
- Post-operative epidural fentanyl consumption in the first 24 hours after surgery.
- Post-operative pain scores in the first 24hours after surgery.

REVIEW OF LITERATURE

"Pain is a perfect misery the worst of all evils and excessively overturns all patients". This was the description given by John Milton in his 'paradise lost'.

Despite many advances in the provision of pain services, acute pain after surgery remains a serious cause of severe suffering that is often under managed despite the best efforts.[9, 10] There is therefore a pressing need for advances in the agents and techniques we can use to improve analgesic efficacy, and perhaps reduce the incidence of chronic suffering after surgery.

The literature examining the efficacy of preoperative administration of analgesic medication for the management of acute postoperative pain has been controversial. Non-steroidal anti-inflammatory drugs, local anaesthetics, $\propto_2$ – agonists and N-methyl – D – aspartate receptor antagonists are the main drug groups, which have been investigated for their synergistic role with opioid analgesics in the management of post-operative pain.[11]

Introduced in 1994 as an antiepileptic drug, gabapentin soon found promise in the treatment of neuropathic pain associated with diabetic neuropathy.[12]

A randomized, double blind, placebo controlled study was conducted. The authors found that gabapentin monotherapy to be efficacious for the treatment of pain and sleep interference associated with diabetic peripheral neuropathy and exhibits positive effects on mood and quality of life.[13]

Kissin I conducted a clinical study and he implicated the role of central neural sensitization in the amplification of postoperative pain.[14]

Jun JH and his colleagues conducted studies in animal models for incisional and thermal injury. They have shown that systemic or intrathecal gabapentin reduces hyperalgesia.[15]

Klaus Eckhardt and his colleagues made an attempt to know whether gabapentin enhances the analgesic effect of morphine in neuropathic pain. Their study revealed both a pharmacodynamics and pharmacokinetic interaction between morphine and gabapentin, leading to an increased analgesic effect of morphine and gabapentin.[16]

These previous studies raised considerable interest in the potential use of gabapentin for postoperative pain relief.

Fassoulaki A et al., conducted a study to explore the analgesic effect of gabapentin, mexiletine and placebo after breast surgery for cancer in 76 patients. They assumed gabapentin and mexiletine reduces postoperative analgesic consumption from 35% to 45%. The patients were randomized to receive in a double blinded manner, mexiletine 600 mg/d, gabapentin 1200 mg / day, or placebo for 10 days.The authors found consumption of rescue analgesic was reduced by 50% as compared to placebo. They found that gabapentin and mexiletine reduced the pain at rest and after movement on the third postoperative day ($p<0.05$). Pain after movement also was reduced by gabapentin between the second and fifth postoperative day ($p<0.005$). However, burning pain was more frequent in the control group ($p=0.033$).[17]

Pandey et al., evaluated the comparative pre emptive effects of oral gabapentin (300 mg), oral tramadol (100 mg) and placebo on post operative pain and intravenous fentanyl requirement in laparoscopic cholecystectomy. They assumed that preoperative gabapentin decreases postoperative fentanyl consumption by 20%. 499 ASA grade I and II patients were randomly selected and cap gabapentin 300 mg, tab tramadol 100 mg and placebo were given 2 hours before the surgery. Postoperative pain scores were recorded on a visual analogue scale. The authors found the mean pain scores were statistically significant ($p<0.05$) in gabapentin group as compared to tramadol and placebo group. The authors also found that the mean fentanyl consumed as rescue analgesic was significantly less in gabapentin group ($p<0.05$) as compared to placebo and tramadol.[18]

Turan et al., compared preoperative gabapentin with placebo to evaluate the analgesic effect of gabapentin after total abdominal hysterectomy and tramadol consumption. Reason for choosing gabapentin over NSAIDs by them was the use of NSAIDs was limited by adverse renal, gastrointestinal and hemostatic effects. They chose a sample size of 25 patients to detect a significant difference of 15% or more in tramadol consumption. They found a reduction of 35.55% in fentanyl consumption in gabapentin group at the end of 24hrs after surgery. Postoperative pain scores were reduced by 68.75%at the end of 24hr after surgery in the gabapentin group.[1]

As gabapentin started to show analgesic effects anaesthesiologists begin to use it more and more for postoperative pain relief. A study was done to determine the analgesic efficacy of gabapentin and to compare it with placebo in monitored anaesthesia care of patients undergoing rhinoplasty or endoscopic sinus surgery. The authors assumed that with preoperative gabapentin therapy postoperative analgesic consumption would

decrease by 40%. They found that the total fentanyl consumption was reduced by 17.56% in gabapentin group as compared to placebo and first analgesic requirement time was also increased significantly ($p < 0.001$) as compared with the placebo group.[19]

Pandey et al., randomly allocated 56 patients into two equal groups to receive either gabapentin 300 mg or placebo two hours before lumbar discoidectomy. After surgery, the pain was assessed on a visual analogue scale. On the assumption that a 25% difference in fentanyl consumption between the groups would be of clinical interest, 22 subjects were chosen in each group. They found with preoperative gabapentin, the total 24hr fentanyl consumption was reduced by 35% in the gabapentin group as compared to placebo group .The postoperative pain scores were also significantly less in the gabapentin group throughout the study as compared to the placebo group with $p<0.05$.[20]

A randomized, double blind placebo controlled study was conducted to compare the efficacy of oral gabapentin in patients undergoing elective thyroidectomy. Assuming a target of 25% reduction in morphine consumption, a sample size of 30 patients per group was calculated. Post thyroidectomy pain was assessed on a visual analogue scale at rest and during swallowing in the first 24 hours postoperatively. Morphine 3 mg IV was used as rescue analgesic. The authors found morphine consumption was reduced by 48.47% in the gabapentin group as compared to the placebo group in the 24hr after surgery. The postoperative pain scores were significant with $p<0.01$.[21]

Gilron. I et al., has explored the effect of combination of gabapentin (1800 mg / day) and rofecoxib after abdominal hysterectomy. They divided the subjects into 4 groups. Group1 (control) received oral placebo, group2 received oral placebo and

rofecoxib 50mg,group3 received oral gabapentin 1.2gm and group4 received oral gabapentin 1.2gm and rofecoxib 50mg.Patient controlled analgesia containing morphine was used. The authors found that total PCA morphine usage was decreased by 43%, 24% and 54% in-group 2, 3, 4 respectively as compared to group1. Thus they concluded that combination was more effective than placebo and either single agent alone.[22]

This metaanalysis reviewed the efficacy of oral gabapentin. Studies were selected comparing oral gabapentin with either placebo or active treatment in adults with acute postoperative pain. Note was made about the details of postoperative pain scores at rest and on mobilization and amount of rescue analgesic demanded. Seven double blind placebo controlled trails had information from 907 patients for evaluation of efficacy. In five of the eight studies, postoperative pain scores were low at rest in the gabapentin groups. In seven of the eight studies conducted found lower opioid consumption in the gabapentin group.[11]

Turan et al., conducted study on 40 patients to evaluate the effect of oral gabapentin as an adjuvant to epidural analgesia. The authors chose a sample size of 25 patients per group to detect a significant difference of 10% or more in epidural consumption. The patients undergoing lower extremity surgery were randomly selected to receive placebo capsules (control) or gabapentin 1.2 g / day) before and 2 days after surgery. Anaesthesia technique was standardized. The pain scores were assessed using verbal rating scores. The VRS pain scores were significantly greater at 1,4,8,12 and 16hr after operation in patients receiving placebo than in the gabapentin group ($p=0.001$). Duration of patient controlled epidural analgesia usage was also reduced in the gabapentin group (38hrs) as compared to 57hrs in the placebo group. Time to the return

of bowel function after surgery in the gabapentin group was 16.3 hrs as compared to the placebo group 18.4 hrs.[23]

A study was conducted to know whether gabapentin provides effective postoperative analgesia whether administered preemptively or post incision in patients undergoing open donor nephrectomy. 60 ASA subjects were chosen. Assuming that a 25% reduction in the mean fentanyl consumption, each group had 25 subjects. The authors found that the total fentanyl used in the gabapentin group who received it preoperatively was 39.08% less as compared to the placebo group. They also found that the total fentanyl consumed in subjects who received gabapentin postincisionally was 32.51% less as compared to placebo. Thus they concluded that preincision administration of 600 mg gabapentin has no added benefit over post incision administration in terms of pain scores and fentanyl consumption.[24]

Recently a study was done to evaluate the role of gabapentin as pre-emptive analgesic in patients undergoing total abdominal hysterectomy in epidural anaesthesia. Assuming that following preoperative gabapentin therapy, VAS would reduce by 50%, 25 patients were enrolled in each group. Fifty patients with ASA grade I and II were assigned to receive 300 mg gabapentin or placebo two hours before surgery. The authors noticed that mean number of top-ups required were significantly less in the gabapentin group (3.4) as compared to the placebo group 5.6 in the first 24hr of surgery. The patient in the gabapentin group was significantly lower VAS scores at all times2, 4,8,12 and 24hrs than those in the placebo group.[25]

Patients are understandably anxious during the perioperative period and this can be a significant problem in some. Gabapentin has anxiolytic properties. [26]

Menigause et al., in their study, administered gabapentin orally 24 hours before surgery to patients undergoing arthroscopic cruciate ligament repair under general anaesthesia. Preinduction VAS anxiety scores were impressively less in the gabapentin group (28 mm Vs 68mm $p<0.0001$); postoperative pain control and early knee mobility were also significantly better.[27]

As more researchers got interested in gabapentin, they have compared pre operative gabapentin with placebo and opioids. They found that it is more effective non-invasive adjuvant to regional anaesthetic technique.

So we decided to compare preoperative gabapentin with placebo.

BASIC SCIENCES

Historical review:

Man has been afflicted with the EVIL (pain) since his beginning, for as the records of every race are examined, one finds testimonials to the omnipresence of pain. Prayers, exorcisms and incantations bearing testimony to the prevalence of pain are found on Babylonian clay tablets, in Papyri written in the days of pyramid builders, in Persian leather documents, in inscriptions from Mycenae, on parchment rolls from Troy. Such records continue down through the ages in every civilization and in every culture.

Pain has been one of the greatest factors to affect the course of human events, for scarcely and man has escaped its throes. The cause of painful disease, in prehistoric time was linked with intrusion of magic fluids, evil spirits, or pain demons into the body. Treatment consists of extracting the intruding object or frightening away the pain demons.

The ancient Egyptians believed painful afflictions other than wounds were caused by religious influences of their gods or spirits of the dead. The routes of departure of the intruding demons could be vomit, urine or the sweat.

In ancient India the earliest concepts of pain and other medical knowledge were attributed to the god Indra, as recorded in the Vedas and Upanishads. Buddha, in 500 B.C., attributed the universality of pain in life to the frustration of desires: “Birth is attended with pain, decay is painful, and disease is painful. Union with the unpleasant is painful; painful is separation from the pleasant and any craving that is unsatisfied, that too is painful.” Charaka, the first of India’s great teachers of medicine, stated that “All joy and pain was experienced in the heart”, which was considered the seat of consciousness.

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

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

In the middle ages the centre of medicine shifted to Arabia. Avicenna in his "Cannon of Medicine" codified all available medical knowledge and described aetiology of 15 different types of pain. In 1804, Descartes in his book "L Homme (Man)" described the conduction of sensation including pain via delicate threads contained in the nerves, which connected the tissue to the brain.[28]

The new era of analgesia was initiated with the discovery of nitrous oxide by Joseph Pristley. Modern approach to the scientific study of pain and its control began in the 19th century. Charles Beu described that the functions of dorsal root are distinct from those of the ventral root. After 156 years Johannes Muller fully expounded this idea. The modern era of systemic analgesia began in 1806, when morphine was isolated by Sertuner and it was frequently used intramuscularly for preoperative medication and postoperative analgesia.

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

Regional analgesia for the management of intractable pain was also introduced in the last century. The 19th century was to produce still another great advance in conquer of pain by neurosurgical techniques. Surgeons started interruption of afferent pathways to control pain.

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

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

ANATOMICAL AND PHYSIOLOGICAL ASPECTS OF PAIN PERCEPTION

Definition of pain:

Pain is an extraordinarily complex sensation which is difficult to define and equally difficult to measure in an accurate objective manner. It has been variously defined as:

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damages (International Association for the Study of Pain (IASP), 1986).

Pain is a complex constellation of unpleasant sensory, perceptional, and emotional experiences with associated autonomic, psychological and behavioral responses.[28, 29]

Pain can be represented as a VENN DIAGRAM

This shows that the sensation of pain differs among individual patients.

Emotional – varies according to patient's psychological composition.

Rational – varies with patient's previous experience, insight and motivation.

Physical – varies with type and site of surgery.

Postoperative pain is usually transitory, which shows progressive improvement over a relatively short time course.

All pain perception depends upon the transmission of impulse through pathways within the nervous system from the site of the stimulus to the higher centres of the brain; they may impinge upon our consciousness and be interpreted. The principal parts of the nervous system involved in this process are:

- Receptors in the skin and other organ.
- Peripheral nerves.
- Neuronal aggregates in the spinal cord and associated fiber tracts.
- The brainstem and thalamus
- The limbic system
- The cerebral cortex
- Other parts of the brain indirectly involved.

PAIN THEORIES IN THE TWENTIETH CENTURY

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

Central summation theory by Livingston in 1943 suggested that the intense stimulation resulting from nerve and tissue damage activates fibers that project to intern- uncial neuron pools in the spinal cord, which in turn project to brain mechanisms that underline pain perception.

Strong proposed **the Fourth Theory of Pain** and believed that pain can be separated into two components: the perception of pain and the reaction to pain.

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

Gate control theory: The term "Gate Control" is now applied to the rapidly acting mechanisms which accept and control the passage of impulses from the afferent fiber input to cells which may then trigger the various effector systems and evoke sensation (Melzack and Wall 1965, Wall 1978).

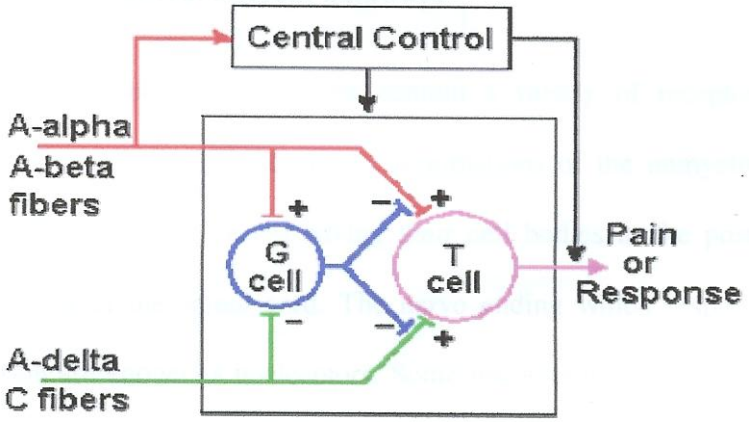


Fig. 2: Gate control theory

Melzack and Wall (1956) observed in decerebrated and spinal cats, that peripheral stimulation of large myelinated fibers produced a negative dorsal root potential and that stimulation of C fibers caused a positive dorsal root potential. They postulated that these potentials, which were a reflection of presynaptic inhibition or excitation, modulated the activity of secondary transmitting neurons (T cells) in the dorsal horn, and that this

modulation was mediated through an inhibitory interneuron (I cell) placed the T cell in lamina V of the dorsal horn and the still unidentified cells, in laminae II and III. The essence of this theory is the large diameter fibers excite the I cells, which in turn cause a presynaptic inhibition of T cells. Conversely the small pain afferent fibers inhibit the I cells leaving the T cells in an excitatory state.

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

Pain receptors and peripheral afferent pathways:

The skin and subcutaneous tissues contain a variety of receptors of varying degree of complexity. These are the terminations of the unmyelinated and finely myelinated afferent nerves having their cell bodies in the posterior (dorsal) root ganglia of the spinal cord. The nerve endings which respond to painful stimulation are known as nociceptors. Some nociceptors respond mainly to mechanical injury whereas others, polymodal nociceptors are responsive to noxious heat and chemical irritation as well as mechanical injury. Receptors similar to those innervating the skin are found in muscle and viscera. Their response differs however and they will produce pain of a dull, vague nature following distension, stretch or traction and will not respond to burning, crush or incision. Central representation of somatic and visceral nociception may be different thus according for some of the paradoxical difference between these two types of pain.

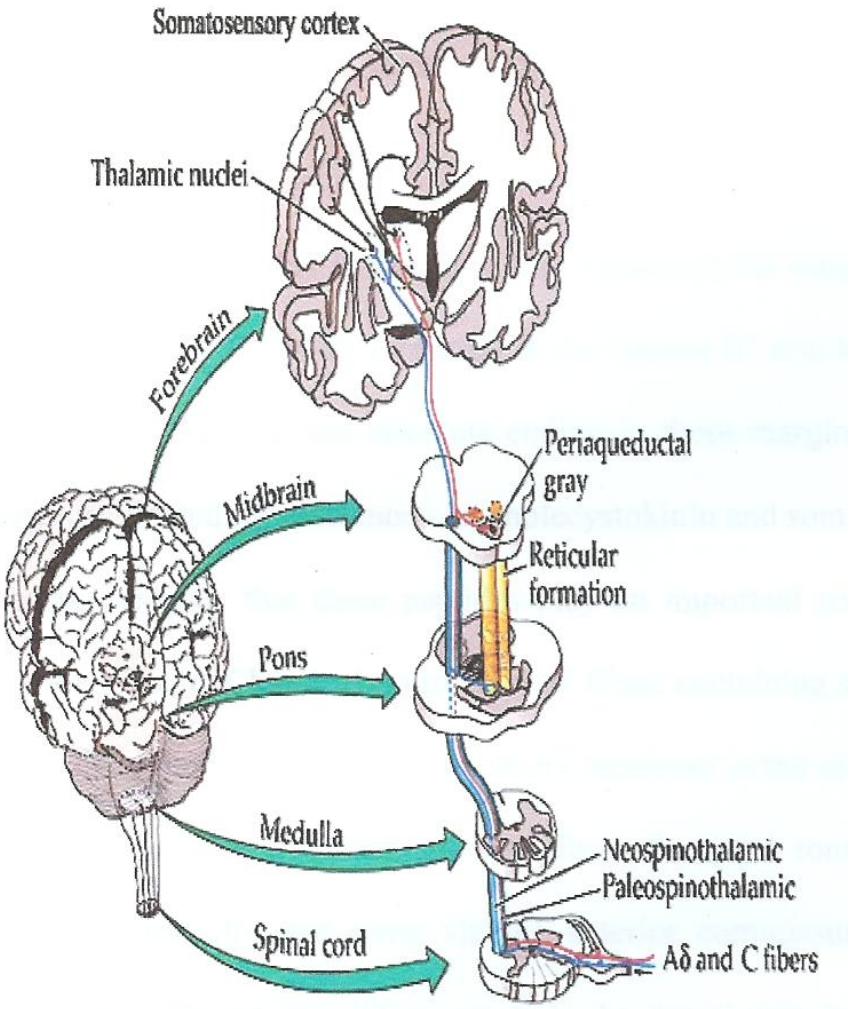


Fig. 3 : Pain pathways

Afferent conduction:

The nerve fibers of which the nociceptors are the terminal portion are relatively small in cross section and comprise of finely myelinated A-delta fibers 1-5 micrometer in diameter with conduction rate at 5-45 m/sec. the unmyelinated C fiber diameter 0.4-1.1 micro meters conducting at 0.5-2.0m/sec. other modalities of sensation are transmitted in

the rapid myelinated A–Beta fibers of 5-15 micrometer diameter with conduction at 30-100 m/sec. A–delta generated pain is well localized whereas C fiber pain is poorly localized.

Organization of pain pathways:

The cell bodies of the primary pain afferents (i.e. the first order neurons) are located in the dorsal root ganglia. Central extensions of the primary neurons project via the dorsal root to the dorsal horn of the spinal cord and in the case of cranial pain afferents, to the nucleus of the trigeminal nerve. These A-delta and C fibers occupy the lateral part of the root entry zone and within the spinal cord form a discrete bundle, the 'tract of lissauer' (Neospinothalamic tract). After traversing the lissauer's tract, they synapse in the dorsal horn of the spinal cord. In the dorsal horn, cell bodies are arranged in series of laminae some of which have classical names, but which are most simply given roman numerical by Rexed i.e. laminae I-IX.

The A-delta fibers terminate in lamina I, also known as the marginal cell layer of waldeyer, where "C" fibers terminate in the lamina II also known as ' substantia gelationosa'. Many of the afferents ending in these marginal layers contain neuropeptides, including substance – p, cholecystockinin and somatostain. There is increasing evidence that these peptides play an important role in the normal transmission of pain. Chemical destruction of fibers containing substance – P in animals produces analgesia. Most of the fibers terminate in the segment of their entry into the cord, but some extend rostrally and caudal to one or two adjacent segments ipsilaterally and some via the anterior commissure to the contralateral dorsal horn. Some pain fibers penetrate the dorsal gray matter and terminate in lamina V.

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

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

In addition to the lateral spinothalamic tract, which is a fast conduction pathway that projects directly to the thalamus, the anteriolateral fasiculus of the spinal cord contains a slowly conducting, medially placed system of fibers, which reaches the thalamus via one or more relays in the reticular core of the brain stem. This latter group of fibers is referred to as spinoreticulothalamic tract or paleospinothalamic tract. The conduction of diffuse, poorly localized pain arising from the deep structures (gut/ periosteum) has been ascribed to this tract.

Thalamic terminus:

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

Thalamo cortical projections:

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

Physiology and Psychology of pain:

Stimuli that produce pain vary for different tissues. An adequate stimulus for skin is one that produces tissue damage or injury viz, pricking, cutting crushing, burning and freezing. However these stimuli are inadequate when applied to stomach and intestines where the local effects of an engorged or inflamed mucosa, distension or spasm of smooth muscle and traction on the mesenteric attachment produces pain. In skeletal muscle, pain is produced by ischemia (intermittent claudication), necrosis, hemorrhage, injuries to connective tissue sheaths and injection of irritating solutions. Prolonged contraction of the skeletal muscle produces an aching type of pain. Ischemia is also the most important cause of pain in cardiac muscle. Joints are insensitive to pricking, cutting and cautery, but pain is produced by inflammation of the synovial membrane and by exposure to the hypertonic saline.

Perception of pain:

The threshold for the perceptions of pain i.e. the lower intensity of stimulus recognized as pain is approximately the same in all persons. However, the emotional reaction and verbalization vary from individual with the personality and character of the individual. The threshold for pain is lowered by inflammation and raised by centrally acting analgesic drugs and lesions of the nervous system. Neurotic patients in general have the same pain threshold as normal subjects, but their reaction may be excessive or abnormal.

The conscious awareness of pain occurs only when the pain impulses reach the thalamocortical levels. The precise roles of the thalamus and cortical sensory areas in this mental process are not fully understood. However, it is traditional teaching that the recognition of a noxious stimulus as such is the function of the thalamus, and that the parietal cortex is essential for the appreciation of the intensity, localization and other discriminating aspects of sensation. This seems to be an over simplification. Probably a close and harmonious relationship between the thalamus and cortex must exist in order for a sensory experience to be complete, that the cerebral cortex governs the patients reaction to pain cannot be doubted as frontal lobotomized subject react briefly, if at all to pain.

Methods of pain measurement:

One cannot determine for the individual patient how much nociception occurs in response to tissue damage for which we have to rely on the expression of the patient to accurately measure the subjective nature of pain.

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

a. Withdrawing
b. Grimacing

c. Crying

d. Asking for analgesics

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

Introspective method:

Patient or trained attender attempts to assess pain.

Behaviourise method:

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

Pain as self-report on a single dimension:

Verbal descriptor Scales – Melzack and Torgerson introduced the following scale for pain intensity: "Mild, Discomforting, Distress, Horrible, Excruciating."

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

Visual Analogue Scale (VAS):

Currently, the most commonly used method; first described by Aitken is 1966. The subject makes a mark on a 10 cms line horizontal or vertical, one end of which is marked as " No pain" and the other as " The worst pain one can imagine". The position of the mark on the line measures how much pain the subject experiences.

Oral analogue Scale (OAS):

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

Pain as self – reports on multiple dimensions:

McGill pain questionnaire – It scales pain in three dimensions: sensory, affective, and evaluative.

West Haven – Yale Multidimensional pain inventory – This has been designed to be briefer and more classical in its psychometric approach.

Brief pain inventory – is a quick, multidimensional pain measurement that has demonstrated reliability and validity.

Memorial pain assessment card – It scales pain, relief and mood on VAS and adds a set of adjectives reflecting pain intensity.

Pain perception profile is based on cross-modality matching.

ACUTE POSTOPERATIVE PAIN

Postoperative pain is under treated for a number of reasons which include, lack of knowledge regarding the effective dose ranges and duration of action of opioids and unfounded fear of respiratory depression and addiction in hospitalized patients experiencing pain. The concept of postoperative pain management by anaesthesiologists is growing. These, along with the advent of newer opioids with higher safety levels and better techniques of administration, have brought about large improvements in the successful alleviation of postoperative pain.

Factors that modify postoperative pain:

a. The site, nature and duration of surgery.
b. The type and extent of the incision and other surgical trauma
c. The physiological and psychological make up of the patient.
d. Presence of complications related to surgery.
e. Preoperative psychological, physiologic and pharmacologic preparation of the patient.
f. The anaesthetic management before, during and after the surgery.
g. The quality of post operative care.[30]

Adverse effect caused by postoperative pain:

Physiologic:

Include pulmonary, cardiovascular, gastrointestinal and urinary dysfunction, impairment of muscle metabolism and function and neuroendocrine and metabolic changes.

Respiratory:

Surgery including that of the upper abdomen or thorax produces a number of pulmonary changes, including reduced vital capacity and forced expiratory volume. Upper abdominal incisions result in reflex mediated increase in tone of abdominal muscles during expiration and a decrease in diaphragmatic function. The results are reduced pulmonary compliance, muscle splinting and inability to breath deeply or cough forcefully leading to hypoxia, hypercarbia, retention of secretions, atelectasis, and pneumonia. Increased muscle tone increases oxygen consumption and lactic acid production.

Cardiovascular:

Pain causes stimulation of sympathetic neurons and subsequent tachycardia, increased stroke volume, cardiac work and myocardial oxygen consumption. The risk of myocardial ischemia or infarction may be increased as is the risk of deep vein thrombosis when fear of aggravating pain results in reduced physical activity, venous stasis and platelet aggregations.

Gastrointestinal and urinary:

Ileus, nausea, vomiting, hypomotility of the urethra and bladder and retention of urine can occur for a number of reasons that include nociceptive impulses from viscera and somatic structure.

Neuroendocrine and metabolic:

Suprasegemental reflex responses to pain, result in increased sympathetic tone, hypothalamic stimulation, increased catecholamine and catabolic hormone like cortisol,

adrenocorticotrophic hormone, antidiuretic hormone, growth hormone, cyclic adenosine monophosphate, glucagons, aldosterone, renin, angiotensin 2 and decreased secretion of anabolic hormones insulin and testosterone. The effects of these changes include sodium and water retention and increased blood glucose, free fatty acids, ketone bodies, and lactate. Metabolism and oxygen consumption are increased and metabolic substrates are mobilized from storage depots. A catabolic state and negative nitrogen balance result, if the process continues.

Psychological:

Postoperative pain is a major source of fear and anxiety for patient and if prolonged, leads to anger, resentment and lack of trust in the doctors and nurses who are perceived to be withholding pain relief. Pain leads to insomnia with further delayed recovery. Some patients may even try self medication which could be hazardous.

The common methods adopted for giving postoperative pain relief are:

By increasing the pain threshold:

Pharmacologic

a. Centrally acting analgesics
b. Peripherally acting analgesics
c. Adjuvants like gabapentin, pregabalin, $\propto_2$ agonist.

Non-pharmacologic

a. Counseling
b. Hypnosis

By modulating the pain pathways

a. Transcutaneous electrical nerve stimulation (TENS)

b. Acupuncture

c. Cryotherapy

d. Heat therapy

By interrupting the nociceptive pathway

a. Nerve blocks and neurolysis

b. Surgical ablation – Cryoanalgesia

APPLIED ANATOMY AND PHYSIOLOGY OF EPIDURAL SPACE

Anatomy of epidural space:

The epidural space forms part of the vertebral column lying between the spinal durameter internally and the periosteal lining of the vertebral canal externally. The spinal durameter represents the meningeal layer of the durameter of the brain.

Boundaries:

Superiorly - foramen magnum

Inferiorly – the sacrococcygeal membrane and sacral hiatus

Anteriorly – Posterior longitudinal ligament covering the vertebral bodies and intervertebral disc

Posteriorly – the periosteum of anterior surfaces of laminae, articular processes and their connecting ligaments, roots of vertebral spines and the interlaminar space filled by ligamentum flavum.

Laterally: The periosteum of pedicles of the vertebrae and the inter vertebral foramina.

Size: Average size is 5 mm to 6 mm

It is 1.5mm at cervical region, 2.5 to 3 mm at upper thoracic level

4-5 mm at lower thoracic level

5-6 mm at lumbar level

Contents of epidural space:

It includes dural sac, spinal nerve roots, extradural plexus of veins, spinal arteries, lymphatics and fat.

Physiology of epidural blockade

The physiological responses to epidural blockade with currently available local anaesthetic agents implies sympathetic blockade accompanied by somatic blockade which may involve sensory and motor blockade alone or in combination.

Anaesthetic drug injected epidurally, block nerve conduction depending upon the concentration and volume injected, the sensitivity of different fibre types and the drug employed.

Factors influencing the distribution of local anaesthetic

1. Patient characteristic
    a. Age
    b. Height
    c. Weight
    d. Gender
    e. Intra abdominal pressure
    f. Anatomic configuration of spinal column position
    g. Position of the patient.
2. Technique of injection
    a. Site of injection
    b. Direction of injection (needle)
    c. Direction of bevel
    d. Rate of injection

3. Characteristic of anaesthetic solution
    a. Density
    b. Amount
    c. Concentration
    d. Temperature
    e. Vasoconstriction
    f. Other additives like neostigmine, midazolam

Site of action of local anesthetic agent in the epidural space:

1. The site of action may be on anterior and posterior nerve roots with their ganglia, in the epidural space
2. On the mixed nerve roots in the paraverteral space after they have shed their dural sheaths
3. On the visceral afferents accompanying sympathetic fibres, white and grey communicans.
4. On the nerve roots in the intradural or sub arachnoid space after inward diffusion of the drug across the dura.
5. Diffusion into the subperineural and subpial spaces from the so called 'ink cuff' zone where the anterior and posterior nerve roots fuses and it may eventually pass centripetally and reach the substance of the cord and diffuse from these into the CSF.
6. Peripherally placed ascending and sympathetic excitatory tracts.

Complications of epidural block are

A Immediate	Delayed
1. Bradycardia 2. Hypotension 3. Cardiac arrest 4. Respiratory arrest	1. Meningitis 2. Anterior spinal artery syndrome 3. Epidural haematoma, abscess 4. Root damage 5. VI cranial nerve palsy 6. Paraplegia 7. Backache

GABAPENTIN

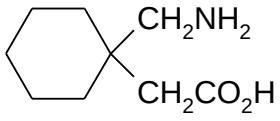
Gabapentin is a novel anticonvulsant drug.

Chemistry:

Gabapentin, a structural analogue of GABA is a water soluble, bitter tasting, white crystalline substance with a structure resembling GABA.

The molecular weight of gabapentin is 171.34. At physiological pH, it is highly charged existing as Zwitterion with two pKa values of 3.68 and 10.7

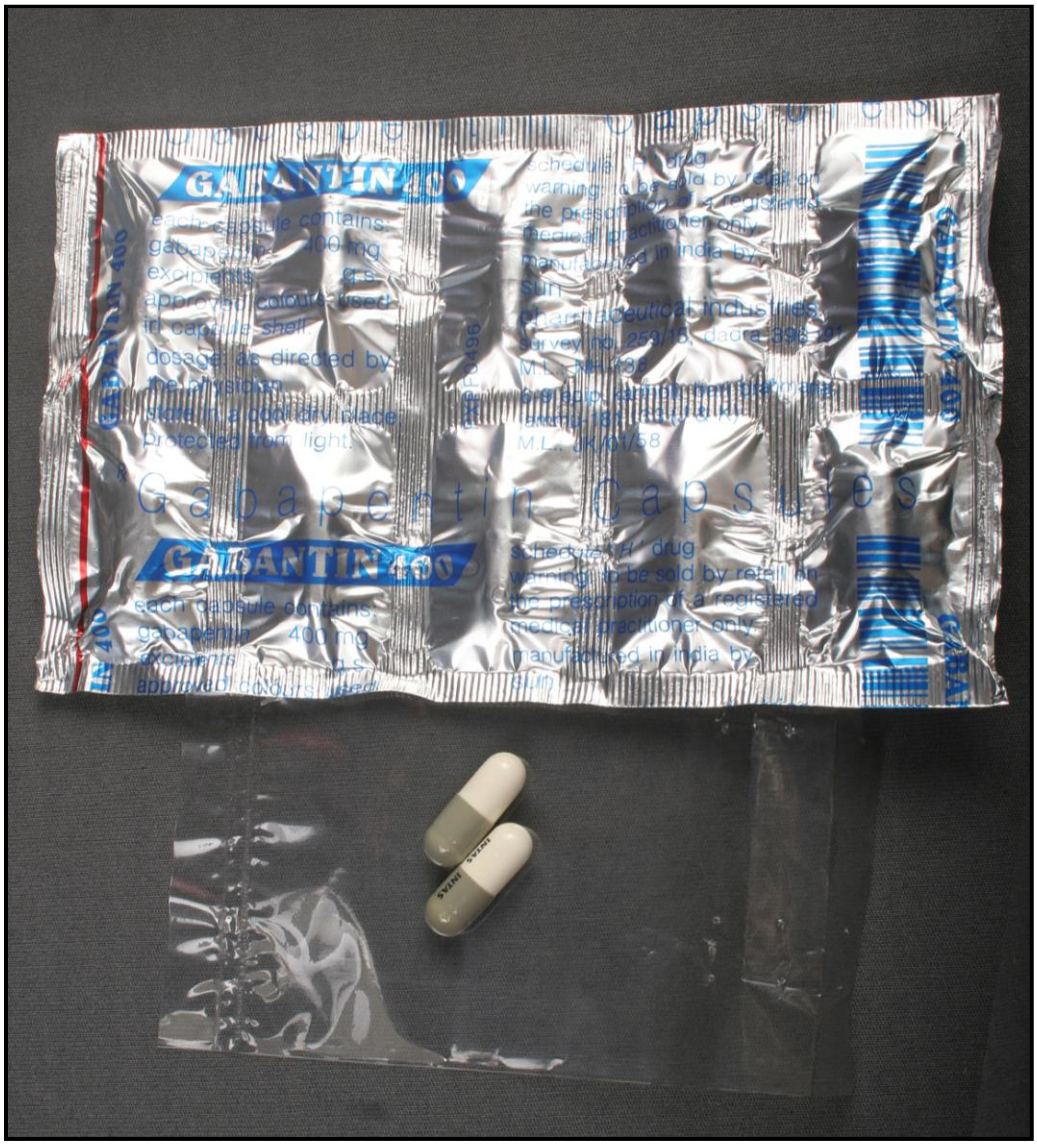
Structure of gabapentin:



Pharmacokinetics:

Gabapentin is available only as oral preparation. It is absorbed in the small intenstine by a combination of diffusion and facilitated transport. The bioavailability of a 300mg dose is ≈60%, 600 mg is ≈ 40%, and 1600 mg is 35%.It is extensively distributed with volume of distribution 0.6-0.84 L/kg.

Gabapentin is not metabolized in humans. Eliminated unchanged in the urine. The elimination half life is i.e. between 4.8 to 8.7 hr.



Capsule gabapentin 400 mg

Interactions:

No pharmacokinetics interaction has been demonstrated with other anticonvulsant drugs. Cemetidine decreases the clearance of drug by 12%.

Mechanism of action:

Gabapentin has no direct gabaergic action. It doesn't block GABA uptake or metabolism. It acts at the undescribed receptor limited with the L-system aminoacid transporter protein. The mode of action in the treatment of neuropathic pain has not been fully elucidated. The gabapentin doesn't bind to $GABA_A$ or $GABA_B$ receptor.But increased synthesis and reduced breakdown of GABA have been described.

Adverse effects:

Gabapentin is well tolerated with few serious side effects. They are somnolence, dizziness, ataxia, fatigue.

Indication:

1. Seizures – partial seizure – 900 to 1800 mg/day
2. Neuropathic pain
    i. Diabetic neuropathy
    ii. Trigeminal neuralgia 600-1200 mg/day
    iii. Multiple sclerosis
    iv. Complex regional pain syndrome
    v. Post poliomyelitis pain
3. As an adjuvant to other drugs in postoperative pain.[35]

METHODOLOGY

After obtaining institutional ethical committee clearance, the present study was undertaken on 66 patients. The gabapentin group i.e. study group included 33 patients. The control group i.e placebo group included 33 patients. Patients aged between 18-65 years of either sexes belonging to ASA grade I and II scheduled for elective lower abdominal surgeries viz. total abdominal hysterectomy, appendicectomy, meshplasty under epidural block were included in the study after obtaining written informed consent at KLES Hospital and MRC, Belgaum.

Sample size calculation:

A sample size of 66 was selected by calculating percentage of mean difference of 42 for the placebo group for postoperative pain scores and percentage of mean difference of 72 for the gabapentin group in first 16 hour after surgery. The effect size was 30% i.e. assuming that the gabapentin reduces total fentanyl consumption by 30%. With power of 80% and α value of 0.05.[1]

P1 = 72% P2 = 42% P = 57%

$Z_{\alpha} = 1.65$ $Z_{\beta} = 0.84$

$$\text{Sample size (n)} = \frac{2 (Z_{\alpha} + Z_{\beta})^2 P(1-P)}{(P_1-P_2)^2}$$

$$= n = 33.$$

The sample size of 33 was taken in each group.

Study design : A randomized double blind placebo control trial

Inclusion criteria:

- Patients between 18 – 65 years of age
- No clinically significant cardiovascular and central nervous system disease
- ASA grade I and II
- Patients undergoing lower abdominal surgeries. Such as total abdominal hysterectomy, appendicectomy and meshplasty were included.

Exclusion criteria:

- Allergy to bupivacaine
- Renal insufficiency
- History of anticonvulsant intake
- History of bleeding diathesis
- Appendicular abscess, strangulated and obstructed inguinal hernia

Methodology

Preanaesthetic evaluation was done a day before the surgery. The postoperative pain scores were recorded on a visual analogue scale. Patients were taught to read the visual analogue scale a day before the surgery. A written informed consent was taken from the patients. Participants were randomly allocated into two groups using computerized simple randomized technique.

a. Control group (Placebo) – 800 mg capsules similar (2 capsules of placebo 400 mg) to gabapentin capsules in colour and size containing starch powder

b. Study group : Gabapentin 800 mg, (2 capsules of gabapentin 400 mg each) was administered 1 hr before surgery with sips of water.

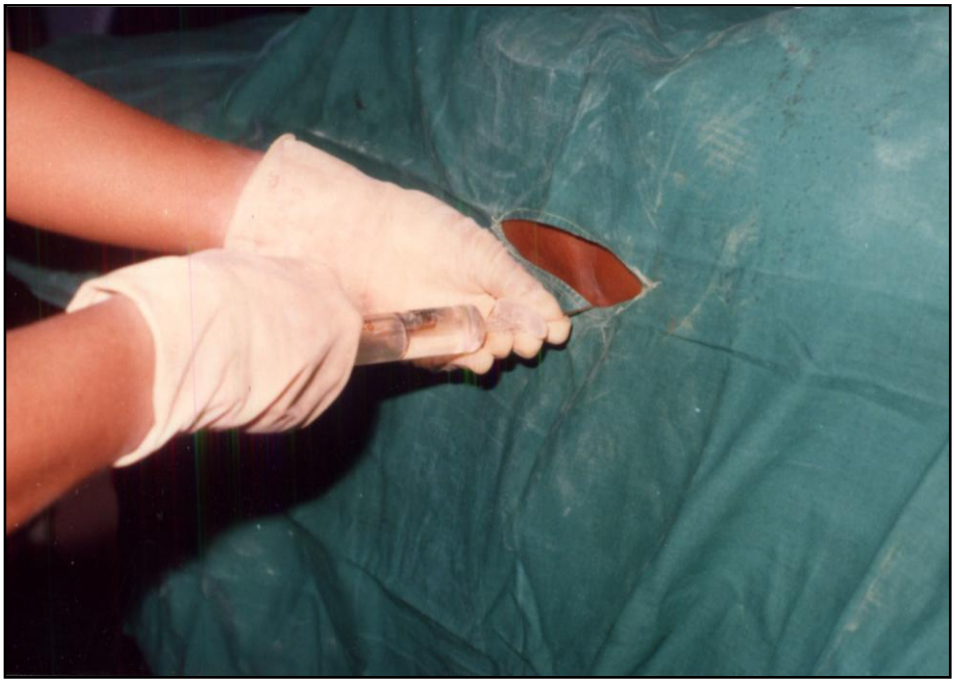
c. Intra venous line was secured using 18 gauge IV cannula and crystalloid was started.

Heart rate, non-invasive blood pressure and oxygen saturation were monitored before and during surgery.

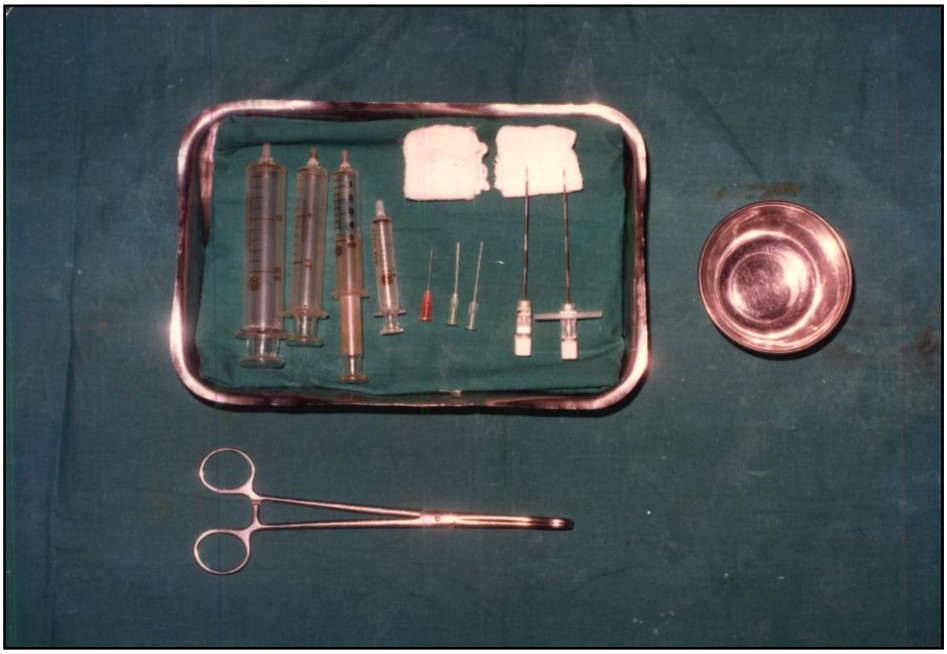
Under strict aseptic precaution, a 18 gauge Tuohy needle was used to insert an epidural catheter at a suitable interspace i.e., for lower abdominal operation with incision through T_{10} to L_1 to L_2 the catheter tip was placed at T_{12} to L_1 using a mid line approach. The epidural space was identified using loss of resistance technique for air using 18 gauge Tuohy needle. After confirming negative aspiration for blood or CSF, an epidural catheter of 20 gauge was secured into the above said interspace and Tuohy needle was withdrawn. A test dose of 3 cc solution containing 5 mg / cc of lignocaine + 5µg / cc of adrenaline (1:200000) was injected into epidural space. The patient was monitored for 2-5 minute for spinal blockade and tachycardia. Depending upon the no. of segments to be blocked, the volume of epidural drug requirement was calculated. A compound solution containing 0.5% bupivacaine and 2% lignocaine in the ratio of 1: 4 was prepared. For lumbar region 2 cc/ segment and for thoracic region 1.5 cc / segment adjusted to the body weight and age was selected.

After injecting the compound solution in 5 cc increments the surgery was commenced.

The hypotension (mean arterial blood pressure < 25%) below baseline was treated with ephedrine 5-10 mg IV and bradycardia (heart rate < 50/ min) was treated with atropine 0.6mg. Intra operative blood loss was replaced with crystalloid fluids at a 3:1 ratio or allogenic blood transfusion at a 1 : 1 ratio.



Technique of epidural anaesthesia



Contents of Epidural Tray

The postoperative pain scores were recorded using visual analogue scale (VAS). The patient was assessed with VAS every half an hour for first four hours and every 2 hours for the next 20 hours after surgery. The patient was monitored for pain by a on duty nursing staff. The time at which the patient complained of pain was recorded and if the post operative pain score was ≥ 4 on the visual analogue scale, the rescue analgesic in the form of fentanyl at a dose 20 µg mixed with 10ml of normal saline through the epidural catheter was administered. This was taken as first analgesic requirement time.

The postoperative pain scores for 24 hours were assessed and the first rescue analgesic requirement time, the total fentanyl consumption were recorded in the gabapentin and placebo group.

Statistical analysis:

After completion of the study, the data were unblinded and entered into the statistical software package Med-Calc version 9.0. The mean and SD of pain score for both the groups at time intervals of every half hourly for the first four hours and every two hourly for the next 20 hours and the total fentanyl top ups received by both the groups were calculated and were analyzed using non parametric Mann-Whitney 'U' test.

p value < 0.05 was taken as significant.

Mean and SD for Age, duration of surgery, total analgesic consumption and first analgesic requirement time were calculated and analysed using student unpaired 't' test.

p value < 0.05 was taken as significant

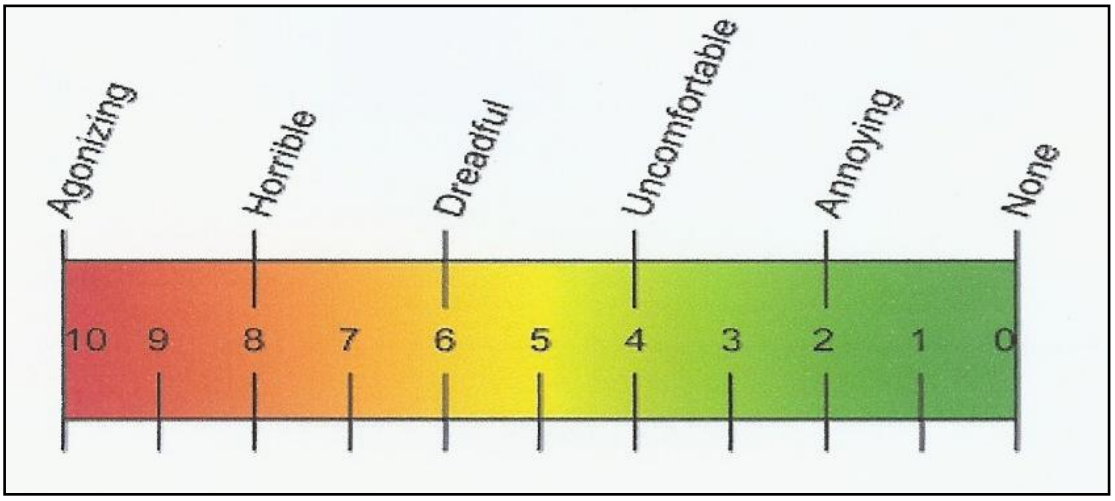


Figure 4: Visual Analogue Scale

RESULTS

The present study was undertaken in 66 ASA grade I and grade II patients of both sex aged 18 to 65 years scheduled for lower abdominal surgeries viz, appendicectomy, total abdominal hysterectomy and meshplasty. All patients enrolled completed the study.

Table No. 1 : Gender Distribution

Groups	Male	Female
Control groups	14	19
Study groups	20	13

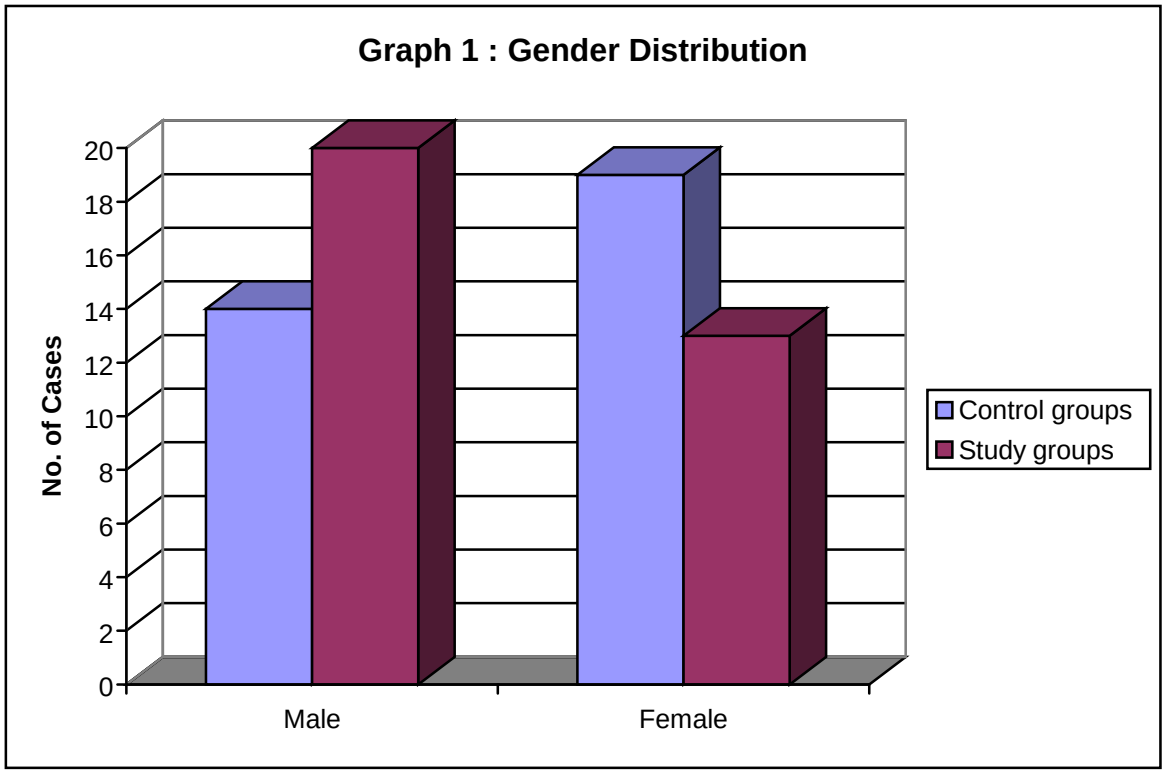


Table No. 2 : Age distribution

Groups	**Mean (Yrs)**	**SD (Yrs)**
Study groups	41.64	13.64
Control groups	36.67	10.86

The demographic data with respect to age and gender were comparable between the two group as shown in table 1 and 2.

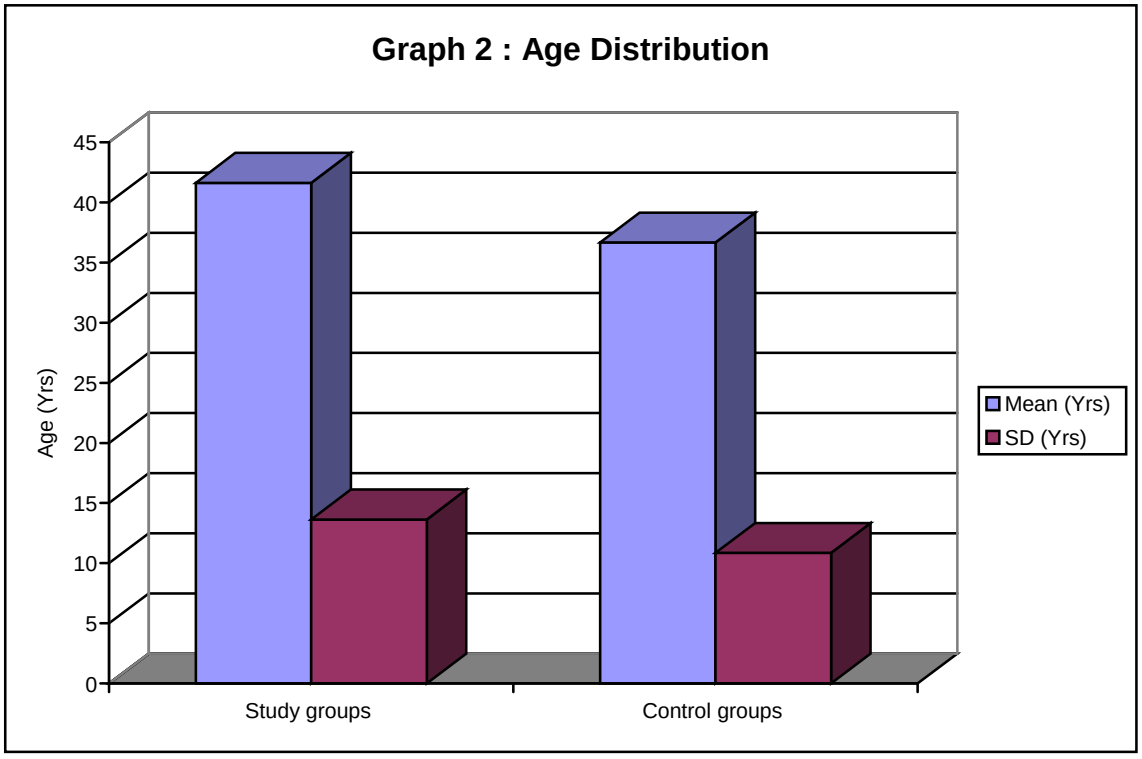


Table No. 3 : ASA grading

Groups	ASA grade I	ASA Grade II
Study groups	28	5
Control groups	24	9

ASA grading was comparable between two groups

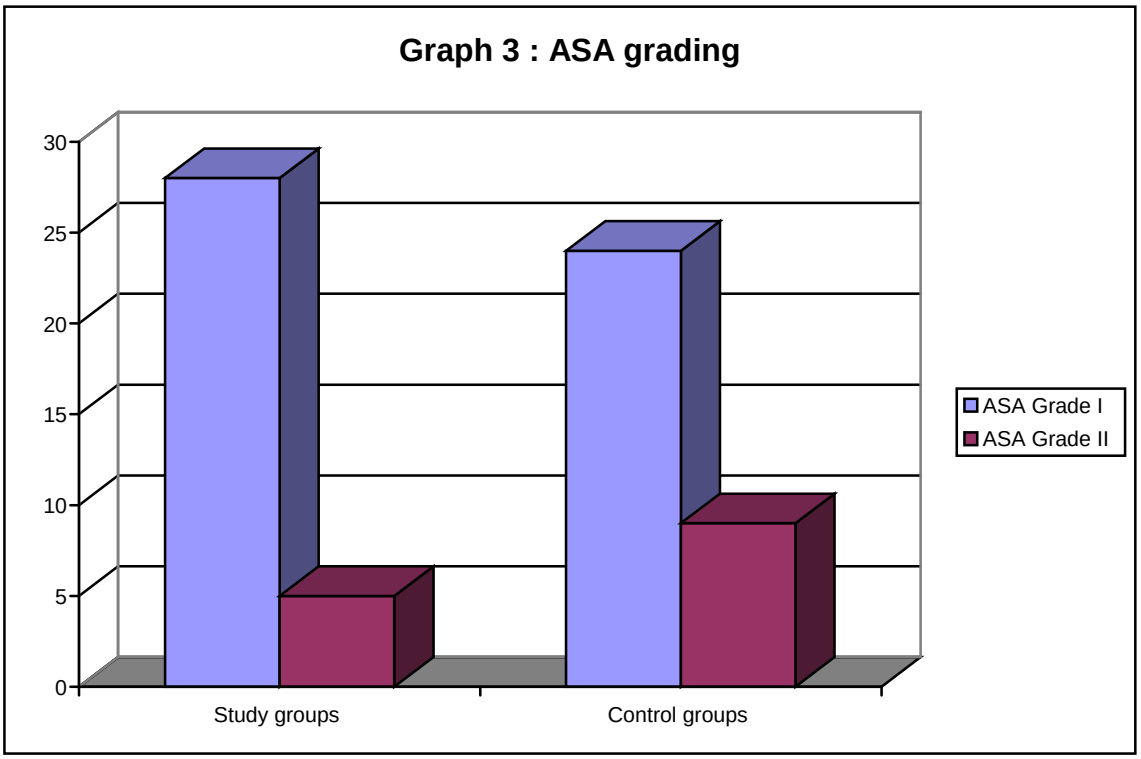


Table No. 4 : Duration of surgery

Groups	Mean (Hrs)	SD (Hrs)
Study groups	1.86	0.45
Control groups	1.76	0.34

The total duration of surgery in control group was (1.86 ± 0.45 hrs) and in study group it was (1.76 ± 0.34 hrs) p value was 0.0746020. The duration of surgery was comparable between two groups.

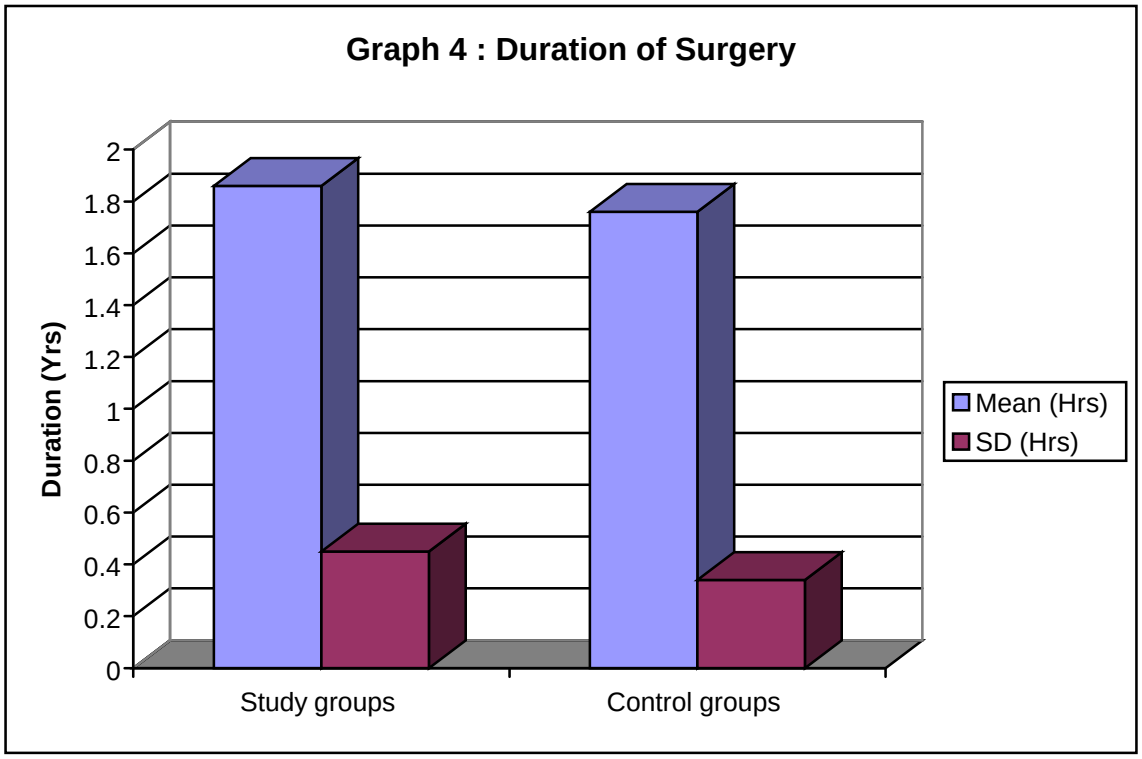


Table No. : 5 : Post operative pain scores

Time (Hrs)	Control group		Study group		P value (<0.05)	Inference
	Mean	SD	Mean	SD		
0.5	0.06	0.35	0.00	0.00	0.8324	Not significant
1	0.36	0.90	0.00	0.00	0.2042	Not significant
1.5	0.70	1.38	0.00	0.00	0.0905	Not significant
2	1.67	1.69	0.09	0.38	0.0001	Significant
2.5	2.21	2.12	0.55	1.06	0.0026	Significant
3	1.79	1.96	1.70	1.36	0.8374	Not significant
3.5	2.00	1.80	2.55	1.60	0.1802	Not significant
4	2.55	1.94	2.70	1.81	0.898	Not significant
6	1.73	1.92	1.55	2.03	0.6306	Not significant
8	2.15	1.66	1.70	1.67	0.2432	Not significant
10	2.58	1.87	2.52	1.84	0.9081	Not significant
12	2.30	2.14	2.18	2.14	0.7778	Not significant
14	2.06	2.05	1.79	1.76	0.7147	Not significant
16	2.15	2.06	2.18	1.78	0.9234	Not significant
18	2.18	2.02	2.18	2.07	0.9847	Not significant
20	1.70	1.98	1.70	1.88	0.9847	Not significant
22	2.03	1.61	1.79	1.63	0.4248	Not significant
24	2.70	1.70	2.00	1.58	0.0627	Not significant

The postoperative pain scores were comparable between the two groups for the first 1.5 hr after surgery. (Table no 5). There was significant difference in the pain scores between the two groups during 2 to 2.5 hrs. After 2.5 hrs, the two groups were comparable (Table no 5).

Graph 5 : Post Operative Pain Score

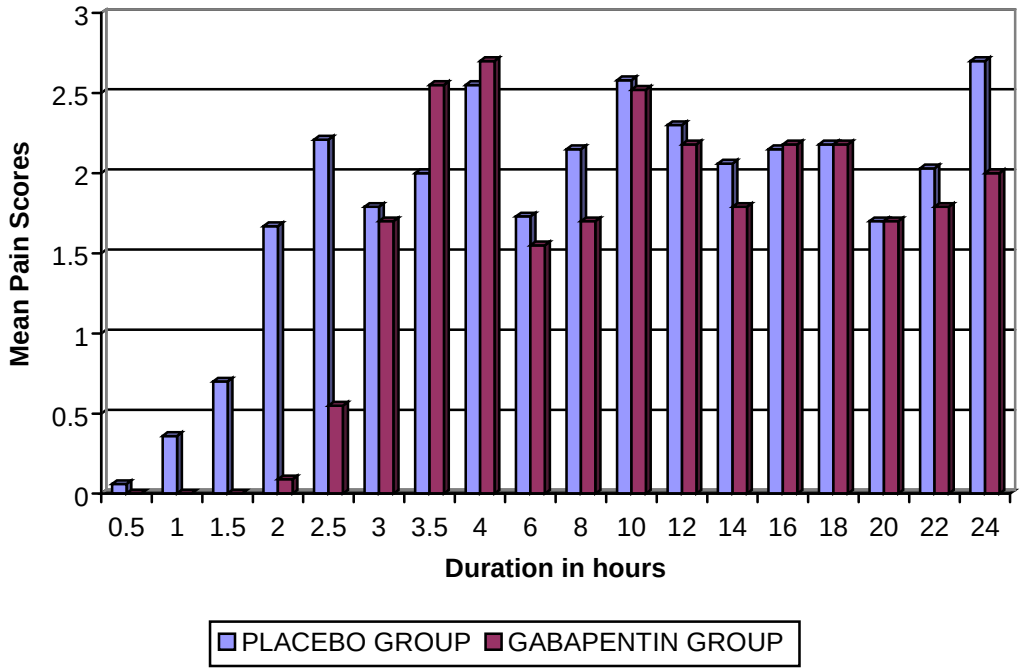


Table No. 6 : First analgesic requirement time

Groups	Mean	SD
Control groups	2.62	0.82
Study groups	4.27	1.24

The first analgesic requirement time in the postoperative period in the gabapentin group (4.27±1.24 hrs) was significantly more than ($p<0.0001$) in the placebo group (2.62±0.82 hrs).

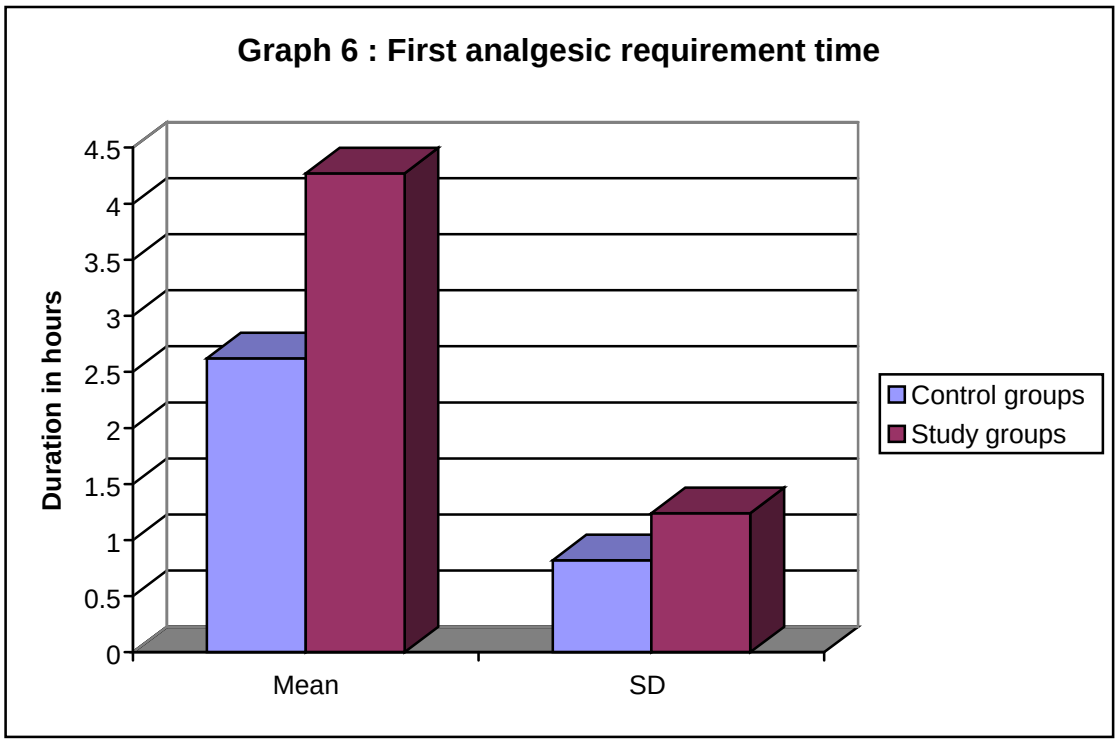
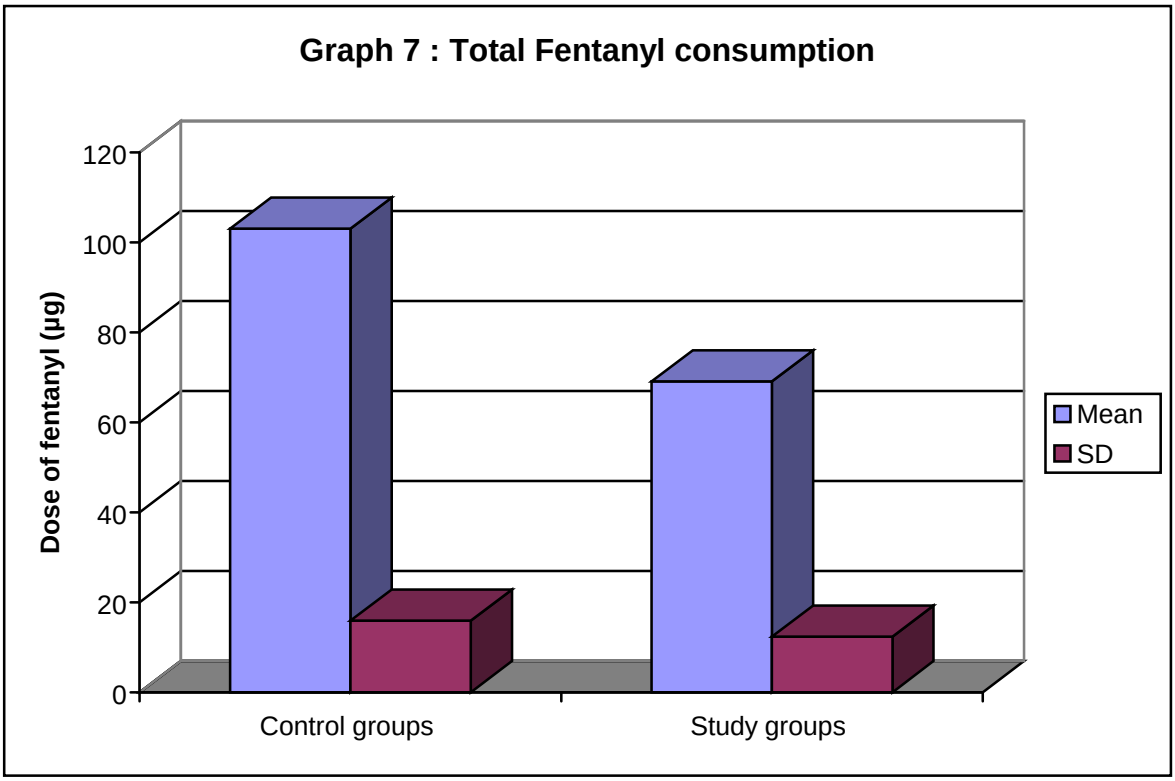


Table No. 7 : Total fentanyl consumption

Groups	Mean	SD
Control groups	103.03	15.91
Study groups	69.09	12.34

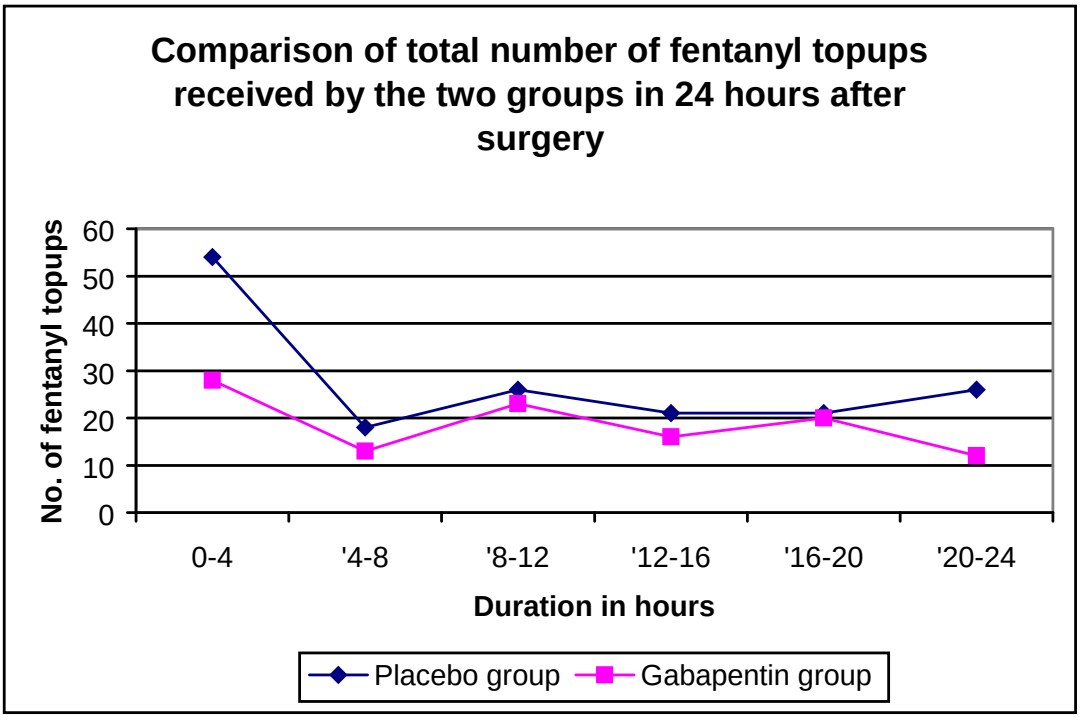


The total fentanyl consumption in the first 24 hours after surgery in the gabapentin group i.e. study group (69.09±12.34 µg) was significantly (p value of <0.0001) less than in the placebo group i.e. control group (103.03 ± 15.91 µg).

Table 8 : Comparison of total number of fentanyl topups received by the two groups in 24 hours after surgery

Time in hrs	Placebo group	Gabapentin group
0-4	54	28
4-8	18	13
8-12	26	23
12-16	21	16
16-20	21	20
20-24	26	12

The number of fentanyl top ups received by patients in the gabapentin group was less (28) as compared to placebo group (54) in the first four hours of the study. The total number of fentanyl top ups received by the gabapentin group at the end of 24 hours was also less (112) as compared to the placebo group (166).



DISCUSSION

Postoperative pain which is very unpleasant and physiologically stressful is very common problem in postoperative period.

Today, the knowledge on mechanism of production of acute pain has advanced sufficiently over the past decade. So that rational rather than empirically derived therapy can be used by aiming specifically at interrupting the mechanism responsible for the generation of clinical pain. This concept is more relevant in the management of surgical pain than in any other scenario.

Pain in the postoperative period does not bear a direct relationship with the surgical injury. Due to peripheral and central hypersensitivity or the wind up phenomenon post operative pain is always more severe for any surgical injury. Any therapeutic regimen that will prevent or modulate this sensitization should be helpful in the effective management of postoperative pain. Preemptive analgesia is one such intervention. The underlying principle would be that therapeutic intervention is made in advance of pain rather than in reaction to it.

Numerous antihyperalgesic methods and drugs have been evaluated in order to reduce the central neuronal hyperexcitability which theoretically, may amplify postoperative pain.[31] Although gabapentin has been used in the treatment of neuropathic pain syndromes, it has also demonstrated potent antihyperalgesic properties in preclinical and clinical studies, without affecting acute nociception.[15-17,32-33]

There are various methods to tackle the postoperative pain. They are

1. Opioid analgesia
2. Cyclooxygenase – 2- selective inhibitors
3. Non steroidal anti inflammatory drugs (NSAIDs)
4. Epidural anaesthesia
5. Adjuvants to epidural anesthesia viz gabapentin, clonidine, neostigmine.

Of these, adjuvant like gabapentin to epidural anesthesia has been in an experimental stage.

Gabapentin is an antiepileptic drug and a structural analogue of gamma amino butyric acid (GABA). Gabapentin does not bind with plasma protein and is not metabolized in humans. After a single oral dose, mean maximum plasma concentrations are attained in two to three hours. Gabapentin significantly improves the quality of an opioid analgesia, reduces opioid requirement, possibly prevents or reduces opioid tolerance and relieves anxiety. In the Indian set up we could not find a single study. So we decided to do this study.

We conducted this study to know the effect of oral gabapentin as an adjuvant to post operative epidural analgesia for lower abdominal surgeries.

In the present study we administered fentanyl 20 µg through epidural route as a rescue analgesic.

In our study the demographic data were comparable for age, sex in both the groups (table 1 and 2). ASA status was comparable between the two groups.(table 3)

The total duration of surgery (table 4) in the control group (placebo group) was 1.86±0.45 hrs compared to the study group (gabapentin group) wherein the duration of surgery was 1.76 ± 0.34 hrs. The duration of surgery has a bearing on the postoperative analgesic requirement as prolonged duration of tissue handling increases the local production of inflammatory substances and oedema, hence increasing the requirement for analgesics. In our study the mean duration of surgery was comparable between the two groups (p value 0.074602).

It has been demonstrated that a 600 mg single dose of gabapentin enhanced the effect of morphine, but side effects appeared approximately in 40% of volunteers when these drugs were used concomitantly.[16]

In another study conducted by Pandey et al, the postoperative pain scores were significantly less in the gabapentin group throughout the study ($p<0.05$).[20]

In our study, the mean pain scores in the placebo group were significantly high between 1.5 to 2.5 hrs. This can be explained on the fact that at this time, the local anesthetic action would have worn off. The patient in the gabapentin group would be still experiencing significantly less pain, as the half-life of gabapentin is 5 to 7 hrs. The patient in gabapentin group started complaining of pain 4 hrs after surgery. The patient in both the groups received inj fentanyl through the epidural route as a rescue analgesic. After 4 hrs, the patients in the two groups were comparable (table 5).

The exact duration of post operative pain differs widely among individuals and is influenced by a multitude of inter connected factors. Isolation of individual factors that may influence the duration of postoperative pain is therefore impossible. Compounded on this difficulty is the fact that pain being a multi dimensional sensation is not easy to quantify exactly. The visual analogue scale used in this study to determine the intensity of pain is unidimensional and therefore has its limitation. It was used however because it had some important advantages in our setting. The patients understood it easily and even illiterate subjects could participate.

In the present study the first analgesic requirement time in the postoperative period in the gabapentin group (4.27±1.24 hrs) was significantly ($p < 0.0001$) more than in the placebo group (2.62 ± 0.82 hrs) (table 6). A study conducted by Turan A and his colleagues found that the time for first analgesic request (18±9h v/s 9± 7 hrs) was significantly ($p < 0.0001$) longer in the gabapentin group[19]. This study supports our view.

The amount of Inj. fentanyl required as rescue analgesia was noted in each group (table no. 7). In the control group it was 103.03±15.91µg and in study group it was 69.09 ± 12.34 µg. The difference in the requirement of rescue analgesic between the groups was found to be significant ($p<0.0001$). In the present study, the total fentanyl consumption in 24 hrs after surgery was reduced by 33% in gabapentin group. The lower requirement of fentanly in the study group is helpful in reducing the opioid associated side effects like pruritus, nausea, vomiting.

We did not observe any side effects associated with a single oral dose of gabapentin.

The number of fentanyl topups received by the patient in the gabapentin group was less (28) as compared to placebo group (54) in the first 4 hrs after surgery. The total number of fentanyl topups received by the patients in the gabapentin group was a significantly less (112) as compared to the placebo group in the first 24 hours after surgery (table 8).

Recently a study was done to evaluate the role of gabapentin as preemptive analgesic in patients undergoing total abdominal hysterectomy under epidural anesthesia. The authors noticed that the amount of rescue analgesic needed was reduced by 50% in the gabapentin group as compared to the placebo group.[25] As in our study the authors used rescue analgesia through the epidural route.

Recent studies suggest that gabapentin may be useful in the perioperative setting, as an adjuvant to parenteral opioid analgesics. Our study is the first clinical study using gabapentin as an adjuvant to regional analgesia and we used rescue analgesic through epidural route. The main aim of combining different analgesic drugs and techniques is to obtain synergistic or additive actions that allow a smaller dose of each agent to be used and, thereby improve the safety profile. This can be achieved by combining analgesic acting at different locations, for example, centrally and peripherally acting analgesics.

In the present study gabapentin was administered one hour before surgery. Contrary to the other studies where gabapentin was administrated 2 hours before the surgery.[17-23,25-27] A study conducted by Dirks et al, found a substantial reduction in postoperative morphine consumption without significant side effects.[31] Another study conducted by Turan et al, found significant decrease in post operative pain score in the early postoperative period and decreased postoperative epidural analgesic consumption throughout the study period and had a higher satisfaction score than the control group.[23]

In the search for literature we could find a few studies, which had contrasting results. In one study regarding acute pain, it has been demonstrated that gabapentin had no analgesic effect on its own when given as a single oral dose of 600mg in volunteers, although it enhances the analgesic effect of morphine.[16] In another study a single dose of 300 mg of the drug given one hour before laparoscopic cholecystectomy failed to attenuate acute postoperative pain.[34]

There is a paucity of data regarding dose response characteristics of gabapentin. However, by choosing the highest reasonable dose, we avoided the risk of a considerably larger study with a potentially negative outcome. Another limitation might be that gabapentin was given as a single dose, which may have resulted with a decreased effect over time. The half-life of gabapentin is 5 – 7 hours and further studies with divided doses are needed.

Non-steroidal anti-inflammatory drugs are commonly used analgesics for minor surgery and are useful adjunctive analgesics in patients undergoing major surgery, decreasing pain and opioid requirements. They are well established, effective and inexpensive. However, their use in some groups of patients may be limited by adverse renal, gastrointestinal and hemostatic effects. Gabapentin is less well established at present. More studies are needed to establish the gabapentin as a better opioid sparing drug and to prove that it has lesser side effects as compared to NSAIDs. Gabapentin is well tolerated. It has few side effects and minor interactions with other drugs when used for the treatment of chronic pain.[32] But in the present study, we did not observe any side effects associated with a single oral dose of gabapentin.

Based on the results obtained from our study we conclude that, the preoperative administration of 800 mg of oral gabapentin an hour before the surgery significantly ($p<0.0001$) prolongs the time at which patient requires rescue analgesic (4.27 ± 1.24 hrs) compared with placebo (2.62 ± 0.82 hrs). The total fentanyl consumption after surgery in the first 24 hours in the gabapentin group i.e., study group was (69.09 ± 12.34 μg) was significantly ($p<0.0001$) less than in the placebo group (103.03 ± 15.91μg). The postoperative pain scores were significantly less in the early hours in the study group i.e, from 1.5 hr to 2.5 hr as compared to the placebo group.

Oral gabapentin is an effective, noninvasive adjuvant to postoperative epidural analgesia for lower abdominal surgeries.

FUTURE SCOPE: In our study only a single dose of 800mg of oral gabapentin was used an hour before surgery which did reduce postoperative pain scores for the first 2.5hrs after surgery. There is a scope for study to use different dose of gabapentin in preoperative period till an optimum dose of gabapentin is determined.

CONCLUSION

Based on the results obtained from our study we conclude that, the preoperative administration of 800 mg of oral gabapentin an hour before the surgery significantly ($p<0.0001$) prolongs the time at which patient requires rescue analgesic (4.27 ± 1.24 hrs) compared with placebo (2.62 ± 0.82 hrs). The total fentanyl consumption after surgery in the first 24 hours in the gabapentin group i.e, study group was (69.09 ± 12.34 μg) was significantly ($p<0.0001$) less than in the placebo group (103.03 ± 15.91 μg). The postoperative pain scores were significantly less in the early hours in the study group i.e, from 1.5 hr to 2.5 hr as compared to the placebo group.

Oral gabapentin is an effective, noninvasive adjuvant to postoperative epidural analgesia for lower abdominal surgeries.

SUMMARY

To summarize, the present study was undertaken on 66 ASA grade I and II patients, of either sex, aged 18 to 65 years scheduled for elective lower abdominal surgeries under epidural block after obtaining their written informed consent.

The objectives of the present study were to determine whether adjuvanting epidural anaesthesia with gabapentin can alter:

First analgesic requirement time

Postoperative epidural fentanyl consumption in first 24 hrs after surgery.

Postoperative pain scores in first 24hrs after surgery

After obtaining approval from the institutional ethical committee, all the 66 participants in the study were randomly allocated into 2 groups of 33 each by computer generated randomization table; study group and control group. After a thorough pre-anaesthetic evaluation, the study group received oral gabapentin 800 mg and control group received 800 mg of placeboes. All participants were administered epidural block in left lateral position using 0.5% Bupivacaine and 2% lignocaine to obtain a sensory blockade of T_6 –T_8 under strict monitoring. The anesthesia was standardized.

Postoperatively pain was assessed at half an hour for the first four hours and every two hourly for the next 20 hours using a visual analogue scale. If the visual analogue scale any time during study was more or equal to four then inj. Fentanyl 20 μg mixed with 10ml of normal saline was administered through epidural route as rescue analgesic. Time at which rescue analgesic was given and the total fentanyl consumption during 24 hours after the surgery was noted.

Both the groups were demographically comparable. The mean duration of surgery was also comparable.

We observed that the first analgesic requirement time in the postoperative period in the gabapentin group (4.27 ± 1.24 hrs) was significant (P<0.0001) than in the placebo group (2.62 ± 0.82 hrs).

The total fentanyl consumption after surgery in the first 24 hours in the gabapentin group i.e, study group was (69.09 ± 12.34 μg) was significantly (p<0.0001) less than in the placebo group (103.03 ± 15.91 μg).

But the postoperative pain scores were significant only at 2 and 2.5 hours after the surgery.

Based on the results obtained from our study we conclude that, 800mg of preoperative administration of oral gabapentin prolongs the time at which patient requires rescue analgesic and also reduces total fentanyl consumption in the first 24 hours after surgery when compared with placebo.

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INFORMED CONSENT FORM

"The effect of oral gabapentin as an adjuant to post operative epidural analgesia for lower abdominal surgeries –a randomised placebo controlled double blind trial". conducted by Dr. Sujay J.N., Postgraduate student in MD Anaesthesiology, JNMC, Belgaum. under the guidance of Dr. V.K. Dhulkhed, Professor and Head, Dept of Anaesthesiology, J.N. Medical College, Nehru Nagar, Belgaum under KLE Academy of Higher Education, Belgaum.

Respected Sir/ Madam we request you to participate in our study as you are eligible for the study. During the study you will be asked some questions regarding your present, past medical history and you are supposed to answer to the best of your knowledge.

Your participation in research is voluntary. Your decision whether or not to participate in the study will not affect your relationship with J.N.M.C. If you decide to participate you are free to withdraw at any time.

The purpose of the research is to compare the effectiveness of oral gabapentin with that of oral placebo in post-operative epidural analgesia.

Procedures involved:

If you agree to enroll yourself in my study, I will ask your present, past and family history. Then you will be clinically examined in detail and investigations like Hb%, urine routine, bleeding time and clotting time will be done. Depending on the group you will be administered oral gabapentin or oral placebo.

Study Group– Gabapentin 800mg (2 capsules of 400mg each)

Control Group – Oral Placebo

Risks and Benefits:

The side effects of gabapentin is sedation, dizziness, ataxia and fatigue. The absorption of gabapentin from the intestine depends on aminoacid carrier system and shows the property of saturability which means increasing the dose does not proportionately increase the amount absorbed. This makes gabapentin relatively safe.

Benefits gained by enrolling yourself in the study is you receive adequate post-operative pain relief.

Alternatives:

Even if you decline the participation in the study, you will get the routine line of management.

Privacy and confidentiality:

The only people to know that you are a research subject are members of the research team. No information provided by you during the research will be disclosed to others without your written permission except:

- In emergency to protect your health.
- If required by law.

Authorization to publish results:

When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with you will remain confidential.

Compensation:

In the event of injury related to the study, treatment will be made available through KLESH and MRC, Belgaum. there is no compensation or payments for such medical treatment by law. If you are injured you may contact Dr. Sujay J.N., PG, MD Anaesthesiology, KLESH and MRC, Belgaum, Phone : 9448157085.

Questions :

In case you have any questions related to the study you can contact Dr. Sujay JN. Phone : 9448157085.

In case you have any questions about your rights as a study participants, you can contact Dr. V.D. Patil, Principal, JNMC, Belgaum. Phone: 0831-2471350

CONSENT FOR PARTICIPATION IN RESEARCH TRIAL:

I Mr./Mrs. _____voluntarily agree for the participation as a subject of study. By signing this consent form I am not giving up any of my legal rights, I may withdraw from the study at anytime. I am signing the consent form after having read or been read for me in my vernacular language including the risks and the benefits and having all questions answered.

Name of the Participant :_____

Signature or the left thumb print of Participant _____

Witness Name: _____Signature: _____

Investigators Name: _____Signature: _____

Date:

Place:

VISUAL ANALOGUE SCALE [28]

Instructions: Mark on the line below how strong your pain is right now.

0 10

No pain at all ——————————————— The worst pain imaginable

PROFORMA

"THE EFFECT OF ORAL GABAPENTIN AS AN ADJUANT TO POST OPERATIVE EPIDURAL ANALGESIA FOR LOWER ABDOMINAL SURGERIES –A RANDOMISED PLACEBO CONTROLLED DOUBLE BLIND TRIAL".

Name: Age (in yrs): Sex: (M/F)

Ward: IP No.: Religion:

Address:

On General Physical examination:

Weight: Height : Temperature:

Pallor: Cynosis: Pedal edema: Clubbing:

Pulse: BP: RR:

CVS:

Heart Sounds:

RS:

Breath Sounds: Trachea:

CNS:

SPINE:

PREVIOUS SURGERIES:

INVESTIGATIONS:

Hb%:

BT: CT:

CHEST X-RAY if required:

ASA STATUS:

DIAGNOSIS:

PROPOSED SURGERY:

Preoperative : PR /min BP: mm/Hg

ANAESTHETIC PROCEDURE:

Intravenous line will be secured using 18 gauge IV Cannula and Crystalloid will be started.

Heart rate, non-invasive blood pressure and oxygen saturation will be monitored before and during surgery.

Under strict asepsis, A 18 gauze Tuohy needle will be used to insert an epidural catheter at the suitable interspace ie, for lower abdominal operation with incision through T-10 to L_1 to L_2 using a midline approach. The epidural space will be identified using loss of resistance technique using 18 gauge tuohy needle. If there is no blood or CSF aspiration, a testdose of 3 cc solutions containing 5mg./cc of lignocaine + 5 μg/cc of Adrenaline (1:1000) is injected into epidural space. The patient is monitered for 3 –5 minute for spinal blockade and tachycardia. After 5 minutes of injecting the test dose, the epidural catheter will be secured at the above said interspace and tuohy needle will be withdrawn. Depending upon the no. of segments to be blocked, the volume of epidural drug requirement is calculated. A compound solution containing 0.5% bupivacaine and 2% lignocaine in ratio of 1:4 is prepared. For lumbar region 2cc/segment and for thoracic region 1.5 cc/segment adjusted to the body weight and age is selected.

The epidural catheter will be secured at the above said interspace and tuohy needle will be withdrawn. The compound solution will be injected in 5cc increments through the catheter into the epidural space and surgery will be commenced.

The hypotension (mean arterial blood pressure <25%) below baseline will be treated with ephedrine 5-10mg IV and bradycardia (heart rate <50/ min will be treated with atropine 20 μg/kg. Intra-operative blood loss will be replaced with crystalloid fluids at a 3:1 ratio or allogenic blood transfusion at a 1:1 ratio.

Monitors : ECG, NIBP, SpO_2 and $ETCO_2$

Study groups:

Placebo group (control)

Study group - Gabapentin 800mg (2 capsules of gabapentin 400mg each)

SIDE EFFECTS IF ANY:

Duration of Surgery Duration of Anaesthesia

Readings of post-operative pain scores on visual analogues scale

First four hours

Time in mins	0	30	60	90	120	150	180	210	240
Post operative pain scores									

Next Twenty hours

Time in hrs	0	2	4	6	8	10	12	14	16	18	20
Post operative pain scores											

Fentanyl consumption (μg)

Time (hrs) at which fentanyl (μg) administered	0-6	6-12	12-18	18-24

First analgesic requirement time (hrs): _____

SIGNATURE OF STAFF INCHARGE

K. L. E. SOCIETY'S
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRUNAGAR, BELGAUM-590010 (KARNATAKA-INDIA)
(Affiliated to KAHE_Deemed University, Belgaum)

Website : HTTP/WWW.Jnmc.edu
E-Mail : domejnmc@sancharnet.in
: jnmc@sancharnet.in

☎+91-(0)831 Office : 2471350
Principal : 2471701
FAX :+91 (0)831-2470759

Ref. No. : MDC/TECHSR/2515 Date : 5-12-2006

To,

Dr. Sujay J.N,
Postgraduate student in
Department of Anaesthesiology,
J.N.Medical College,
Belgaum.

Dear Dr. Sujay J.N,

The JNMC – Institutional Ethics Committee on Human Subjects Research met on 28th November, 2006 to consider your application for approval of the research project **"The effect of oral gabapentin as an adjuant to post operative epidural analgesia for lower abdominal surgerie-A randomised placebo controlled double blind trial".**

After review of the documents submitted by you and satisfactory explanations provided to the members, the committee has provided approval date through November 27th, 2007 at which time the study will be reviewed by the committee.

If you have any questions concerning the above, please feel free to contact the committee office.

Sincerely,

(Dr.V.D.Patil)
Chairman,
JNMC Institutional Ethics Committee on
Human Subjects Research

KEY TO MASTER CHART

Cms	centimeter
DUB	dysfunctional uterine bleeding
F	Female
Hr	Hour
Lt	left
M	Male
Mcg	microgram
PID	Pelvic inflammatory diseases
Rt	Right
SD	Standard deviation

Control Group (Placebo 800 mg)

S No.	In Patient No.	AGE	SEX	ASA	Proposed Diagnosis	Proposed Surgery	Duration of Surgery (Hrs)	VISUAL ANALOGUE SCORE																		1st Analgesic requirement time (hr)	Total Fentanyl consumed (mcg)
								0.5 hr	1 hr	1.5 hr	2 hr	2.5 hr	3 hr	3.5 hr	4 hr	6 hr	8 hr	10 hr	12 hr	14 hr	16 hr	18 hr	20 hr	22 hr	24 hr		
1	215472	38	F	1	Fibroid Uterus	Abdominal Hysterectomy	2.000	0	0	0	2	5	0	0	4	3	5	0	1	4	0	4	0	2	4	2.5	120
2	214380	50	F	1	Fibroid Uterus	Abdominal Hysterectomy	3.000	0	2	5	0	2	6	0	2	4	0	3	5	0	6	0	0	4	0	1.5	120
3	230881	45	M	1	Chronic PID	Abdominal Hysterectomy	2.500	2	4	0	0	0	0	0	4	0	2	5	0	2	5	0	0	2	4	1	100
4	234213	62	F	1	Rt Inguinal Hernia	Meshplasty	2.000	0	0	2	4	0	2	4	0	1	3	5	0	2	4	0	2	4	0	2	100
5	234264	45	F	2	Rt Inguinal Hernia	Meshplasty	2.000	0	2	4	2	3	4	0	0	5	0	2	4	0	4	0	0	3	2	1.5	100
6	242113	35	F	1	Fibroid Uterus	Abdominal Hysterectomy	2.167	0	0	0	2	4	0	2	4	0	3	5	0	2	6	0	4	0	4	2.5	120
7	236943	46	M	2	Fibroid Uterus	Total Abdominal Hysterectomy	2.500	0	0	0	2	5	0	2	4	0	2	5	0	3	0	4	2	4	0	2.5	100
8	242221	52	F	1	Rt Inguinal Hernia	Meshplasty	1.500	0	0	0	2	4	0	3	4	0	4	0	3	5	0	2	5	0	4	2.5	120
9	231506	48	M	2	Rt Inguinal Hernia	Meshplasty	2.000	0	0	0	0	0	2	5	0	2	4	0	4	5	0	4	0	2	4	3.5	120
10	238501	35	F	1	Lt Inguinal Hernia	Meshplasty	1.500	0	0	0	2	4	0	3	5	0	2	4	0	4	3	2	2	2	4	2.5	100
11	238602	28	M	1	Fibroid Uterus	Abdominal Hysterectomy	2.000	0	0	0	0	0	4	0	4	0	4	2	4	0	2	4	0	2	4	3	120
12	242544	46	M	2	Lt Inguinal Hernia	Meshplasty	2.500	0	0	0	0	3	5	0	2	4	0	2	4	0	2	6	0	0	4	3	100
13	242572	65	M	1	Rt Inguinal Hernia	Meshplasty	2.250	0	0	0	0	2	5	0	2	4	0	2	4	0	3	4	0	3	4	3	100
14	245616	34	M	1	Fibroid Uterus	Abdominal Hysterectomy	1.660	0	0	2	5	0	4	0	2	4	0	3	5	0	3	4	0	2	4	2	120
15	245624	40	F	2	Rt Inguinal Hernia	Meshplasty	1.500	0	0	0	2	5	0	4	0	2	4	0	5	0	4	0	0	2	4	2.5	120
16	246251	23	M	1	Lt Inguinal Hernia	Meshplasty	2.330	0	0	0	2	5	0	2	4	0	2	5	0	2	4	0	4	2	4	2	120
17	249402	42	F	1	Chronic Appendicitis	Appendicectomy	1.330	0	1	2	4	0	2	4	0	2	5	0	3	6	0	5	0	2	4	2	120
18	249950	28	F	1	Lt Inguianl Hernia	Meshplasty	1..75	0	1	2	4	0	2	5	0	0	2	4	0	4	1	0	2	4	0	2	100
19	253642	30	M	1	Chronic Appendicitis	Appendicectomy	2.250	0	0	0	2	4	0	2	5	0	1	2	6	0	0	2	4	0	4	2.5	100
20	253682	21	F	1	Fibroid Uterus	Abdominal Hysterectomy	1.500	0	0	0	4	2	4	0	2	2	4	0	3	5	0	2	4	0	4	2	120
21	254472	39	F	1	Chronic PID	Abdominal Hysterectomy	1.500	0	2	4	3	3	4	0	0	2	2	4	0	0	4	0	2	4	0	1.5	100
22	259552	28	F	1	DUB	Abdominal Hysterectomy	2.083	0	0	0	0	0	3	4	0	0	2	4	0	0	0	4	0	0	4	3.5	80
23	255889	36	F	1	Lt Inguianl Hernia	Meshplasty	1.750	0	0	0	2	5	0	3	5	0	3	5	0	4	1	2	6	0	4	2.5	120
24	258280	30	F	1	Chronic Appendicitis	Appendicectomy	2.083	0	0	0	0	3	5	0	2	6	0	2	5	0	3	3	5	0	2	3.5	80
25	258994	23	F	1	Rt Inguinal Hernia	Meshplasty	1.750	0	0	0	1	4	0	2	4	0	1	3	5	0	3	6	0	4	0	2.5	100
26	261504	31	F	1	Chronic Appendicitis	Appendicectomy	2.167	0	0	2	6	0	2	5	0	4	0	2	4	0	5	5	0	2	2	2	120
27	252590	35	M	1	Chronic Appendicitis	Appendicectomy	1.667	0	0	0	0	0	0	2	4	1	2	4	0	0	4	0	2	4	0	4	80
28	264432	25	M	1	Lt Inguinal Hernia	Meshplasty	1.750	0	0	0	2	6	2	5	0	4	0	2	5	3	0	2	4	0	2	2.5	100
29	266097	28	M	1	Chronic Appendicitis	Appendicectomy	1.500	0	0	0	0	0	2	3	5	2	4	0	2	4	0	0	0	5	2	4	80
30	265487	38	F	1	Chronic Appendicitis	Appendicectomy	1.250	0	0	0	0	0	0	0	4	0	4	0	2	5	0	1	2	4	0	4	80
31	266847	26	M	1	Recurrent Appendicitis	Appendicectomy	1.083	0	0	0	0	0	1	2	5	0	3	4	0	2	4	0	1	2	4	4	80
32	267092	30	F	1	Chronic Appendicitis	Appendicectomy	1.167	0	0	0	0	0	0	2	4	0	3	5	0	2	0	4	0	2	4	4	80
33	267193	28	M	1	Chronic Appendicitis	Appendicectomy	1.333	0	0	0	2	4	0	2	3	5	0	1	2	4	0	2	5	0	3	2.5	80
MEAN		36.67					1.861563	0.1	0	0.7	2	2.2	2	2	3	2	2	3	2	2	2	2	2	2	3	2.62121212	103.0303
S.D.		10.86					0.452407	0.3	1	1.4	2	2.1	2	1.8	2	2	2	2	2	2	2	2	2	2	2	0.81996859	15.906926
							MED	0	0	0	2	2	2	2	3	1	2	2	2	2	2	2	2	2	4		

LOWER	0	0	0	0	0	0	0	1	0	1	2	0	0	0	0	0	1	2
UPPER	0	0	0	2	4	2	3	4	2	3	4	4	4	4	4	4	3	4

Study Group (Gabapentin 800mg)

S No.	In Patient No.	AGE	SEX	ASA	Proposed Diagnosis	Proposed Surgery	Duration of Surgery (Hrs)	VISUAL ANALOGUE SCORE																			TIME (hr)	FENTANYL (mcg)
								0.5 hr	1 hr	1.5 hr	2 hr	2.5 hr	3 hr	3.5 hr	4 hr	6 hr	8 hr	10 hr	12 hr	14 hr	16 hr	18 hr	20 hr	22 hr	24 hr		
1	216472	35	F	1	Fibroid Uterus	Total Abdominal Hysterectomy	2	0	0	0	0	0	2	5	2	5	0	0	5	1	4	0	0	2	3	3.5	80
2	234218	40	F	1	Fibroid Uterus	Total Abdominal Hysterectomy	2	0	0	0	0	1	1	2	4	0	0	1	4	0	1	4	0	1	2	4	60
3	234273	40	F	2	Rt Inguinal Hernia	Meshplasty	2.500	0	0	0	0	0	2	3	4	0	0	4	0	2	5	0	0	4	0	4	80
4	236344	40	M	1	Rt Inguinal Hernia	Meshplasty	2.000	0	0	0	0	0	0	0	0	2	4	0	0	1	2	4	0	2	3	8	40
5	226652	64	M	2	Lt Inguinal Hernia	Meshplasty	1.750	0	0	0	0	2	4	0	0	2	6	0	0	5	0	0	4	0	2	3	80
6	237886	54	F	2	DUB	Abdominal Hysterectomy	2.250	0	0	0	0	0	2	4	0	5	0	0	6	0	2	4	0	0	3	3.5	80
7	237880	35	F	1	Fibroid Uterus	Abdominal Hysterectomy	2.000	0	0	0	0	0	2	4	0	0	3	5	0	2	4	0	2	4	0	3.5	80
8	238283	29	M	1	Rt Inguinal Hernia	Meshplasty	1.450	0	0	0	0	2	3	3	4	0	2	5	0	2	3	5	0	2	3	4	60
9	237207	35	M	1	Fibroid Uterus	Abdominal Hysterectomy	1.750	0	0	0	0	0	2	3	4	0	2	5	0	0	4	0	2	3	4	4	80
10	242211	58	M	1	Rt Inguinal Hernia	Meshplasty	1.500	0	0	0	0	0	2	5	2	2	4	0	2	5	0	0	4	0	0	3.5	80
11	242212	48	F	1	DUB	Abdominal Hysterectomy	1.500	0	0	0	0	2	4	0	4	0	0	2	4	0	3	6	0	0	2	3	80
12	241115	40	M	1	Chronic PID	Abdominal Hysterectomy	2.000	0	0	0	0	0	0	2	4	0	2	5	0	3	5	0	0	2	3	4	60
13	247521	45	M	1	Lt Inguinal Hernia	Meshplasty	1.500	0	0	0	0	4	0	0	0	2	4	0	0	2	5	0	0	2	3	2.5	60
14	246535	56	F	1	DUB	Abdominal Hysterectomy	1.333	0	0	0	0	0	2	5	0	2	3	4	0	2	3	5	0	2	4	3.5	80
15	247530	55	M	1	Rt Inguinal Hernia	Meshplasty	2.083	0	0	0	2	3	5	0	4	0	2	4	0	2	3	5	0	2	4	3	100
16	246766	72	M	1	Chronic Appendicitis	Appendicectomy	2.083	0	0	0	1	2	3	3	4	0	1	2	4	0	2	4	0	2	5	4	80
17	245858	24	M	2	Fibroid Uterus	Total Abdominal Hysterectomy	1.500	0	0	0	0	0	2	3	4	0	0	5	0	2	3	5	0	2	3	4	60
18	248118	68	M	2	Appendicitis	Appendicectomy	1.500	0	0	0	0	2	3	3	4	0	2	3	5	0	2	2	3	4	0	4	60
19	248806	24	M	1	Fibroid Uterus	Abdominal Hysterectomy	1.667	0	0	0	0	0	0	0	5	0	0	2	4	0	2	3	6	0	2	6	60
20	248853	38	F	1	Fibroid Uterus	Abdominal Hysterectomy	1.750	0	0	0	0	0	0	2	4	0	2	3	6	0	2	5	0	2	3	4	60
21	249778	40	F	1	Lt Inguinal Hernia	Meshplasty	2.500	0	0	0	0	0	0	2	4	2	2	5	0	2	4	0	3	6	0	4	80
22	249400	32	F	1	Chronic Appendicitis	Appendicectomy	2.250	0	0	0	0	0	3	4	3	6	3	5	0	2	4	0	2	4	0	3.5	80
23	251703	58	M	2	Fibroid Uterus	Abdominal Hysterectomy	2.000	0	0	0	0	0	2	3	3	5	0	2	3	4	0	2	4	0	2	6	60
24	252902	26	F	1	Chronic PID	Abdominal Hysterectomy	2.000	0	0	0	0	0	0	2	4	0	0	2	4	0	0	2	4	0	2	6	60
25	253794	56	M	1	Chronic PID	Abdominal Hysterectomy	1.583	0	0	0	0	0	2	3	4	0	2	3	4	0	2	4	0	0	2	4	60
26	257350	28	M	1	Fibroid Uterus	Abdominal Hysterectomy	1.500	0	0	0	0	0	2	3	3	6	0	2	3	5	0	2	4	0	0	6	60
27	258418	30	M	1	Chronic Appendicitis	Appendicectomy	1.500	0	0	0	0	0	0	2	2	4	0	2	3	4	0	2	3	4	0	6	60
28	258818	52	M	2	Rt Inguinal Hernia	Meshplasty	1.500	0	0	0	0	0	0	0	4	0	0	3	4	0	0	2	4	0	0	6	60
29	259924	40	M	2	Chronic Appendicitis	Appendicectomy	1.333	0	0	0	0	0	0	3	4	0	2	3	5	0	0	2	4	0	2	4	60
30	266166	24	M	1	Chronic Appendicitis	Appendicectomy	1.333	0	0	0	0	0	2	3	0	4	0	2	3	5	0	0	4	2	3	6	60
31	264210	31	F	1	Chronic Appendicitis	Appendicectomy	1.500	0	0	0	0	0	2	4	0	2	4	0	1	3	5	0	2	4	0	3.5	80
32	266502	32	M	1	Chronic Appendicitis	Appendicectomy	1.333	0	0	0	0	0	2	5	0	2	4	0	2	4	0	0	1	2	5	3.5	80
33	267224	25	F	2	Chronic Appendicitis	Appendicectomy	1.500	0	0	0	0	0	2	3	5	0	2	4	0	1	2	4	0	1	1	4	60

MEAN		41.64					1.756	0	0	0	0	0.5	2	2.5	3	2	2	3	2	2	2	2	2	2	2	4.27	69.09
S.D.		13.64					0.341	0	0	0	0	1.1	1	1.6	2	2	2	2	2	2	2	2	2	2	2	1.24	12.34
							MED	0	0	0	0	0	2	3	4	0	2	2	2	2	2	2	2	2	2		
							LOWER	0	0	0	0	0	1	2	2	0	0	2	0	0	1	0	0	0	0		
							UPPER	0	0	0	0	0	2	3	4	2	2	4	4	2	3	4	4	2	3		

MANN-WHITNEY TEST								0.8	0	0.1	0	0	1	0.2	1	1	0	1	1	1	1	1	1	0	0		
								NS	NS	NS	S	S	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		
T UNPAIRED t TEST																											
		0.197					0.074602	0.3	0	0	0	0	1	0.2	1	1	0	1	1	1	1	1	1	0	0	1.2838E-08	1.875E-15
		NS					NS	NS	S	S	S	S	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	S	S

S

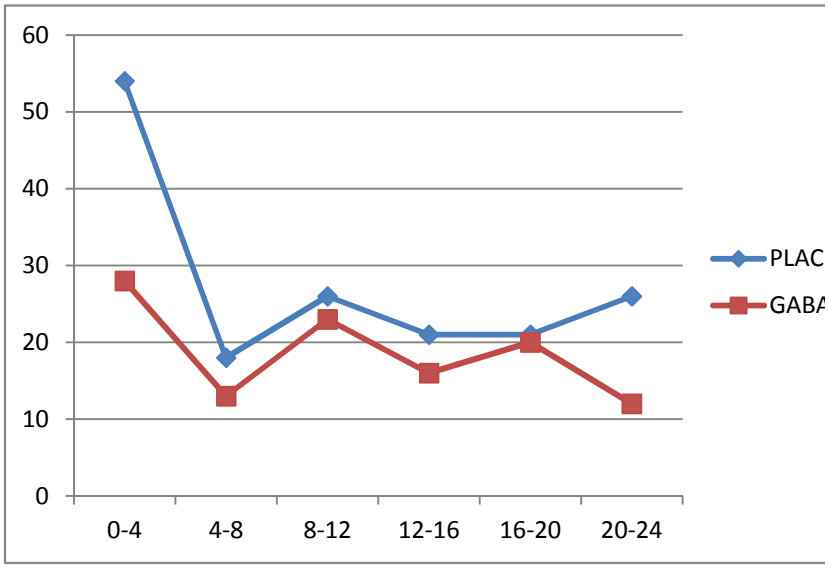
MEANS

	0.5	1	1.5	2	2.5	3	3.5
PLACEBO G	0.060606	0.363636	0.69697	1.666667	2.212121	1.787879	2
GABAPENT	0	0	0	0.090909	0.545455	1.69697	2.545455

S.D.

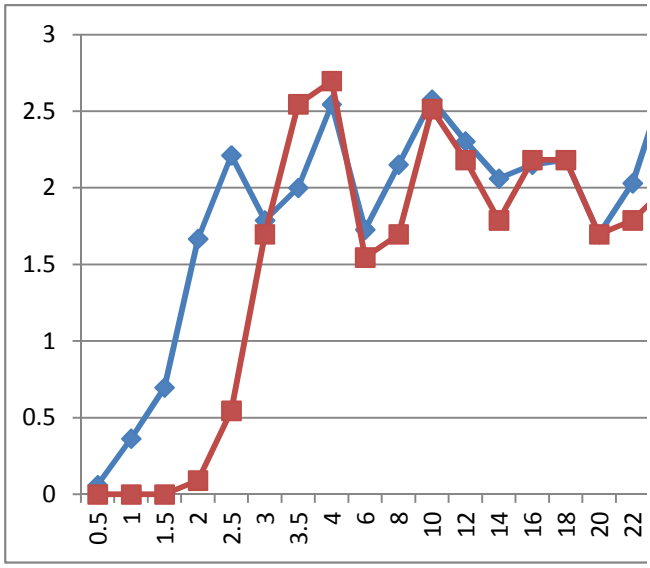
	0.5	1	1.5	2	2.5	3
PLACEBO GROUP	0.35	0.90	1.38	1.69	2.12	1.96
GABAPENTIN GROUP	0.00	0.00	0.00	0.38	1.06	1.36

	0-4	4-8	8-12	12-16	16-20
PLACEBO G	54	18	26	21	21
GABAPENT	28	13	23	16	20



MEAN

4	6	8	10	12	14	16	18	20
2.545455	1.727273	2.151515	2.575758	2.30303	2.060606	2.151515	2.181818	1.69697
2.69697	1.545455	1.69697	2.515152	2.181818	1.787879	2.181818	2.181818	1.69697



3.5	4	6	8	10	12	14	16	18
1.80	1.94	1.92	1.66	1.87	2.14	2.05	2.06	2.02
1.60	1.81	2.03	1.67	1.84	2.14	1.76	1.78	2.07

20-24

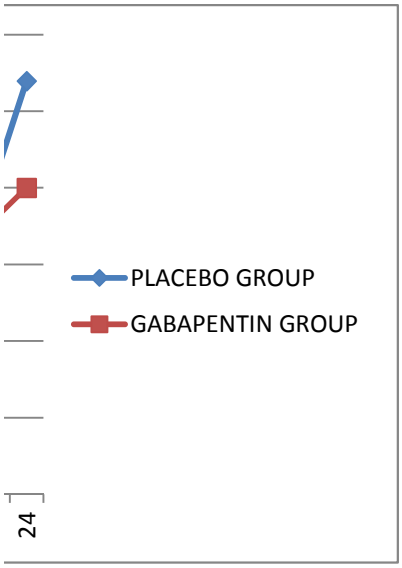
26

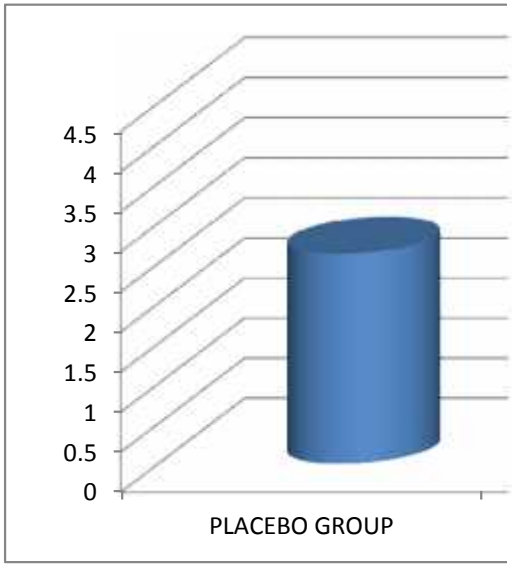
12

:EBO GROUP

APENTIN GROUP

22	24
2.030303	2.69697
1.787879	2





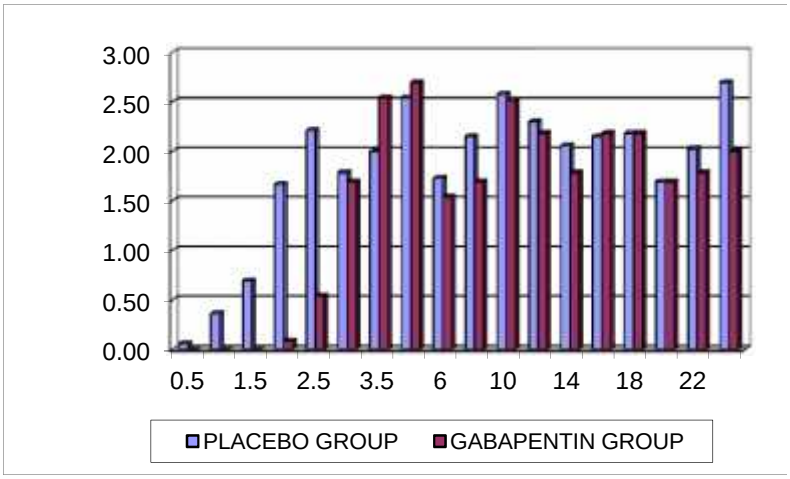
20	22	24
1.98	1.61	1.70
1.88	1.63	1.58

GABAPENTIN GROUP

0.5	0.06	0.00	0.35	0.00
1	0.36	0.00	0.90	0.00
1.5	0.70	0.00	1.38	0.00
2	1.67	0.09	1.69	0.38
2.5	2.21	0.55	2.12	1.06
3	1.79	1.70	1.96	1.36
3.5	2.00	2.55	1.80	1.60
4	2.55	2.70	1.94	1.81
6	1.73	1.55	1.92	2.03
8	2.15	1.70	1.66	1.67
10	2.58	2.52	1.87	1.84
12	2.30	2.18	2.14	2.14
14	2.06	1.79	2.05	1.76
16	2.15	2.18	2.06	1.78
18	2.18	2.18	2.02	2.07
20	1.70	1.70	1.98	1.88
22	2.03	1.79	1.61	1.63
24	2.70	2.00	1.70	1.58

	0.5	1	1.5	2	2.5
PLACEBO G	0.06	0.36	0.70	1.67	2.21
GABAPENT	0.00	0.00	0.00	0.09	0.55

3	3.5	4	6	8	10	12	14	16
1.79	2.00	2.55	1.73	2.15	2.58	2.30	2.06	2.15
1.70	2.55	2.70	1.55	1.70	2.52	2.18	1.79	2.18



18	20	22	24
2.18	1.70	2.03	2.70
2.18	1.70	1.79	2.00