# "EFFECT OF PRE-EMPTIVE MULTIMODAL ANALGESIA REGIMEN ON POST-OPERATIVE EPIDURAL DEMAND BOLUSES IN LOWER LIMB ORTHOPAEDIC SURGERIES"

**By**

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**DISSERTATION SUBMITTED TO SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTER, KOLAR, KARNATAKA**

***In partial fulfillment of the requirements for the degree of***

**DOCTOR OF MEDICINE**

**IN**

**ANAESTHESIOLOGY**

**Under the Guidance of**

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**JUNE 2023**

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**Abstract**

**Introduction:** Orthopaedic procedures on the lower limbs that include femur shaft fractures are linked with excruciating pain. Postoperative pain treatment is still ineffectively used in low-resource environments where opioid-free analgesia and epidural administration are impossible. Preemptive analgesia and the combination of several drugs have been popular lately, although it is still unclear whether the approach is more effective at treating postoperative pain. This study evaluated and compared preemptive multimodal analgesia with a placebo group among patients undertaking lower extremity orthopedic procedures under combined spinal epidural anesthesia.

**Material and methods:** This double-blinded randomized control research included 48 subjects. The study included subjects aged 18-65 with lower limb fractures requiring procedures under combined spinal epidural anaesthesia. Subjects were split up into two groups through random allocation. Group A: The preemptive group received intravenous (IV) paracetamol one g, IV diclofenac sodium 75mg diluted in 100 ml NS, IV tramadol 50 mg diluted in 100 ml NS, and tab pregabalin 75 mg orally 30 mins before surgery. Group B: Placebo group received 3 pints of 100 ml NS IV and tab [illegible] 150 mg 30 mins before surgery. [illegible]

**Results:** A Total of 48 subjects were included in the study. At immediate post operative, [illegible] 12 and 24 hour the VAS was lower among group A subjects relative with group B (P Value [illegible]). A significant

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**Date:** **Dr. MATHEW GEORGE**

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# ABBREVIATIONS

| **Glossary** | **Abbreviations** |
|---|---|
| CSF | Cerebrospinal fluid |
| FDC | Fixed-dose combination |
| GA | General Anaesthesia |
| GABA | Gamma-amino butyric acid |
| GI | Gastrointestinal |
| MMA | Multimodal analgesia |
| NMDA | N-methyl-D-aspartate |
| NSAID | Nonsteroidal anti-inflammatory medication |
| NTN | Needle through needle technique |
| OIH | Opioid-induced hyperalgesia |
| PA | Pre-emptive analgesia |
| PE | Pre-emptive |
| PG | Prostaglandin |
| THA/TKA | Total hip and total knee arthroplasty |
| VAS | Visual analogue scale |
| mg | Milligram |
| LCP | Locking Compression Plate |
| CRIF | Closed reduction-internal fixation |
| IT | Intertrochanteric |
| IMIL | Intramedullary interlocking nail |
| hr | Hour |

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# ABSTRACT

**“EFFECT OF PRE-EMPTIVE MULTIMODAL ANALGESIA REGIMEN ON POST-OPERATIVE EPIDURAL DEMAND BOLUSES IN LOWER LIMB ORTHOPAEDIC SURGERIES”**

**Introduction:** Orthopaedic procedures on the lower limbs that include femur shaft fractures are linked with excruciating pain. Postoperative pain treatment is still ineffectively used in low-resource environments where opioid-free analgesia and epidural administration are impossible. Preemptive analgesia and the combination of several drugs have been popular lately, although it is still unclear whether the approach is more effective at treating postoperative pain. This study evaluated and compared preemptive multimodal analgesia with a placebo group among patients undertaking lower extremity orthopedic procedures under combined spinal epidural anesthesia.

**Material and methods:** This double-blinded randomized control research included 48 subjects. The study included subjects aged 18-65 with lower limb fractures requiring procedures under combined spinal epidural anaesthesia. Subjects were split up into two groups through random allocation. Group A: The preemptive group received intravenous (IV) paracetamol one g, IV diclofenac sodium 75mg diluted in 100 ml NS, IV tramadol 50 mg diluted in 100 ml NS, and tab pregabalin 75 mg orally 30 mins before surgery. Group B: Placebo group received 3 pints of 100 ml NS IV and tab ranitidine 150 mg 30 mins before surgery. Intraoperatively, under aseptic precautions patient was stabilized under combined spinal epidural anaesthesia. Visual analogue scale (VAS) was documented directly on shifting to recovery room 0hr (corresponds to 2hrs after giving spinal anesthesia) and then at 1 hr, 4 hr, 8 hr, 12 hr, and 24 hr for both groups. Epidural boluses were given whenever the patient’s visual analogue scale was more than 4. 10 ml of .125 % bupivacaine with two micrograms/ml of fentanyl were administered as an epidural top-up. Total number of epidural boluses given over 24 hours based on visual analogue scales was recorded for both preemptive and placebo group. If the subject still expressed pain, IV diclofenac 75mg was administered if VAS more than 4, IV diclofenac 75mg along with IV tramadol 50 mg was given if VAS more than 6. Patient satisfaction with anesthesia care, in general, was assessed 24 hours post-operatively.

**Results**: A Total of 48 subjects were included in the study. At immediate post-operative, 8, 12, and 24 hour the VAS was lesser among group A subjects relative with group B (P Value $<0.001$). A significant increase in the demand of epidural bolus immediate postoperatively among group B (70.83%) relative to group A (4.17%) P value of $<0.001$. At 8 hour, 12 hour and 24 hour group A found significantly less need of epidural boluses compared to Group B. The mean total number of epidural boluses given in group A was lower than in group B ($1.79 \pm 0.41$ VS $3.33 \pm 0.48$, P Value $<0.001$). In group A, all 100% reported no requirement for diclofenac and tramadol. In group B, 8.33% required diclofenac 75 mg, and remaining 91.66% had no requirement for diclofenac and tramadol. The difference in subject satisfaction with anaesthesia care in general between two study groups was determined to be significant having a P value of .027. Group A people were very satisfied compared with group B.

**Conclusions**: The study results found preemptive multimodal analgesia group had better postoperative pain control because they required fewer epidural boluses and no extra analgesics postoperatively comparing with placebo group. Pre-emptive group was more satisfied with anaesthesia care in general.

**Key words:** Epidural, multimodal, pre-emptive, VAS

# INTRODUCTION

# INTRODUCTION:

The worldwide prevalence of post-operative pain ranges from 14 to 70%, and in India, post- operative pain is experienced by more than 80% of patients.[1–3] It is necessary to conduct prospective randomized research to evaluate the most effective non-narcotic postoperative medication regimens to strike an equilibrium between appropriate narcotic prescribing trends and practical postoperative pain treatment. Excruciating pain is associated with lower limb orthopedic surgeries involving the fracture shaft of the femur. Acute postoperative pain management is crucial because untreated pain can cause sickness, vomiting, delayed feeding, and immobility, increasing postoperative morbidity and death.[4] When selecting an anesthetic agent, it is crucial to consider the effectiveness of postoperative recovery. This includes managing postoperative pain, nausea, vomiting, and urine retention. These side effects may result in a delayed hospital discharge or unexpected readmission.[5]

Lower limb orthopedic surgeries are more commonly performed under combined spinal epidural anesthesia. Epidural and SA are safe and simple procedures for lower limb surgery due to their simplicity and portability.[6] Not only does central neuraxial blockade provide good anesthetic and surgical conditions, but it also has advantages over general anesthesia. Advantages include reduced airway and pulmonary complications. Complications include a lower risk of pulmonary aspiration and a lower stress response.[7] Studies have shown better analgesic effect with epidural and spinal anesthesia compared to general anesthesia in subjects with lower limb surgeries.[8,9]

Adopting multimodal analgesic approaches as the standard way for pain control both before and after surgery is one method for optimizing the recovery process.[10,11]

Multimodal analgesia (MMA), which employs a variety of methods, addresses several nociceptive pathways (both peripheral and central), leading to the cumulative or simultaneous effects of analgesia medicines.[12,13] MMA's effectiveness in the management of postsurgical discomfort was well-known twenty years ago,[14] it has lately undergone a thorough re-evaluation in clinical practice.[15]

“Pre-emptive analgesia” (PA) is an anti-nociceptive therapy which lessens pain after lower limb procedures.[16] Crile proposed PA in 1913, and it was popularized by Wall and Woolf.[17] Woolf stated that by decreasing central sensory processing, PA might change the magnitude and time of pain after surgery.

There is a growing need for total knee as well as total hip arthroplasty (TKA/THA) procedures on the lower limbs, which necessitates methods to limit opioid access and safeguard patients against long-term opioid addiction.[18] Recent research has shown that postoperative opioid prescribing after elective THA and TKA is reduced by more than 18.5% when using multimodal nonopioid analgesia.[19] Typically, nerve blocks, catheters, and local permeation  are used in concert with systemic medications as part of an MMA regimen for TJA .[20]

Studies show that after orthopedic fracture surgery, individuals who take very few opioids report greater levels of satisfaction and less discomfort than those who take more opioids.[21,22,23] Pre-emptive analgesia is a multimodal approach that includes providing pain medication before surgery. Our study attempted to determine effectiveness of a combination of opioid-free analgesics (diclofenac and paracetamol), pregabalin, and the least potent opioid (tramadol) as preventive analgesia in patients having lower limb orthopedic procedures. A recent study, which used a similar combination as pre-emptive

MMA in subjects undergoing elective abdominal surgery, found that a pre-emptive combination of paracetamol and tramadol reduced tramadol requirement and increased the time to receive 1st analgesic comparing with paracetamol alone.[24] Similarly, a study has shown preemptive pregabalin 150mg was efficient in reducing postoperative discomforts, especially in lower limb orthopedic surgeries.[25] In addition, Bupivacaine and fentanyl as an epidural bolus for pain reduction in orthopedic surgeries reduced post -operative pain effectively.[26]

## Need of the study

To provide better pain liberation with lower drug dosages and fewer adverse effects than monomodal treatment, multiple classes of pharmacological pharmaceuticals are administered along with a variety of analgesic agents and procedures. This process is known as multimodal analgesia (MMA).[27] Strong evidence exists that MMA effectively manages both acute and long-standing pain.[11] Effective implementation of MMA on pre- and postoperative pain treatment, however, is reportedly only applicable to routine surgical measures performed under GA, such as the spine, hernia operation, total hip and knee arthroplasty, colorectal surgery non-cosmetic breast surgery, cholecystectomy, laparoscopic procedures, and cardiothoracic procedures.[28] Limited research has been done on the impact of pre-emptive MMA on the demand for epidural boluses in trauma patients for lower limb orthopedic procedures. As a result, we attempted to assess the efficacy of MMA in subjects with a lower extremity orthopedic surgery.

# AIMS & OBJECTIVES

# AIMS AND OBJECTIVES

1) To evaluate the effectiveness of pre-emptive multimodal analgesia in minimizing the requirement of epidural demand boluses post-operatively.
2) To evaluate how long it takes to get the first epidural bolus.

# REVIEW OF LITERATURE

# REVIEW OF LITERATURE:

## RELEVANT ANATOMY AND PHYSIOLOGY

### Spinal anesthesia (SA)

The first regional anesthetic therapy to be employed was spinal anesthesia, which was initially carried out by August Bier in Germany in 1898. For giving spinal anesthesia, good posture and familiarity with neuraxial structures are essential. Spinal anesthesia is utilized in lumbar region, particularly middle to lower lumbar regions, to protect the spinal cord from damage and to avoid intrathecally administered drugs from working in the upper thoracic and cervical regions. Terminal end of spinal cord is located at the bottom of the first or second lumbar vertebral body.[29] As the dural sac extends to the S2/3 region, a spinal needle is commonly placed for spinal anesthesia in the L3/4 or L4/5 interspace. Higher interspaces increase risk of spinal cord injury, particularly in overweight people.[30]

### Spinal anatomy

The arachnoid membrane is a crucial component because medications for the spine must be administered within its boundaries. The arachnoid membrane is made up of sheets connected by tight connections. This anatomical feature makes the arachnoid membrane the main meningeal barrier. The neural root cuffs, which allows flow of materials from the CSF to epidural region in one direction, serve as a site of active transport of compounds via the arachnoid membrane and may help with the clearance of spinal anesthetic drugs. The arachnoid membrane actively transfers things that try to pass through the meninges in addition to serving as a passive reservoir for CSF. Before the effector areas of the CNS are impacted, dilution with the CSF takes place after the spinal anesthesia is delivered.

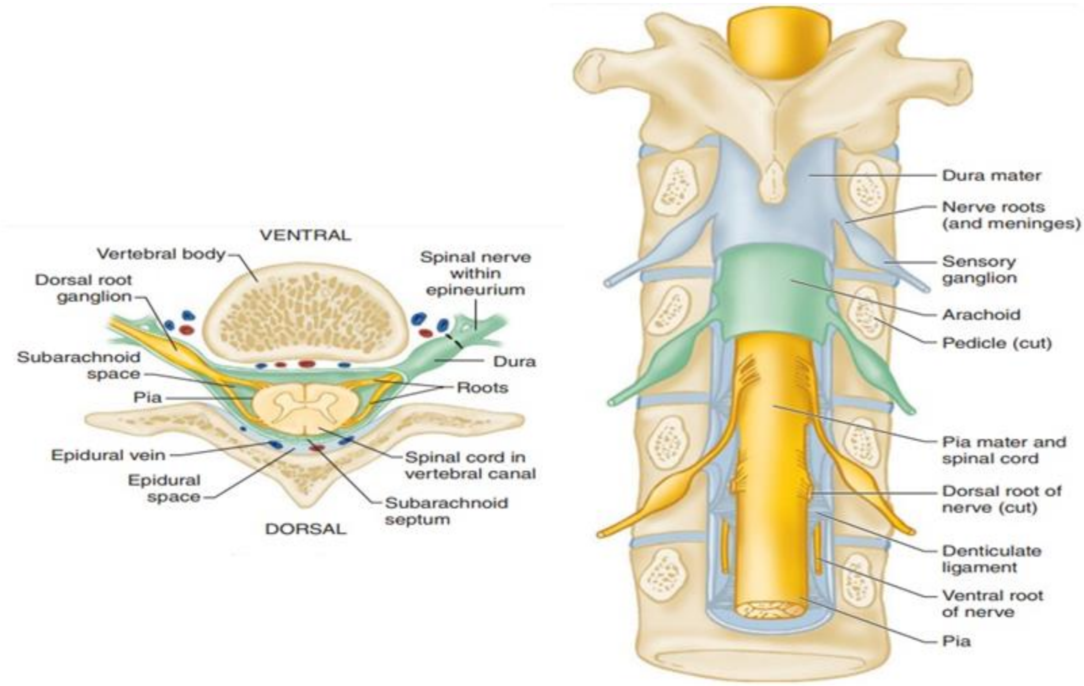


**Figure 1: MENINGIAL LAYERS OF SPINAL-CORD**

### Epidural Anatomy

It lies between the dura mater and ligamentum flavum, which covers dural sac, comprises fatty tissue and blood veins with thin walls. Owing to protrusions in spinal cord the higher and lower thoracic areas, epidural space is limited there, it is broader below the level at which the spinal cord ends. The distribution of epidural fat, as opposed to connective tissue, influences how the epidural catheter moves inside the epidural space. Studies show that the epidural needle's tip makes interfaces with the dura as soon as it reaches the epidural space.[31] With the needle through needle CSE technique, it is necessary to advance the spinal needle past the epidural needle tip for puncturing the elastic dura.[32] As a result, CSE sets feature added -long spinal needles, and it's critical to execute CSE caudad to the spinal cord's termination at L2.[33]

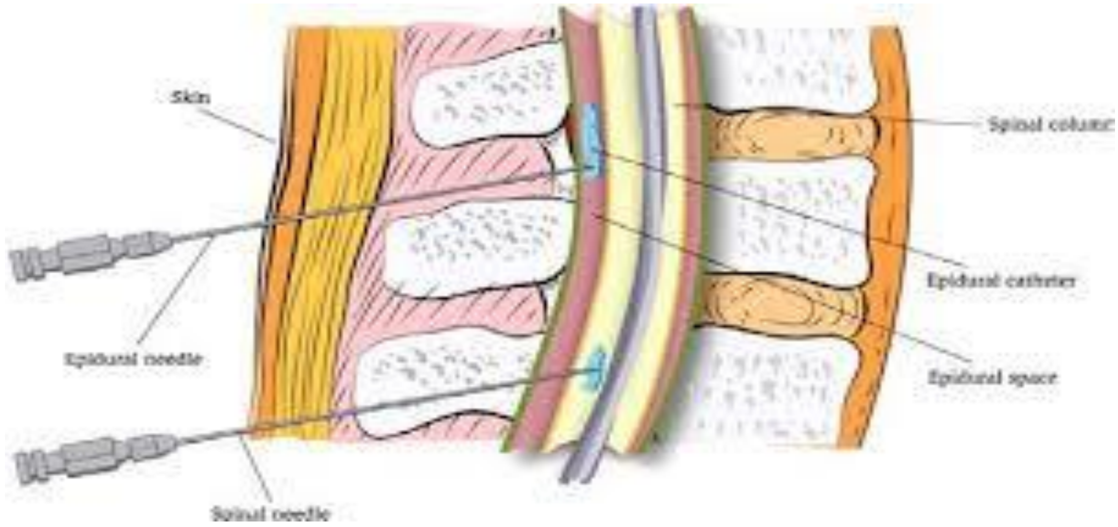


**Figure 2: ANATOMY CSEA.**[11]

When compared to dosages required with epidural anesthetic alone, CSE anesthesia generally causes more widespread block than predicted, and epidural dosage desired to prolong the block is frequently lower. There are two plausible reasons for this observation. First, by reducing sub-atmospheric pressure prior to administration of the local anesthetic, Tuohy needle lowers the amount of subarachnoid space in dural sac and prolongs the degree of spinal anesthesia. Secondly, due to dural sac deformation following local anesthetic injection in the epidural region, transport of LA substances from epidural area to subarachnoid area via the dural hole is feasible.[34]

**Combined spinal Epidural analgesia (CSE) given post-operatively in lower limb orthopedic surgeries**

The spinal component of the CSE has the advantage of generating neuraxial block quickly, the epidural catheter has the potential to lengthen or alter the block.[35] "Soresi" used the single needle – single interspace technique to introduce it in 1937.[36] Later on, other adaptations and approaches were developed, each with its own set of advantages. Curelaru executed the first combination of spinal and epidural anesthesia. Procedures below the umbilical level necessitate excellent operating circumstances as well as long-term, efficient analgesia. CSEA has been advocated as a substitute for normal spinal anesthesia.[37] Employing 150 patients and two distinct interspaces, Dr. I. Curelaru presented research in 1979 using CSE anesthesia: The epidural catheter was implanted first, and then Dixidextracaine was injected into subarachnoid space two levels lower to epidural placement. Dr. Curelaru found that CSE anesthesia has various benefits, including good quality anesthesia that may be prolonged as required, sustained postoperative pain management, analgesia that covers a sufficient number of dermatomes, low local anesthetic drug toxicity, and no respiratory problems.[38]

## CSEA TECHNIQUE

The notion of anti-nociceptive interaction guides the selection of drugs in CSEA: Fentanyl or sufentanil are subarachnoid lipid-soluble opioids that give fast relief (within 5-10 min) the inception of analgesia, expand surgical blockade quality, and augment the effect of trivial subarachnoid local anesthesia.[33] The block can sustain as needed with low-dose epidural medicines; subarachnoid injection yields quick action with less doses of local anesthetics with opioids. Furthermore, sequential CSE approach can be utilized to prolong the block's dermatomal dissemination with a small amount of drug.[37] Epidural catheter improves safety of CSE anesthesia by allowing the lowest effective local anesthetic dose to be used, preventing overshooting in terms of spinal anesthesia duration.

## TECHNIQUES

Coates described the first "spinal needle over epidural needle" approach.[39] Needle is used as an introducer after identifying the epidura, and the spinal needle is pushed via the epidural needle, puncturing the dura. Epidural catheter is implanted after medications are administered into the subarachnoid area. After a dura perforation, the "hanging drop" method is indicated for locating the spinal space.[40]

The 2 elements of CSE are administered using discrete needles placed in the same or different intervertebral spaces in the separate needle technique. In this method, the epidural needle is inserted into the same interspace as the spinal needle as an introducer. The spinal needle is first inserted to pierce the dura and permit the subarachnoid drug administration, and then the epidural catheter is inserted.[41]

Despite the fact that CSE anesthesia was initially described for urologic operation, its uses have expanded recently. This approach allows patients to leave the hospital and go home sooner.[32] CSE approach has grown in popularity over the last 20 years, and it is a more sophisticated procedure that necessitates a thorough consideration of epidural and spinal physiology and pharmacology.

**TYPES OF SPINAL NEEDLE**

Commonly used needles are quincke, whitacre, sprotte

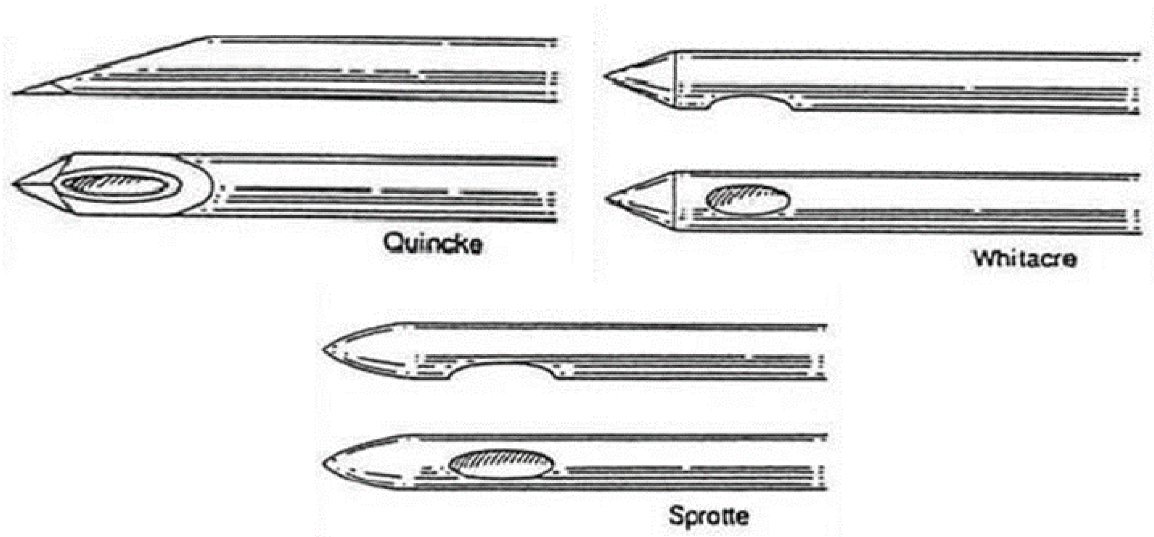


**Figure 3: TYPES OF SPINAL NEEDLE**

## EPIDURAL NEEDLES

A variety of epidural needles are utilized. The most often used needles are Tuohy needles, which feature a 15 to 30° curved, blunt "Huber" tip decreases the risk of an unintended dural perforation. They are 16–18 G in size. At 1 cm intervals, the needle shaft is visible to show penetration depth. Radiopaque Plastic that is flexible, calibrated, and robust is used to make the catheter. Near the tip, it has a single end hole or several side vents.[42]

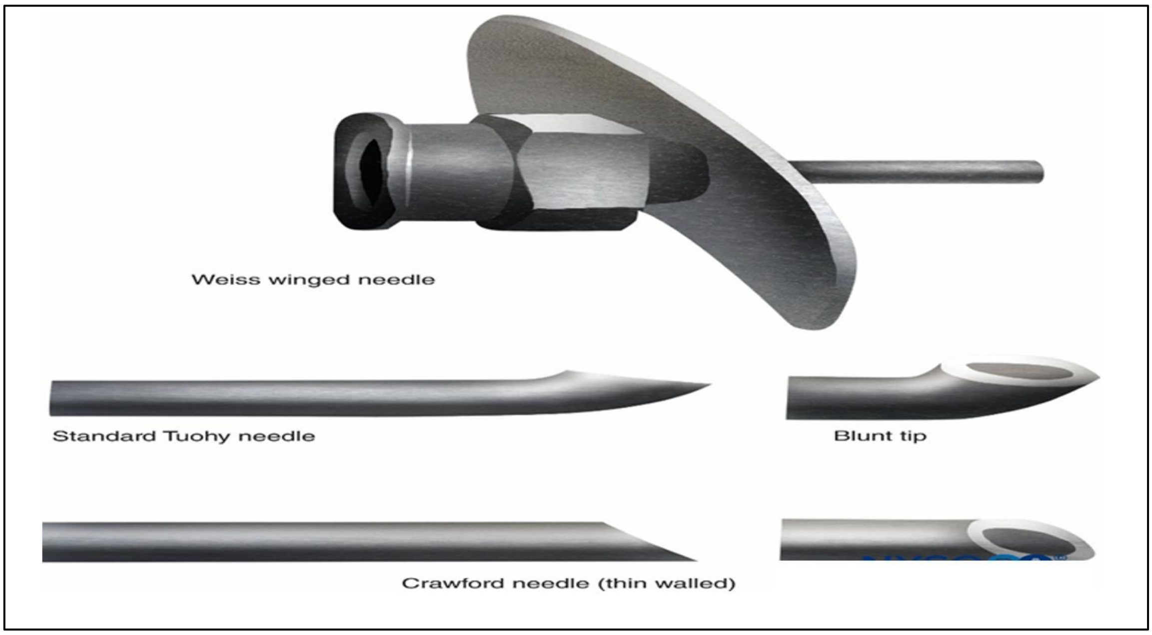


**Figure 4: TYPES OF EPIDURAL NEEDLE**

## COMPLICATIONS

The spinal epidural catheter migration, subdural block risk, and probable subarachnoid delivery of medicine intended for epidural use are all potential issues with the practical implementation of CSE. Potential issues include the test dose not working, headaches following a dural puncture, and the exceedingly uncommon catastrophic consequences of a CNS illness or damage.[33,43]

Paraesthesias occur in 2.6 percent to 10% of CSE instances when the spinal needle is advanced, and prevalence has been reported high i.e., 29% when lengthy spinal needles are utilized. To limit the danger of meningitis, a sterilized technique is required while

CSE and great care must be taken to uphold sterility during the preparation of drug solutions.[37]

Some of the uncommon consequences of CSEA include epidural abscess, paraplegia owing to glue arachnoiditis with severe syringomyelia, and subdural hematoma.[33]

**Combined epidural and spinal needle:**[44]

The technical elements influencing the effectiveness and accomplishment of CSE have been covered in a number of evaluations. Regardless of the fact that CSE is regarded as a relatively recent procedure, Soresi documented deliberate administration of anesthetic drugs both outside and inside the subarachnoid area in 1937. Soresi purposely utilized a single needle, which is rather different from contemporary practice. The remainder of the substance was then given to create a subarachnoid block after injecting some local anesthetic into the epidural area first. Although both spinal and epidural anesthesia was utilized in this method, a catheter was not employed. The first CSE was described by Curelaru in 1979 after a Tuohy needle was implicated to enclosure an epidural catheter. Brownridge recommended using CSE in obstetrics. In 1981, he discussed the effective application of CSE for an elective cesarean section. Carrie published the first article describing its actual application in obstetric practice in 1984. In the late 1990s, the approach started to gain popularity. The most recent literature has reported a number of CSE initiation strategies**.**

**Advantages of placing the epidural catheter first:**

The danger of unintentional intravascular or intrathecal catheter migration is reduced by testing appropriate insertion prior to the direction of spinal medicines. Lessens the risk of brain injury.

**Disadvantages of two needle two interspace technique:**

Time-consuming and it requires 2 separate injections.

**Figure 5: "**Spinal needle threaded into an epidural needle".[44]

**Post- operative analgesia/ pain management**

Despite the abundance of painkillers on the market, poorly managed postoperative pain still exists. Postoperative pain increases morbidity and dysfunction, causes delays in ambulation, and lengthens hospital stays, among other outcomes. Acute postsurgical pain can become chronic postoperative pain if it is not appropriately controlled, which can cause dysfunction, disability, and depression and be challenging to treat. The most extreme postoperative pain often occurs initially and lessens as the tissue heals, following a fairly predictable pattern. Pharmacological interventions are used to treat acute postoperative pain, and they are occasionally combined in multimodal analgesic regimes.[45]

MMA regimens pair together 2 or more medications with complimentary modes of action in order to cut back on overall opioid use while still providing analgesic relief. Despite the fact that opioids are a hallmark of severe post-operative pain therapy, there is pressure to restrict or halt their usage in this situation. Acute postoperative pain can be lessened, and its chronification may be lessened, with the use of MMA and a better knowledge of acute pain after surgery.[46]

**Pharmacology of paracetamol**

A non-opioid analgesic and non-salicylate antipyretic. A sterile, transparent, colourless, non-pyrogenic, isotonic paracetamol formulation designed for intravenous infusion is known as a paracetamol IV injection.

Molecular formula: $C_8H_9NO_2$

Molecular weight: 151.163 Da

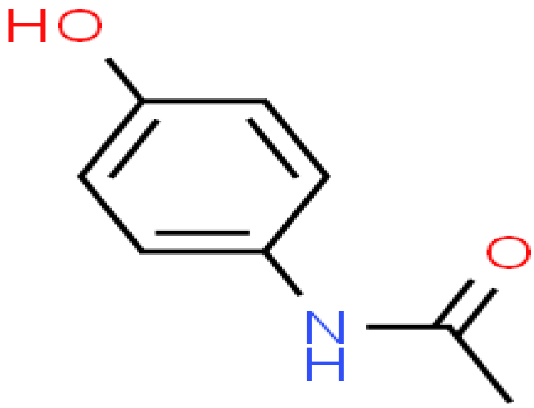


**Figure 6: chemical structure of paracetamol**

**Mechanism of action:**

Paracetamol typically has a lower analgesic effect comparing with NSAIDs or COX-2 selective inhibitors, and is commonly favored due to its better tolerability. Despite the fact that paracetamol and NSAIDs have similar mechanisms of action, it is now widely accepted that paracetamol suppresses Cyclooxygenase-1 and Cyclooxygenase 2 through breakdown by the enzyme activities of these isoenzymes. As a result, the formation of phenoxyl radicals from a key tyrosine residue needed for prostaglandin (PG) synthesis and cyclooxygenase activity is suppressed. Paracetamol particularly prevents the formation of PGs and associated compounds with the presence of trace amounts of arachidonic acid and oxidizing agents.[47]

**Pharmacokinetics of IV paracetamol:**

**Half-life:** 6hrs

Both a prepared injectable formulation and propacetamol are available for the intravenous formulation of paracetamol.[48]

**Dosage:**

The dosage of paracetamol IV that is advised among adults and children weighing 50 kg or more is 1000 mg/6hrs hour or 650 mg/ 4hrs hour. The longest dosage interval is four hours, the highest daily amount of paracetamol is 4000 mg, and single dose of paracetamol IV is 1000 mg. The dosage of paracetamol IV is fifteen mg/kg for every six hours for adults and adolescents under the weight of 50 kg. There is a limit single dose of 15 mg/kg, the least dosage gap of 4 hours, and a highest allowable intake of 75 mg/kg per day.[49]

**Contraindications**

1. known hypersensitivity
2. serious liver disease or severe hepatic impairment

**Side- effects:**

Adverse medication responses are uncommon (>1/10000, 1/1000), or extremely uncommon (1/10000), as they are with all paracetamol medicines. During clinical studies, many adverse responses at the injection site have been documented (pain and burning sensation). The medication must be stopped in extremely rare instances of hypersensitivity responses, which might range from a simple skin rash or urticaria to anaphylactic shock. There have been reports of erythema, flushing, pruritus, and tachycardia.

**Pharmacology of diclofenac IV**

NSAID, analgesic, antipyretic, and anti-inflammatory, activities are all provided by diclofenac. diclofenac is a non-specific COX inhibitor, it effectively inhibits the COX-2 isoform. It has pro-nociceptive effects in the lumbar and peripheral areas and reduces prostaglandin-E2 and thromboxane-A2 formation.[50]

**Molecular formula:** $C_{14}H_{11}Cl_2NO_2$

**Molecular weight:** 296.149

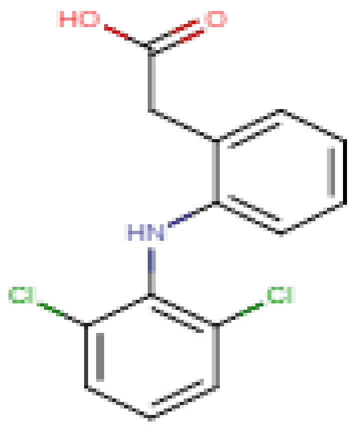


**Figure 7: Chemical structure of diclofenac**[51]

**Mode of action:**

Diclofenac is an NSAID benzene acetic acid derived that has anti-inflammatory effects. Diclofenac, a nonsteroidal anti-inflammatory medication (NSAID), binds and chelates both cyclooxygenase isoforms, stopping arachidonic acid from producing pro-inflammatory prostaglandins. This drug may also stop COX-2-mediated tumor angiogenesis. When diclofenac inhibits COX-2, it may be beneficial in decreasing pain and inflammation, but when it inhibits COX-1, it may have unfavorable side effects on the gastrointestinal system. Compared to a number of other NSAIDs that include carboxylic acids, this chemical may be more potent against COX-2.[51]

**Pharmacokinetics:**

The primary methods by which diclofenac is biotransformed include solitary and repeated methoxylation, hydroxylation, and incomplete glucuronidation, which generate phenolic metabolites that are later renewed into glucuronide conjugates. Eliminated in the bile (35%) and excreted in the urine (65%), the total systemic authorization is 264 mL/min. In plasma, t half is 1 to 2 hours. [52]

**Dosage:**

**For pain management**

Oral:

Take 25 mg of liquid-filled diclofenac potassium capsules four times each day.

18 mg or 35 mg of diclofenac-free acid taken three times daily by mouth Diclofenac instant-release tablets: 50 mg three times daily; for certain people, a 100 mg oral dosage followed by three 50 mg doses may be more effective.

Parenteral: 37.5 mg IV bolus given over 15 sec as needed per 6 hrs to treat pain Maximum Daily Measure: 150 mg

**Indications**

1. Osteo/rheumatoid Arthritis
2. Postoperative pain

3. Migraine
4. Dysmenorrhea

**Contraindications**

1. Hypersensitivity
2. Renal dysfunction
3. Liver diseases

**Side-effects:**

Nausea, vomiting, stomach discomfort, indigestion, gas, diarrhea, constipation, headache, sleepiness, abnormal lab results, itching, perspiration, stuffy nose, elevated BP, distension and aching in your arms or legs.

**Pharmacology of Tramadol**

Tramadol is mild opiod.it stimulates the l-opioid receptor while also inhibiting the re-uptake of monoamine neurotransmitters, which decreases afferent pain signalling and boosts efferent inhibitory signalling. Contrary to other opioids, tramadol mostly affects the descending inhibitory pathway of the CNS, preventing the transmission and experience of pain.[53]

**Molecular formula**: $C_{16}H_{25}NO_2$

**Molecular weight**:263.37

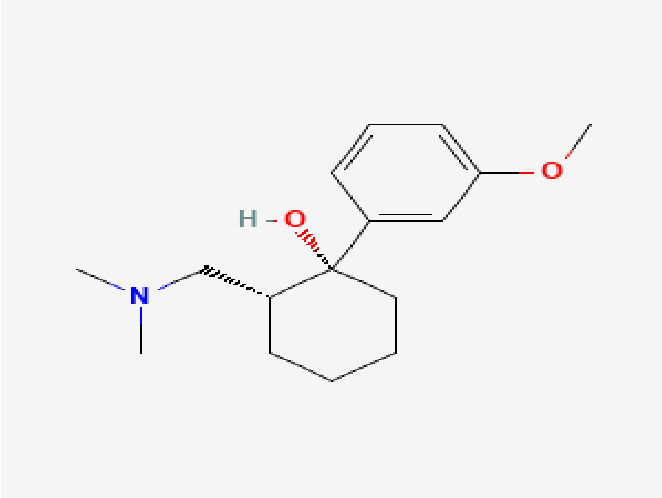


**Figure 8: chemical structure of tramadol**[53]

**Mechanism of action**

Tramadol reduces the transmission of pain by acting predominantly on the central nervous system's descending-inhibitory pathway, unlike other opioids. Tramadol is a racemic molecule, which explains the synergistic activity linked to its palliative and anti-nociceptive actions. The more powerful of the two enantiomers, (+) tramadol is a serotonin reuptake inhibitor and has a greater association for l-opioid receptors, whereas (-) tramadol is a strong norepinephrine inhibitor and activates auto-receptors. [52]

**Pharmacokinetics:**

Time for the medication to reach maximal concentration: six hours

Half-life: six hours

Doses: Immediate release: 50 mg; Immediate release: 100 mg. [52]

**Indications:**

Tramadol is a medication for pain relief that has FDA approval. It has intended applications for many types of pain, from moderate to severe. The FDA has designated it as a class IV pharmaceutical as of July 7th, 2014. Due to the danger of exploitation and obsession, its use needs to be limited to pain which is not responsive to other drugs. Furthermore, individuals receiving tramadol treatment have a minimal risk of developing drug dependence. Tramadol comes in two different formulations. The immediate-release medication should only be used for pain that can last below a week. For pain that lasts longer than a week, extended-release medicine is the optimum course of therapy; it is intended for pain management while being monitored around the clock.[54]

**Side effects**

1. Irritation, perspiration, nausea, somnolence, and dizziness.
2. Treatment with tramadol does not result in respiratory or cardiac depression, unlike other opioid medications.

**Toxicity**

Maintaining a patent airway and maintaining sufficient breathing through aided or regulated ventilation are the major goals of the first therapy. Similar to other opioids, naloxone can partially reverse tramadol's negative effects.[55]

**Contraindications:**[52]

Contraindication includes opioid-induced hypersensitive response; patients less than twelve years, patient under the age of eighteen who had a history of tonsillectomy or adenoidectomy, patients who are presently taking monoamine oxidase (MOAs) or who have taken MOAs within the last 14 days, patients who are on tricyclic antidepressant, a patient who have Gl obstruction.

Patients should abstain from alcohol, benzodiazepines, and other CNS depressants concurrently due to the risk of respiratory suppression as adverse effect. Tramadol is metabolized by the liver. Administration of other medications with hepatic metabolism should be avoided with tramadol.

**Pharmacology of pregabalin**

Gamma-amino butyric acid (GABA) has a 3-isobutyl derivative called pregabalin, which has anticonvulsant, anti-epileptic, antidepressant, and analgesic properties.[56,57]

**Molecular formula:** C8H17NO2

**Molecular weight:** 159.23

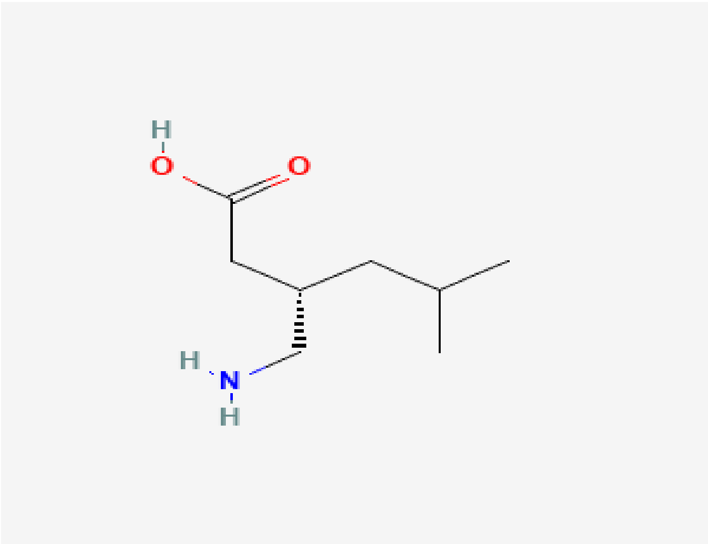


**Figure 9: Structure of pregabalin**[57]

**Mode of action:**

Pregabalin inhibits synaptic transmission and lowers neuronal excitability through attaching to alpha2 delta(A2D) subunits of presynaptic voltage dependent Ca+ channels (VDCC) in the CNS. This blocks calcium entry and the consequent calcium-dependent release of several neurotransmitters from the presynaptic nerve terminals of overexcited neurons, involving nor-epinephrin, serotonin, substance P, glutamate, and dopamine. [57]

**Pharmacokinetics:**

Pregabalin is rapidly engrossed and reaches its peak blood levels in less than an hour. Elimination t½ of pregabalin ranges 5.5 to 6.7 hours. Pregabalin does not enter plasma proteins or undergo liver metabolization. Ninety eight% among ingested dose is removed in the urine by the kidneys. Creatinine clearance and pregabalin elimination are proportional. [57]

**Dosage:**

The dosage is usually started at 50mg three times a day, and depending on effectiveness and tolerability, it can be raised up to 300 milligram/day within a week. Pregabalin is excreted mainly through the kidneys. Hence individuals with impaired renal function should have their dosage modified.

**Indications**

Pregabalin is administered for the management of neuropathic pain, fibromyalgia syndrome, post-dental pain model

**Contraindications** include hypersensitivity to pregabalin.

**Side effects:** [57]

Dizziness, weight gain, myoclonus, asterixis, and gynecomastia are the common adverse effects.

**PHARMACOLOGY OF FENTANYL**

It is a synthetic, lipophilic phenylpiperidine opioid agonist N (1-(2-phenethyl)-4-piperidinyl-N phenyl propanamide

**Chemical formula**: $C_{22}H_{28}N_2O$

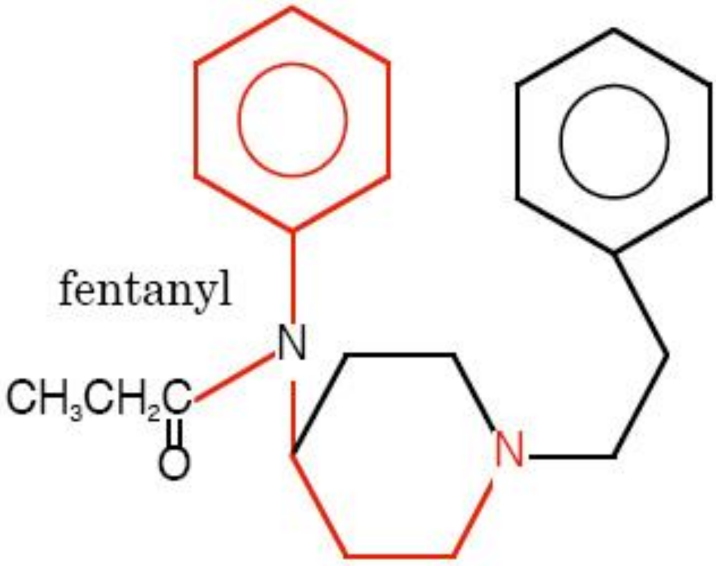


**Figure 10: CHEMICAL STRUCTURE OF FENTANYL**

**MECHANISM OF ACTION**

Fentanyl's pharmacological effects are mediated via the mu opioid receptor, which has a lower affinity for delta and kappa receptors. Mu receptors are classified into two types: mu1 and mu2. Pain relief is caused by the mu1 receptor. Mu2 receptors are involved in bradycardia, respiratory depression, and physical dependency. These receptors are present in CNS and PNS.

Opioid activity is mediated by G protein-coupled receptors. When opioid agonists activate this receptor, VDCC are blocked, lowering cyclic adenosine monophosphate levels. Preventing the efflux of neurotransmitters like substance P and glutamate from nociceptive fibers.

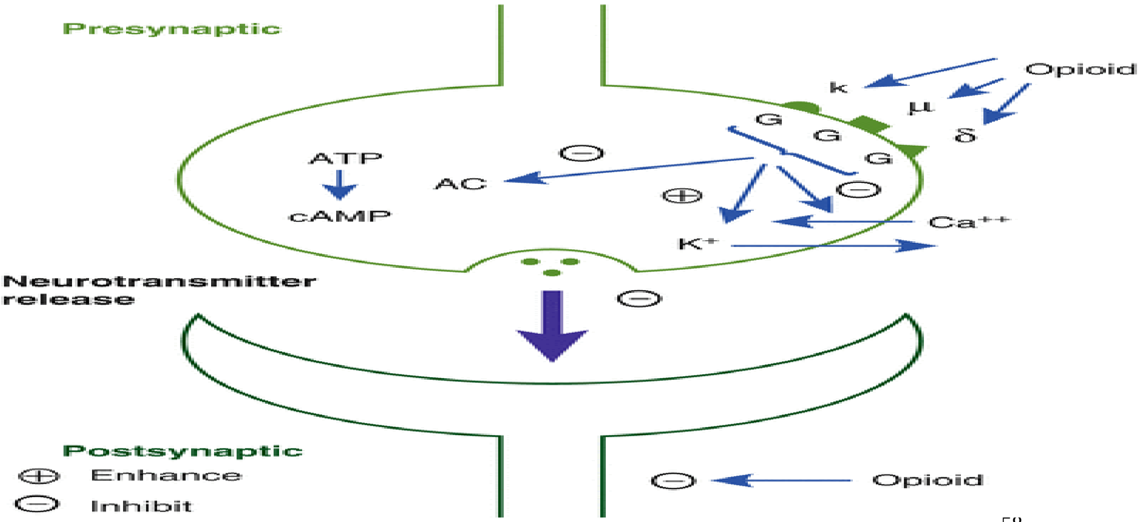


**Figure 11: MECHANISM OF ACTION OF OPIOD AGONISTS**[58]

## PHARMACOKINETICS - FENTANYL

Fentanyl is quickly transported from plasma into vastly vascularised compartments after an intravenous bolus. It is transferred into muscle and fat tissues from systemic circulation. [59]

Elimination half-life is 219 - 853 minutes. Distribution volume is of 3.5-8 litres per kilogram.

Fentanyl has high clearance (30-72L/hr).

## DISTRIBUTION

Fentanyl interacts with plasma proteins because it is very lipophilic. The dose-adjusted serum fentanyl concentrations were considerably lower in patients with a serum albumin of less than 3.5g/dl. At a pH of 7.4, the drug's unionized fraction is 8.5 percent.[59]

## METABOLISM

Dealkylation of fentanyl by CYP3A4 in the liver results in inactive metabolites such as norfentanyl. When compared to mild liver failure, severe liver failure resulted in a sevenfold reduction in fentanyl clearance.[59] Of the metabolites discharged unchanged in the urine, 10% are found in feces, and 9% are found in urine.[60]

## SYSTEMIC EFFECTS OF FENTANYL

### ANALGESIA

The mu1 receptors, which are essential for analgesia, are primarily affected by fentanyl.[61]

### CARDIOVASCULAR SYSTEM

Myocardial oxygen demand will be reduced due to peripheral vasodilatation and thereby causing a drop in preload and afterload. Cardiac output, blood pressure, and heart rate decreased slightly. Change in hemodynamics is minimal.[61]

### RESPIRATORY SYSTEM

Upper airway reflexes are abolished in a dose-dependent manner. Only with subsequent doses do laryngospasm and apnea occurs. Fentanyl gives rise to respiratory depression. It is shown by elevated $ETCO_2$ levels. Once the end-tidal carbon dioxide reaches 50 mmHg, then minute ventilation will be increased. When other sedatives like midazolam accompany fentanyl, respiratory depression will be enhanced. Therefore, such patients are monitored and also supplemented with oxygen.[62]

### ENDOCRINE SYSTEM

When fentanyl is injected at a dose of 10 mcg/kg, usually there will be a fall in plasma levels of free fatty acids, growth hormone, glucose, cortisol and epinephrine.[62]

## INDICATIONS FOR FENTANYL[61]

Analgesic dose is 1-2 micrograms/kg IV. As an adjuvant in spinal anesthesia, a dose of 25 mcg of fentanyl is added to bupivacaine. Adjuvant to GA , a dose of 2-10 mcg/kg .As an adjuvant in labor analgesia in epidural anesthesia in a dose of 2 mcg/ml. For post-surgical pain management IM/IV 50 to 100 mcg every 1 to 2 hrs can be given; alternatively, IV 0.5 to 1.5 mcg/kg/hr as necessary. Consider taking a lower dosage if the patient is 65 or older. For moderate to extreme acute pain 100 mcg is the maximum dose; 1 to 2 mcg/kg/dose is administered intranasally/hr as needed. Use the shortest effective period at the lowest effective dosage.

## SIDE EFFECTS [62]

Adverse effect includes respiratory depression, myoclonic movements, apnea, muscle rigidity, nausea and vomiting bradycardia

## CONTRAINDICATIONS FOR FENTANYL:[61]

Patients having bronchial asthma, COPD or allergic history, patients on MAO inhibitors and head injury should not take fentanyl.

## PHARMACOLOGY OF BUPIVACAINE

### BUPIVACAINE: [63,64]

First used in 1963, bupivacaine is an amide local anaesthetic.[65]

### CHEMICAL STRUCTURE:

A long-acting amide local anesthetic, bupivacaine HCL (1-butyl-2', 6' pipecoloxylidide hydrochloride) is used.

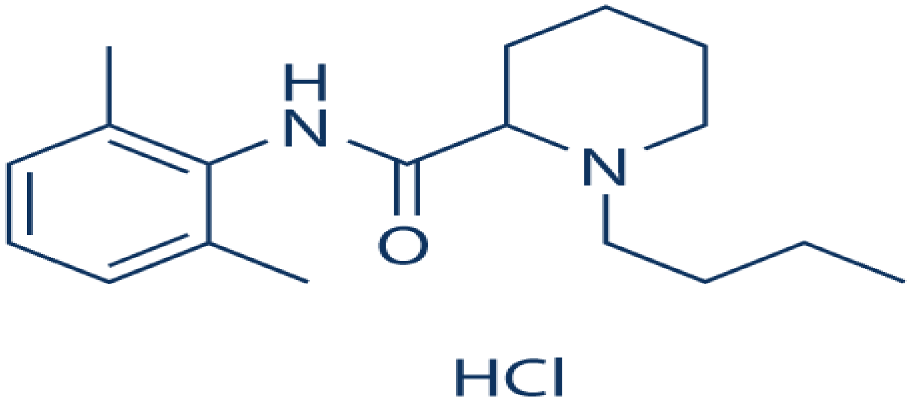


**FIGURE 12: CHEMICAL STRUCTURE OF BUPIVACAINE**

### MECHANISM OF ACTION:[66]

Bupivacaine attaches to an intracellular region of Na channels blocking sodium entry into nerve cells. It blocks the transmission of NMDA receptors in the spinal-cord's dorsal horn. Dose of Bupivacaine is 2-3mg/kg. The beginning of action is 5 to 7 minutes. Period of action is 4 to 6 hours

### Pharmacokinetics:

Base molecular weight is 288 daltons. Pka of bupivacaine is 8.1. 95% is bound in plasma.

Distribution volume is 0.9–0.4 liters/kg. Clearance ranges from 7.1-2.8 ml/min/kg. Peak hour is 0.17 to 0.5 hours. Plasma toxic concentration is more than 1.5 micrograms per milliliter.

Alpha1 acid glycoprotein's is the binding site for plasma proteins. Undergoes enzymatic degradation in liver. Elimination is from the kidney

**CLINICAL USES:**

Central neuraxial blockade is used for peripheral nerve blocks and infiltration analgesia (epidural, caudal, intrathecal).

**TOXICITY:**

Toxicity because of unintended intravascular injection or systemic absorption depend on the dose directed, the presence of adrenaline (adrenaline in solution decreases the systemic absorption by1/3rd), the property of the drug, and the vascularity of the tissue.

**TOXIC FEATURES ARE:**

Mild systemic symptoms such as circumoral numbness, auditory changes like tinnitus, agitation. CNS toxic effects involve CNS depression, seizures, unconsciousness, and respiratory arrest. Cardiovascular system toxic features include bradycardia, tachycardia, ventricular arrhythmias, hypotension or hypertension, and cardiac arrest.

**Role of bupivacaine and fentanyl administered by CSE in lower limb orthopedic surgeries:**

Because of the growing need for postsurgical pain relief and a decrease in the prerequisite for IV analgesic medications during the recovery period, application of neuraxial blocks in orthopedic surgery has quickly expanded in recent decades. The combined spinal epidural approach, which is also a safer and more dependable analgesic treatment, best satisfies these needs. A range of local anesthetics is used by CSE. It is frequently used for local penetration, nerve blocks, spinal anesthesia, and epidural anesthesia. Bupivacaine is a local anesthetic that is a member of the amide group of anesthetic substances. In an effort to further lessen side effects and lengthen the duration of intraoperative and postsurgical analgesia, numerous adjuvants are added to local anesthetics. The inclusion of .125% bupivacaine increases the analgesia of epidural infusions of fentanyl (10 micrograms/ml) after abdominal or thoracic surgery. Another research discovered that bupivacaine of .125percentage with fentanyl 2 mcg/ml combination provided superior pain management during childbirth than bupivacaine .0625% with fentanyl 2 mcg/ml.[67] In contrast to infusions of 0.125% bupivacaine alone, epidural infusions utilizing 0.125% bupivacaine plus 0.0002% fentanyl did not cause a delay in stomach emptying.[67] Additionally, injection of a mixture containing fentanyl and bupivacaine .125% demonstrated equipotent analgesia to that of the latter and resulted in decreased weakening in the lower extremities. The addition of bupivacaine 0.125% had no impact on the amount of fentanyl necessary.[68] It was also demonstrated that the quality of analgesia and discomfort reduction during abdominal surgeries were greatly enhanced by the addition of 2 mcg/ml fentanyl citrate to 0.125 percentage of bupivacaine hydrochloride.[67] Similarly, in lower limb orthopedic and abdominal surgeries, this combination provided a superior analgesic effect with the least hemodynamic changes postoperatively.[69,70]

**Multimodal analgesia**

In order to achieve a synergic effect at lower analgesic dosages, multimodal analgesia integrates analgesics from two or more pharmacology groups targeting peripheral or central pain pathways.[11]

Analgesics include "N-methyl-D-aspartate" (NMDA) receptor antagonist, tricyclic antidepressants, opioid and nonopioid painkillers, "gabapentinoids" (pregabalin, gabapentin), and opioids (epidural and intrathecal)

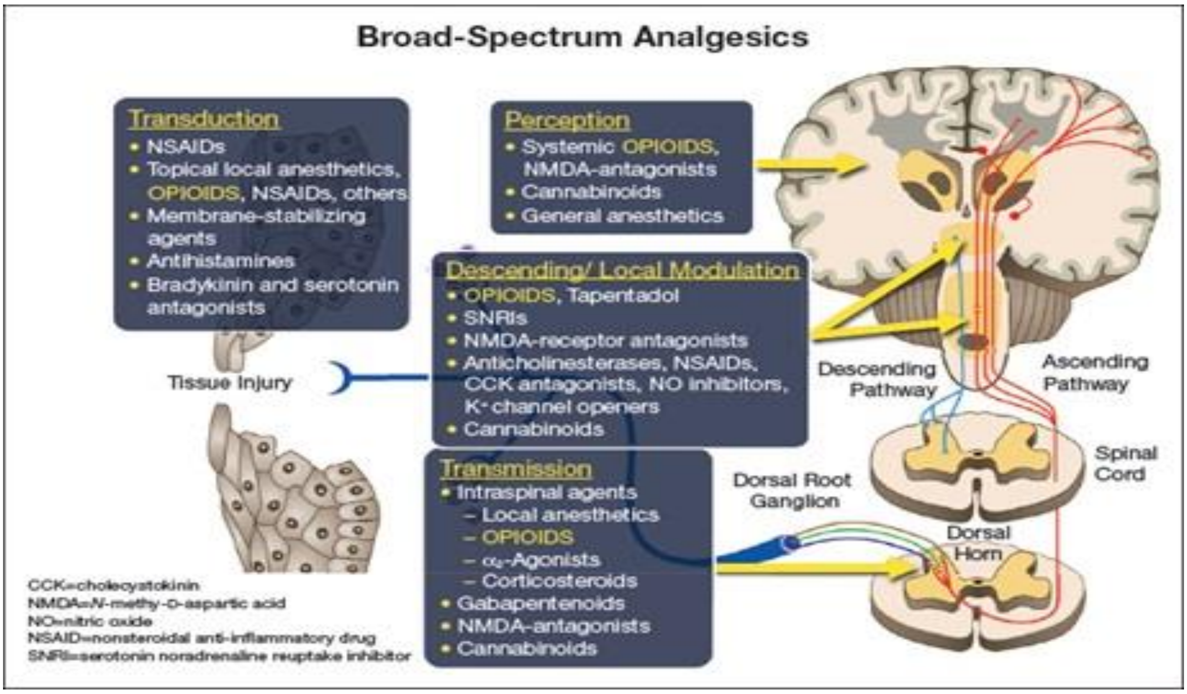


**Figure 13: The multimodal regimens' wide-ranging analgesics can be utilized to address every stage of the nociceptive pain process.**[71]

Physical and behavioural health therapies are a part of MMA methods. It is currently advised to employ multimodal analgesia, which was initially used more than 20 years ago, to treat both critical and long-standing pain. When different parts of the peripheral and central pain pathways are targeted using multimodal regimens, effective analgesia is obtained at lower opioid dosages, lowering associated risk and resulting in fewer side effects.[72]

**Some analgesics can target each stage of the nociceptive pain process**

Transduction, which happens when activated nociceptors emit an electrical signal, can be interrupted by NSAIDs and membrane-stabilizing drugs. Transmission, which happens when an electrical signal transfers from the area of damage to the brain and spinal cord, can be interfered with by LA and gabapentinoids. Systemic opioids and NMDA receptor blockers may lessen the somatosensory cortex in the brain's knowledge or sense of pain. Downward and local attenuation is the adaptive mechanisms by which pain signals can be increased or decreased centrally (by traveling down pathways that start in the brain and extend to the spinal cord) or peripherally. Interventions like nerve blocks, neuraxial therapy, and local permeation are responsive to these processes.

Multimodal treatments are very helpful and frequently recommended for subjects who are opioid-reliant or opioid-lenient due to their opioid-sparing benefits. Plans of care for multimodal analgesics must be tailored to the subjects, the type of pain, the origins of suffering (neuropathic/ inflammatory), the surgical technique, the site of the pain, and the anticipated length of suffering.[71] An example of a "preventive analgesia" approach is preoperative analgesia. Preoperative analgesia has traditionally been referred to as "pre-emptive analgesia," but Dahl and Kehlet argue that the term "preventive" improved captures the practice's underlying premise.[73]

**Postoperative pain relief with multimodal analgesia**

The evidence-based method for acute postsurgical pain prefers MMA since it reduces adverse effects while providing effective pain relief. Results may be less favourable if early postoperative pain is poorly managed. Pain can increase heart rate, while decreasing blood flow because heart requires extra oxygen than the body is capable of providing.[74]

Multimodal analgesia refers to the management of pain using 2 or more pharmacological or non-pharmacological interventions with a complementary mode of action. Peripheral nociceptors, which are pain receptors, detect pain at the location of acute pain related to a peripheral trauma, such as postsurgical pain. Topical anesthetics, oral or topical NSAIDs, opioids, topical capsaicin, acetaminophen, or a combination of these may be used to relieve localized peripheral pain. Non-pharmacological pain management methods include touch therapy, continual passive motion, cryotherapy, and heat therapy.[11] In addition to causing shallow breathing, postoperative discomfort can also produce hypercarbia, hypoxia, and atelectasis, all of which can result in pneumonia. Additionally, unrelieved surgical pain might delay rehabilitation and hinder healing.[75]

The patient's pain threshold is lowered by opioid-induced hyperalgesia (OIH), which raises their sense of pain severity. Consequently, multimodal analgesics can be used to control this. In a poll of 850 chronic pain specialists, 38% reported that more than 5% of their patients had OIH, and 76% said they treated subjects with OIH in their practise. When OIH developed, these doctors most frequently utilized opioid dosage reduction, the inclusion of a nonopioid adjuvant drug, or opioid withdrawal.

Numerous clinical investigations have demonstrated that preoperative gabapentinoids minimize postoperative pain.[76,77] The binding of gabapentinoids to the -2 subunit of P/Q type voltage-gated Ca+ channels reduce glutamate release. By doing this, central sensitization and the propagation of pain impulses are inhibited. The activation of noradrenergic pathways in the brain and spinal cord by gabapentinoids appears to be another manner in which they suppress pain signals.[78]

Fixed-dose combination (FDC) analgesics offer significant advantages such as a less number of pills to swallow, simplicity in administration, and a requirement for lower doses of separate medication components. Merging oral opioids (codeine/tramadol) with non-opioids is a preferable choice (such as paracetamol or NSAIDs). Among the FDCs now on the market, paracetamol is the non-opioid drug that is used the most frequently. The danger of paracetamol's cardiovascular and gastrointestinal (GI) side effects has lately increased in addition to its recognized hepatotoxic potential. Additionally, paracetamol does not have the anti-inflammatory properties often linked to NSAIDs. [79]

Tramadol is a centrally-acting analgesic. Tramadol does not cause respiratory depression. Additionally, stops serotonin and norepinephrine from being reabsorbed in the spinal cord. It may be able to deliver efficient postoperative analgesia following central neuraxial administration without running the risk of respiratory depression.[80]

A recently developed formulation of instant-release tramadol and continuous-release diclofenac is currently widely utilized in clinical practise. This FDC produces multimodal analgesia at levels that are both less intense and more tolerable when compared to either drug alone.[81]

**Pre-emptive multimodal analgesia regimen on reducing post-operative pain in surgeries**

To avoid pain sensitization brought on by incision-related and inflammatory damage that happens during surgery, pre-emptive analgesia, an antinociceptive medication, is started before the operation. Pre-emptive analgesia provides this defence against the nociceptive system. [82]

A 3-armed RCT was conducted by Aweke, Z et al[24], 2020. In patients having laparotomy surgery, the research evaluated the postsurgical analgesic impact of preventive paracetamol, paracetamol with diclofenac, and paracetamol with tramadol combinations. Total tramadol intake in the paracetamol group was substantially greater in comparison to the paracetamol with diclofenac and paracetamol with tramadol groups. The paracetamol group's time to get analgesic request was considerably lower. Preemptive administration of paracetamol with tramadol and paracetamol with diclofenac decreases overall tramadol intake and lengthens the time until the first analgesic request in patients having laparotomy surgery.[24]

Dorsal horn neuron hyperalgesia can be efficiently suppressed by GABA analogs. Pregabalin and gabapentin cause analgesia by attaching to the voltage-gated calcium channel's α-2 delta subunit. Pregabalin had fewer negative side effects and was six times more effective than gabapentin in binding to the α-2 delta subunit.[83] A review found that pregabalin and gabapentin, when administered as PA, might successfully delay the need for the initial analgesic and minimize postoperative analgesic rescue.[84] In the first 24 hours following surgery, gabapentin decreases opioid intake, although this effect is not dose-dependent. Pregabalin and gabapentin have safe upper limits of 1200 mg and 300 mg, correspondingly. Saraswat[85] suggested that the gabapentin group's initial analgesic demand occurred earlier than the groups. Sebastian B et al, demonstrated pregabalin 150 mg used orally as a preemptive analgesic to be efficient in lowering postoperative pain brought on by lower limb orthopedic operations.[25]

**ASSESSMENT OF PAIN**

Pain is a very individualized experience that has a wide range of effects. As a result, measuring it is a critical responsibility for a doctor. There are several verified scales available. The importance of accepting and acting on the patient's self-report cannot be emphasized enough. The doctor needs to remain vigilant since the patient could occasionally exaggerate. Since pain is dynamic, it should be routinely evaluated, and any necessary modifications to therapy should be made. Unidimensional self-report measures are a highly straightforward, practical, and reliable way to evaluate pain. A score from 0 to 10 has been used. It has no pain at the beginning and the vilest agony at the end is a visual analog scale (VAS).[86]

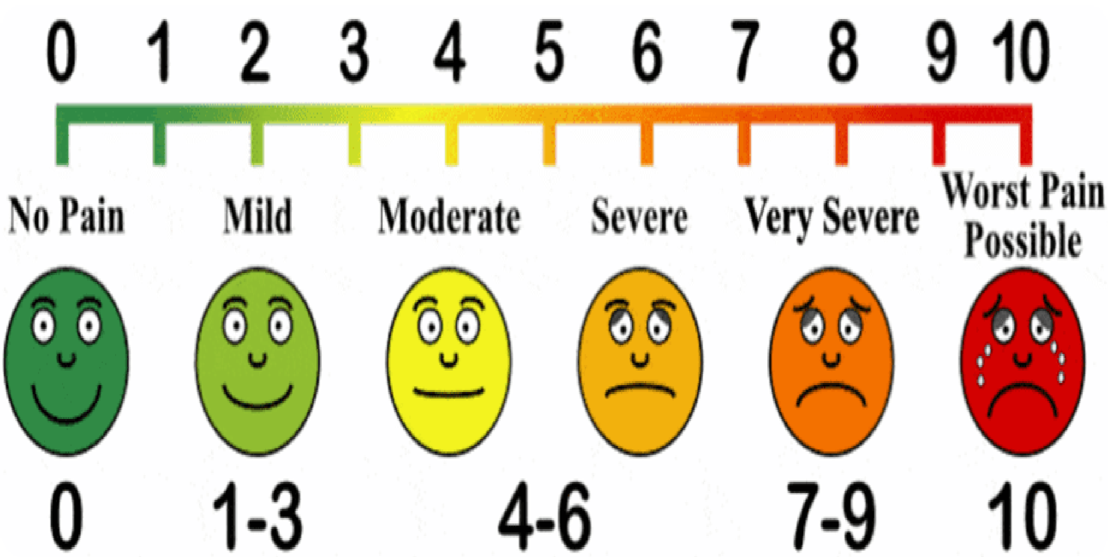


**Figure 14: VAS for pain assessment**

**Measuring Patient satisfaction**

To safeguard the quality of anesthetic care, develop and deepen the doctor-patient relationship, and serve as a marketing tool for client-centeredness, it has become essential to estimate patient satisfaction with anesthesia. The measurement of patient satisfaction might be difficult. Patients typically find it difficult to evaluate and compare the quality of anesthetic care to the overall standard of care received throughout treatment.[87]

**Recent Relevant studies**

1. In the field of TJA, Passias, B et al[88] 2022 aimed to measure how a preventive 3-drug regimen (acetaminophen, celecoxib, gabapentin) affected the use of post-surgical opioids and pain management. They found that celecoxib, acetaminophen, and gabapentin were preemptively administered 30–60 minutes before total joint arthroplasty, and the need for postoperative opioids was only slightly reduced.
2. Ambaram V et al [89]2022 aimed at a placebo-controlled experiment; trial was directed to check the effects of preventive IV paracetamol on the need for postoperative analgesia in subjects undergoing laparoscopic cholecystectomy under General Anaesthesia (GA). Prior administration of 1 gram of paracetamol via IV offered superior eminence analgesia with reduced pain scores throughout the postsurgical period, improved subject approval, and less postoperative fentanyl use in subjects undergoing laparoscopic cholecystectomy.
3. Chen, Z et al[90] 2022 examined how pregabalin affected perioperative pain control in lower extremity orthopedic surgery. This investigation provisions the use of pregabalin before lower limb orthopedic surgery in patients. However, it was concerned about increased dizziness and sedation that would result.

4. A systematic metanalysis by Doleman, B et al[91] 2021, indicated that there is evidence that NSAIDs used for treatment and prevention can lower both morphine consumption and pain levels.

5. Kheirabadi, D et al[92] 2020 equated the preventive effectiveness of pregabalin, gabapentin, and celecoxib on lowering postsurgical pain following lower extremity surgery. Preoperative pain and opioid usage can be decreased, especially in the 1st twenty four hours after surgery by taking 75mg of oral pregabalin.
6. The goal of Aweke, Z et al[24] 2020 aimed to evaluate the postsurgical analgesic effect of preemptive paracetamol, paracetamol with diclofenac, and paracetamol with tramadol combinations in patients undergoing laparotomy surgery. Total tramadol consumption in the paracetamol group was significantly higher than in the paracetamol-diclofenac and paracetamol-tramadol groups. The time to first analgesic request was significantly shorter in the paracetamol group than in the paracetamol-diclofenac and paracetamol-tramadol groups. There was a statistically significant difference at the 4th, 6th, and 8th hour, with the paracetamol-tramadol group having a lower median pain score than the paracetamol group. Preemptive paracetamol-tramadol and paracetamol-diclofenac combinations reduce total tramadol consumption and lengthen the time to the first analgesic request.
7. Makkar, JK et al[14] in 2019 at Puducherry, India aimed to assess the efficiency of a pre-emptive MMA schedule in reducing the epidural request boluses in the initial 48 hours post distressing shaft of femur fractures. This study involved 135 subjects. The subjects received pre-emptive multimodal of IV acetaminophen one gm diclofenac 75mg, morphine 3mg, and 75mg pregabalin per oral. Preemptive MMA regimen decreased the need for epidural demand boluses in the first 48 hours after surgery. The average number of times rescue analgesics were delivered was lower in the preemptive analgesic group.

8. Putta, P et al[93] 2019 study compares the effectiveness of pre-operative and post-operative intraperitoneal local anesthetic instillation in managing postsurgical pain following elective laparoscopic cholecystectomy. A double-dummy technique was used to randomly assign 90 patients either 30 ml of normal saline (C) or 30 ml of 0.5% bupivacaine at the start (PE) or end (PS) of the procedure. Pre-emptive intraperitoneal local anesthetic instillation led to improved postsurgical pain control, a decreased frequency of shoulder aches, and an earlier return to normal activities.
9. M. Haffner and colleagues[94] 2019, Retrospective review, from 2013 to 2017, 185 patients underwent spinal fusion surgery involving five levels at one academic institution. Preoperative administration of a selective COX-2 inhibitor and GABA analog reduced twenty four hour postoperative opioid consumption, VAS pain scores, and reduced time to postoperative mobility.
10. Omara, A et al[95] 2019 found out that preemptive oral pregabalin delayed the need for postoperative analgesics and improved sleep the first night after surgery. The study included sixty adult patients who underwent internal fixation of a femoral fracture while under spinal anesthesia. Oral pregabalin significantly increased the time to two-segment regression of sensory block and improved sleep quality the first night after surgery
11. Memtsoudis, S et al[19] 2018, sought to ascertain the relationship between decreased opioid drug, and complications, with the number and kind of analgesic modalities. 85.6% of patients received multimodal analgesia. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors are considered to be effective modalities used.

12. A double-blinded randomized control trial in 2018 in Boston stated that administering analgesic medicine before the commencement of the painful stimuli is thought to be more effective than administering medication after it begins. A study showed that anticipatory analgesia can greatly lower the demand for opioid drugs in the early postoperative period, which indicates reduced analgesia requirements.[96]
13. A review by Polomano, R et al[71], 2017 found that acute pain can be managed by various multimodal analgesic therapies; discussed regarding their benefits; and summarized results from related research.
14. Koehler, D et al[97] 2017, aimed to find out the effectiveness and safety of a multimodal medication injection at the surgical site for postoperative pain management after operational repair of femoral fractures. Narcotic requirement was lesser in the injection group compared with the control group over the first 8 hours following the surgical procedure.
15. Xu, Z et al[98] 2017 sought to assess the efficiency of PA using celecoxib in combination with low-dose tramadol in the management of postoperative pain in patients undergoing unilateral TKA. This study included 132 patients who were scheduled for TKA. Based on satisfactory intra- and postoperative analgesia, PA with three days of celecoxib and low-dose tramadol may be an effective and safe therapy for patients undergoing TKA in terms of postoperative pain relief.
16. A randomized control trial study was published in 2016 in Korea to find out the effectiveness of a pre-emptive MMA for decreasing postsurgical pain after primary lumbar fusion surgery. The study concluded that the preemptive MMA grouping in this study found to be safe and effective after lumbar fusion surgery.[99]

17. A systematic analysis by Nir, R et al[28], 2016 evaluated the effectiveness of preemptive drug administration in adults undergoing common surgical procedures. The study concluded that post-surgical analgesic requirement is less among the preemptive group.
18. In a RCT by Shah, P et al[82] 2016, Lamotrigine's preventive analgesic efficiency in postoperative pain management was analyzed with diclofenac. The study advised using lamotrigine as a preemptive analgesia for efficient postoperative pain management.
19. Sebastian, B et al.[25] (2017): Pregabalin 150 mg was compared to a placebo in a randomized controlled study to control postoperative pain in patients having elective lower extremity orthopedic procedures under SA and to look for any negative effects. The pregabalin group needed more extended time than the placebo group to achieve rescue analgesia (VAS score >3). Pregabalin group scores on sedation and patient satisfaction were also higher.
20. According to a 2014 New York research, multimodal analgesia is effective for routine surgical procedures. Acetaminophen, NSAIDs, and cyclooxygenase inhibitors are examples of multimodal analgesics that exhibit decreased narcotic needs, greater patient satisfaction, shorter stays in post-anesthesia care units, as well as lower rates of morbidity during the perioperative period.[100]
21. Jebaraj, B et al[101] 2013, discovered that giving patients a 2 g IV injection of propacetamol might lower their need for morphine by up to 46%.

22. Entezariasl, M et al[102] 2013, Pregabalin pre-operative treatment was evaluated for its adequacy and safety on minimizing post-surgery discomforts following lower extremity orthopedic surgery and lowering requirement for opioids and their likely adverse reactions. Pregabalin dramatically decreased visual analog pain levels across the board, according to data on 60 participants compared to the placebo group.
23. McNicol et al.[103] (2011) did a thorough search for solitary-dose, RCT studies using propacetamol or intravenous paracetamol for adults or children experiencing acute postoperative pain. 37% of patients with acute postoperative pain can get 4 hours of effective analgesia with a solitary dose of propacetamol or intravenous paracetamol.
24. According to a 2010 study done in "Connecticut", multimodal analgesics only had fewer side effects such as drowsiness, nausea, sickness, pruritis, and constipation, in addition to providing better pain relief. Studies have indicated that combining multimodal analgesia with a rehabilitation program can result in a quicker recovery, a shorter stay in the hospital, and a shorter convalescence period.[15]

## LACUNAE OF LITERATURE

It has been demonstrated that PA is a better analgesic option for avoiding central sensitization in several areas along the pain pathways and is a useful adjunct to multimodal treatments. Although the majority of research came to the conclusion that different PA agents and procedures had the ability to reduce postoperative pain, none of them stood out as being superior to the others. Clinical failures are still frequent. Based on a better knowledge of the pain mechanism, selecting an appropriate analgesic method (either unaccompanied or in combination) for post-surgery pain management is crucial. Instead of only concentrating on the moment itself, PA should aim to lessen the influence of unpleasant impetuses in advance.

Even today, there are many outstanding concerns regarding PA, including the ideal strategy. What dosage can most effectively stop the central and peripheral sensitization processes? Why is it necessary to continue pre-emptive analgesia into the healing process in order to maintain the initial benefit?

Most encouraging clinical and investigational findings showed that the preventative measure would lessen postoperative discomfort. Maximizing PA's analgesic efficacy is still difficult, though. To create a more thorough strategy, additional research is necessary.

# MATERAIL & METHODS

# MATERIAL AND METHODS

**Study population:** The research population was considered to be all 48 patients scheduled for lower limb orthopedic procedures under spinal with epidural anesthesia in anaesthesiology department at R.L Jalappa Hospital and research center attached with Sri Devaraj Urs Medical College in Tamaka, Kolar.

**Study design:** The current study was a double-blinded RCT.

**Sample size:**

To detect a mean reduction of 1 in the number of epidural demand boluses among the preemptive multimodal analgesia group, considering an α error of 1% with the power of 90% and variance estimate of .81 in the number of epidural demand boluses as reported in a study by Makkar JK et.al. estimated sample size was 24 per group.[14]

**FORMULA:**

$$n = \frac{2s_p^2[z_{1-\dot{\alpha}/2}+z_{1-\beta}]^2}{\mu_d^2}$$

$$s_p^2 = \frac{s_1^2 + s_2^2}{2}$$

**Where,** $s_1^2$= Standard deviation in the first group

$s_2^2$= Standard deviation in the second group

$\mu_d^2$= Mean difference between the samples

$\dot{\alpha}$ = Significance level

1-ß = Power

**Sampling method:** Until the desired sample size was obtained, all of the eligible participants were sequentially recruited into the research using easy sampling.

**Study duration:** Data for the research were gathered between January 2021 and May 2022.

**Inclusion Criteria:**

1. Age 18 to 65 years
2. Patients posted for lower extremity orthopedic operations under spinal with epidural anesthesia
3. ASA 1 and 2

**Exclusion criteria:**

1. Patients with known hypersensitivity to preemptive analgesic drugs.
2. Patients with an associated head injury.
3. Patients with renal impairment
4. Polytrauma patients
5. Patients with psychiatric disorders

**Ethical considerations:** The study was authorized by the institution's human ethics committee. Only individuals who were willing to sign the written informed consent that each study participant supplied were permitted to participate in the study. Before receiving the agreement, the participants were informed about the study's risks and benefits as well as the voluntary nature of participation. The study participants' privacy was protected.

**Data collection tools:** A well-organized research proforma contained documentation of all pertinent parameters.

**Methodology:**

The subject's complete medical history was obtained. A detailed physical examination was performed. Standard investigations were examined. Intravenous lines were secured and IV fluids were connected. Subjects were divided into two groups based on computer-generated randomization. The randomization procedure was concealed by providing with serially numbered wrapped opaque packets. The anaesthesiologist selected a sealed packet using the label on the packet and gave medications 30 mins prior to the scheduled surgery. Group A: Preemptive group received intravenous (IV) paracetamol 1 g, IV tramadol 50 mg diluted in 100 ml NS, IV diclofenac 75mg dissolved in 100 ml NS, and tab pregabalin 75 mg orally, 30 mins before surgery. Group B: Placebo group received 3 pints of 100 ml NS intravenously and tab ranitidine 150 mg orally, 30 mins before surgery. Tablets were given in a powdered form. The drug administered to the patient was unknown to them. Intraoperatively, combined spinal-epidural anaesthesia was administered under all aseptic precautions. Bupivacaine heavy of 3.4 cc was used for giving spinal anaestheisa. Visual analogue scale (VAS) was recorded immediate-postoperatively, and then at 1 hr, 4 hr, 8 hr, 12 hr, and 24 hr for both groups by another anaesthesiology resident. Immediate postoperative (0 hr) corresponds to two hrs after giving spinal anaesthesia. Epidural bolus was given for postoperative pain management in both groups. Epidural boluses were given whenever the patient’s visual analogue scale was more than 4. An epidural bolus of 10 ml of .125% bupivacaine with 2 μg/ml of fentanyl was given. The time at which the first epidural bolus was required by the patient was recorded. Overall number of epidural top-up given during 24 hrs based on visual analogue scales had been recorded for both the preemptive and placebo groups. If subject continued to express pain, IV diclofenac75 mg was administered if VAS was more than 4, IV diclofenac 75 mg along with IV tramadol 50 mg was given if VAS was more than 6. The requirement of IV diclofenac and IV tramadol was noted. Patient satisfaction with anesthesia care, in general, was assessed 24 hrs postoperatively using 4-point Likert scale (very satisfied/satisfied/dissatisfied/very dissatisfied). The 4-point Likert scale was taken from the Bauer questionnaire. [87] The patient was asked to give a reply based on their satisfaction and discomfort levels.

**Parameters Observed:**

1. Immediately after moving to recovery 0 hr (2hrs after giving spinal anaesthesia), as well as after 1hr, 4hr, 8 hr, 12 hr, and 24 hr, VAS was observed.
2. Total number of epidural boluses were given.
3. Time at which the first epidural bolus was given.
4. Requirement of IV diclofenac 75mg and IV tramadol 50mg even after epidural demand boluses.
5. Patient satisfaction with anaesthesia care in general 24hrs postoperatively.

**Statistical methods:**

The two main outcome variables were VAS ratings and epidural bolus. The study group was regarded as the main explanatory factor. Other factors related to the study, such as age, gender, and diagnosis, were taken into consideration.

For categorical data, descriptive analysis was performed using frequency and percentage.

Using an independent sample t-test, the mean values for quantitative parameters with normally distributed distributions were compared between study groups (2 groups).

Cross-tabulation and percentage comparison were used to evaluate the relationship between categorical explanatory factors and categorical outcomes. The statistical significance was evaluated using the Chi-Square test. The threshold for statistical implication was a P value of 0.05. CoGuide software, version 1.01, was used to analyze the data.[104]

# RESULTS

# RESULTS:

Final analysis included 48 subjects.

**Table 1: Descriptive analysis of Study group within the study population (N=48)**

| Study group | Frequency | Percentage |
|---|---|---|
| Group A | 24 | 50% |
| Group B | 24 | 50% |

In study population, 24 (50%) participants were in group A and remaining 24 (50%) participants were in group B. (Table1 & Figure 15)

**Figure 15: Bar chart of Study group in the study population (N=48)**

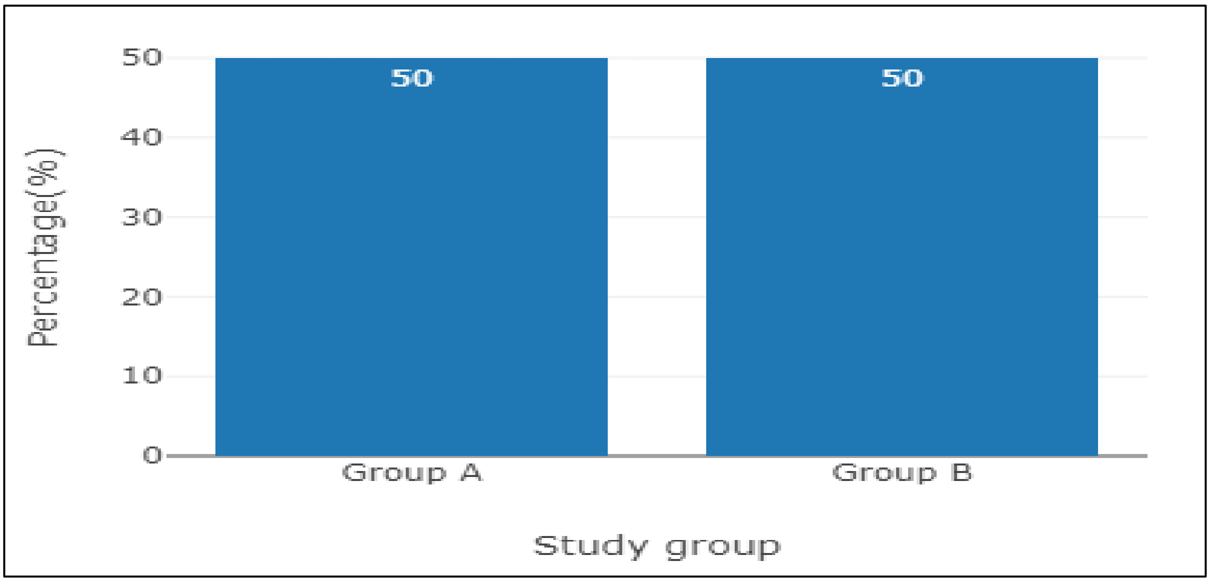

**Table 2: Comparison of Age with Study group in the study population (N=48)**

| Parameter | Study group | | P value |
|---|---|---|---|
| | **Group A (N=24)<br>Mean ± SD** | **Group B (N=24)<br>Mean ± SD** | |
| Age | 42.46 ± 17.24 | 50.88 ± 19.98 | 0.1251 |

The mean age of group A was 42.46 ± 17.24 and group B was 50.88 ± 19.98, the difference between two groups was statistically insignificant (p value 0.1251). (Table 2 & Figure 16)

**Figure 16: Bar chart of age with study group in the study population (N=48)**

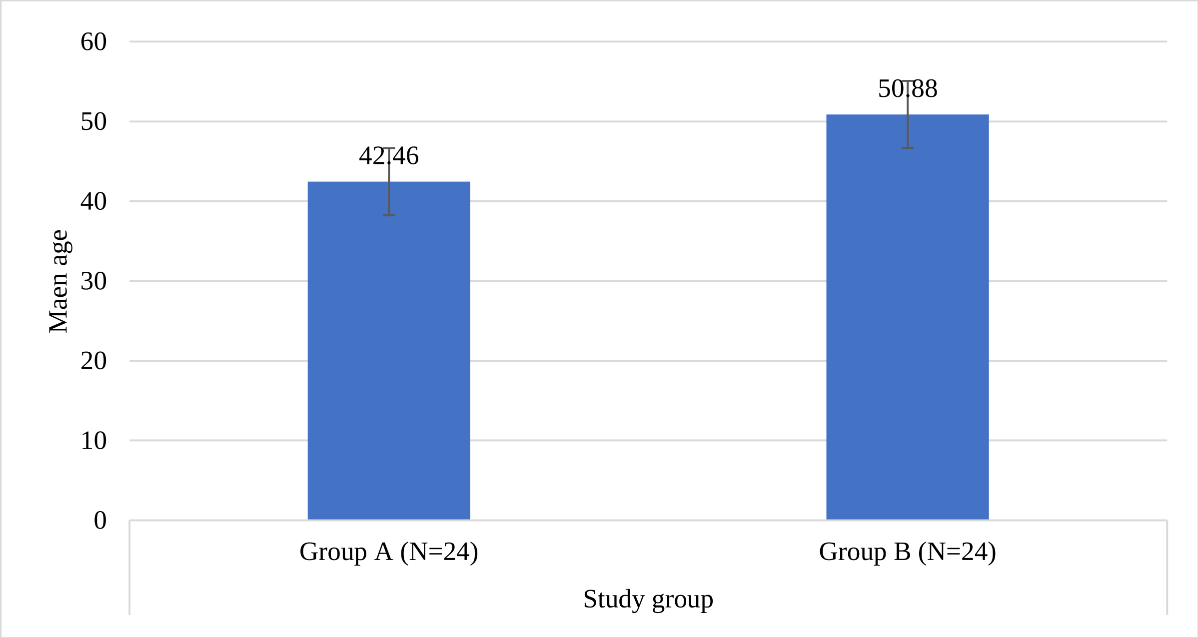

**Table 3: Comparison of Gender with Study group in the study population (N=48)**

| Parameter | Study group | | Chi square value | P value |
|---|---|---|---|---|
| | Group A (N=24) | Group B (N=24) | | |
| Male | 21 (87.50%) | 17 (70.83%) | 2.02 | 0.2865 |
| Female | 3 (12.50%) | 7 (29.17%) | | |

In group A 21 (87.5%) were male, and remaining 3 (12.50%) were female. In group B 17 (70.83%) were male, and remaining 7 (29.17%) were women. The difference in the gender between two groups was not significant (P value .2865). (Table 3 & figure 17)

**Figure 17: Grouped Bar Chart of comparison of Gender with Study group in the study population (N=48)**

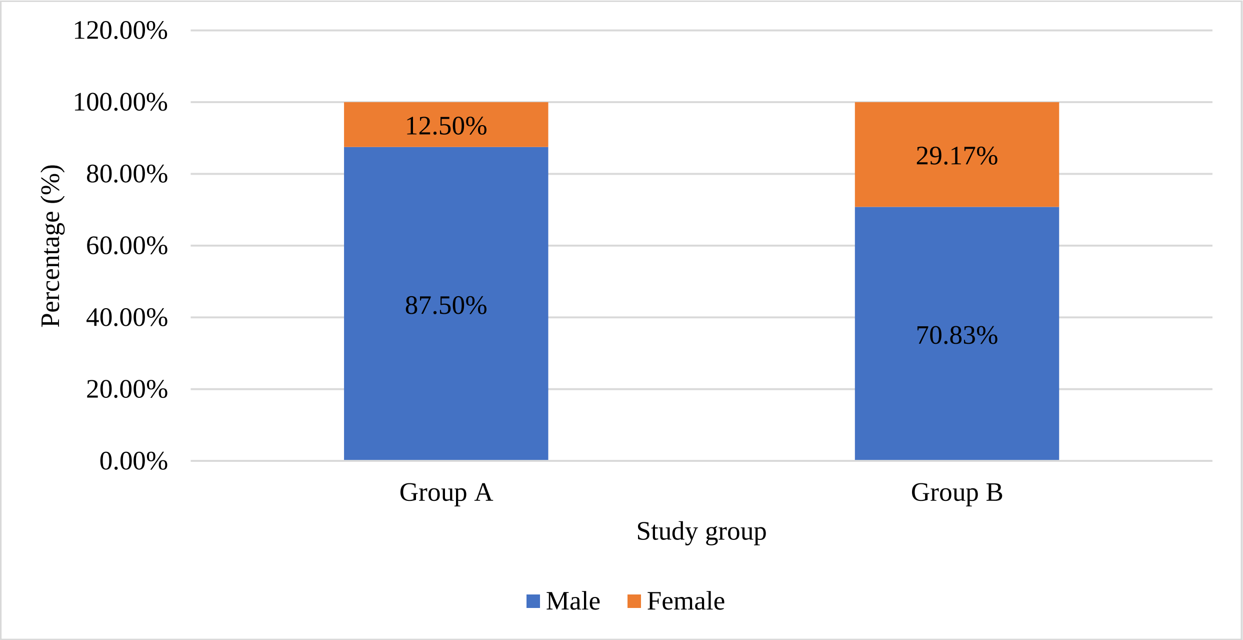

**Table 4: Comparison of mean of VAS scores at different time periods between the Study group (N=48)**

| Parameter | Study group | | P value |
|---|---|---|---|
| | Group A (N=24) Mean ± SD | Group B (N=24) Mean ± SD | |
| VAS score immediate post op | 2.42 ± 0.83 | 4.42 ± 1.38 | <0.001 |
| VAS score after 1 hour | 2.92 ± 0.58 | 3.33 ± 1.17 | 0.1246 |
| VAS score after 4 hours | 3.38 ± 0.92 | 3.13 ± 0.90 | 0.3472 |
| VAS score after 8 hours | 3.08 ± 0.93 | 4.79 ± 1.28 | <0.001 |
| VAS score after 12 hours | 3.17 ± 0.96 | 4.42 ± 1.59 | 0.0019 |
| VAS score after 24 hours | 3.67 ± 0.76 | 5.08 ± 0.83 | <0.001 |

The mean VAS score immediate post op of group A was 2.42 ± 0.83 and group B was 4.42 ± 1.38, the difference in the group A VAS score immediate post op and group B was statistically significant (P Value <0.001). The mean VAS score after one hour of group A was 2.92 ± 0.58 and group B was 3.33 ± 1.17, the difference in the group A VAS score after one hour and group B was statistically not significant (P Value 0.1246). The mean VAS score after 4hr of group A was 3.38 ± 0.92 and group B was 3.13 ± 0.90, the difference in the group A VAS score after 4hr and group B was statistically not significant (P Value 0.3472). The mean VAS score after 8hr of group A was 3.08 ± 0.93 and group B was 4.79 ± 1.28, the difference in the group A VAS score after 8hr and group B was statistically significant (P Value <0.001). The mean VAS score after 12hr of group A was 3.17 ± 0.96 and group B was 4.42 ± 1.59, the difference in the group A VAS score after 12hr and group B was statistically significant (P Value 0.0019).

The mean VAS score after 24hr of group A was 3.67 ± 0.76 and group B was 5.08 ± 0.83, the difference in the group A VAS score after 24hr and group B was statistically significant (P Value <0.001). (Table 4 & Figure 18)

**Figure 18: Line graph of mean of VAS scores at different time periods between the Study group (N=48)**

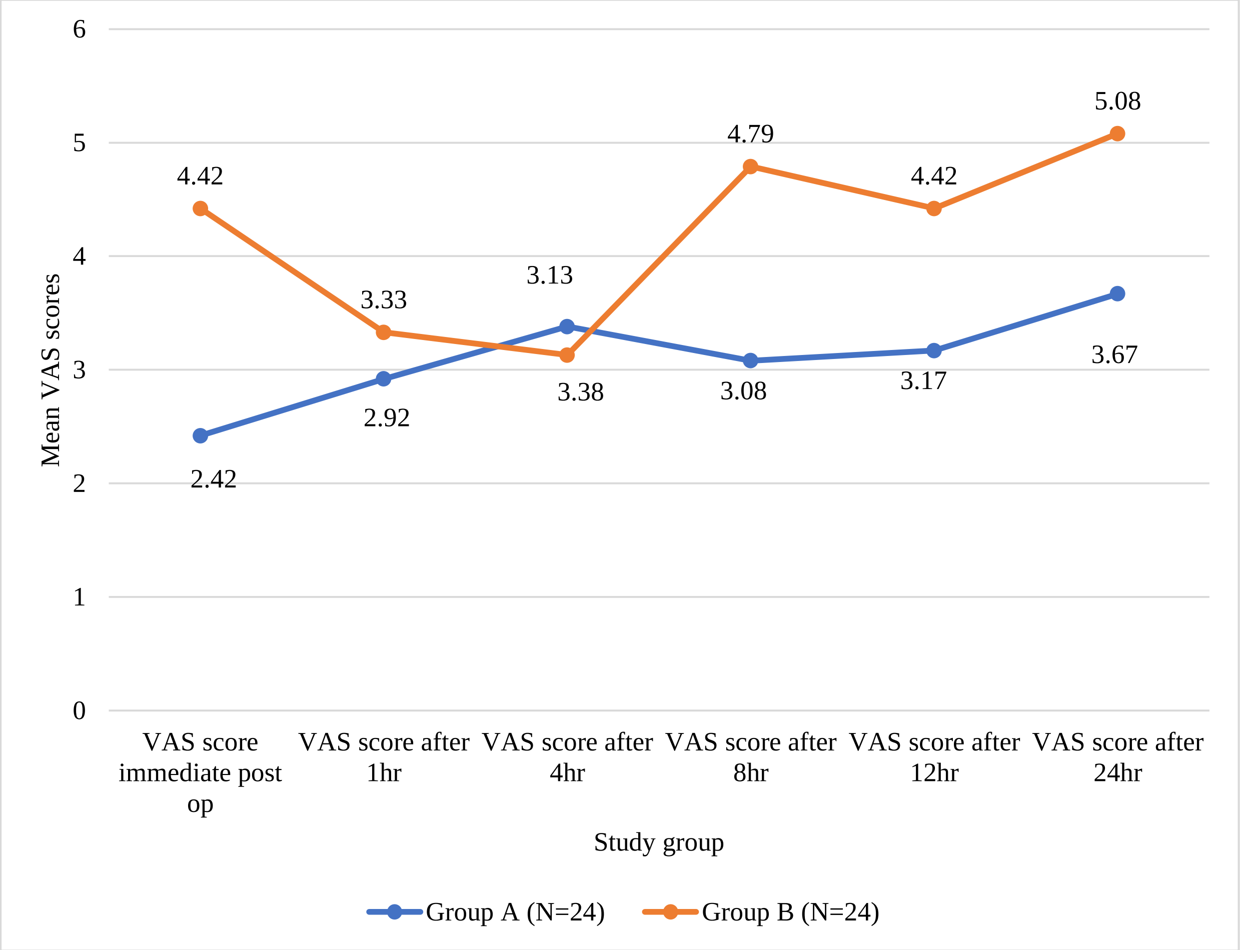

**Table 5: Comparison of Epidural bolus immediate postoperatively 0 hr (corresponds to 2 hours after giving spinal anaesthesia) with Study group in the study population (N=48)**

| Epidural bolus requirement immediate postoperative | Study group | | Chi square value | P value |
|---|---|---|---|---|
| | Group A (N=24) | Group B (N=24) | | |
| Given | 1 (4.17%) | 17 (70.83%) | 22.76 | <0.001 |
| Not given | 23 (95.83%) | 7 (29.17%) | | |

The difference in epidural bolus immediate post op between study groups was found to be significant with a P value of <0.001, with majority of 17 (70.83%) participants were taken epidural bolus immediate postoperatively in group B where as it was only 1(4.17%) in group A. (Table 5 & Figure 19). Immediate post op (0 hr) corresponds to 2 hours after giving spinal anesthesia.

**Figure 19: Grouped Bar Chart of Epidural bolus immediate postoperatively 0 hr (corresponds to 2 hours after giving spinal anaesthesia) with Study group in the study population (N=48)**

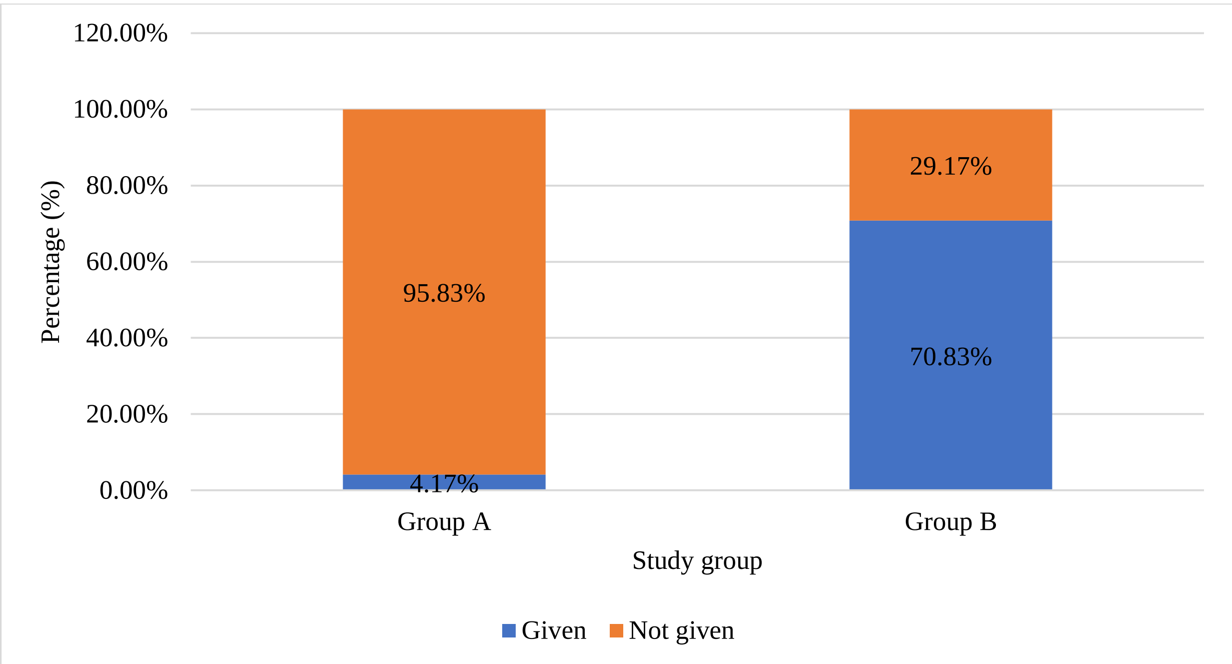

**Table 6: Comparison of Epidural bolus after 1hr with Study group in the study population (N=48)**

| Epidural bolus after 1 hour | Study group | | Chi square value | P value |
|---|---|---|---|---|
| | Group A (N=24) | Group B (N=24) | | |
| Given | 2 (8.33%) | 5 (20.83%) | 1.51 | 0.4158 |
| Not given | 22 (91.67%) | 19 (79.17%) | | |

The difference in epidural bolus after one hr between study groups was found to be not significant with a P value of 0.4158, with majority of 5 (20.83%) participants were taken epidural bolus after one hr in group B where as it was only 2 (8.33%) in group A. (Table 6 & Figure 20)

**Figure 20: Grouped Bar Chart of Epidural bolus after one hr with Study group in the study population (N=48)**

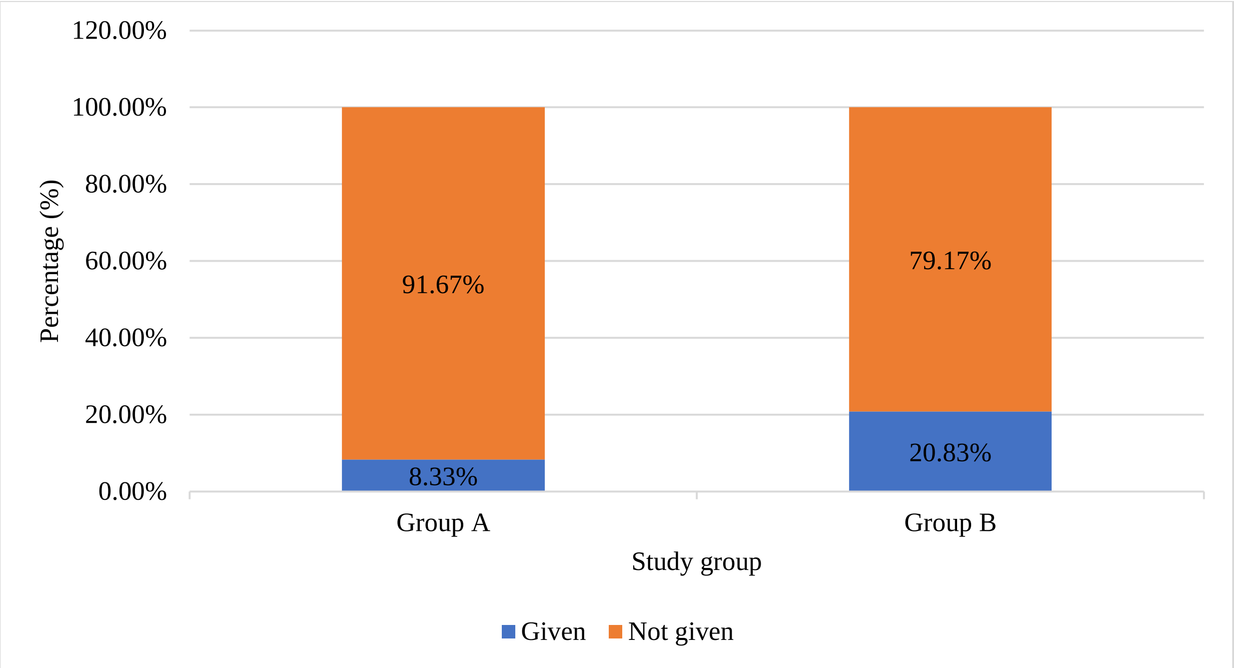

**Table 7: Comparison of Epidural bolus after 4 hours with Study group in the study population (N=48)**

| Epidural bolus after 4 hours | Study group | | Chi square value | P value |
|---|---|---|---|---|
| | Group A (N=24) | Group B (N=24) | | |
| Given | 14 (58.33%) | 2 (8.33%) | 13.50 | <0.001 |
| Not given | 10 (41.67%) | 22 (91.67%) | | |

The difference in epidural bolus after 4hr between study groups was found to be significant with a P value of <0.001, with majority of 14 (58.33%) participants were taken epidural bolus after 4hr in group A whereas it was only 2 (8.33%) in group B. (Table 7 & Figure 21)

**Figure 21: Grouped Bar Chart of Epidural bolus after 4hr with Study group in the study population (N=48)**

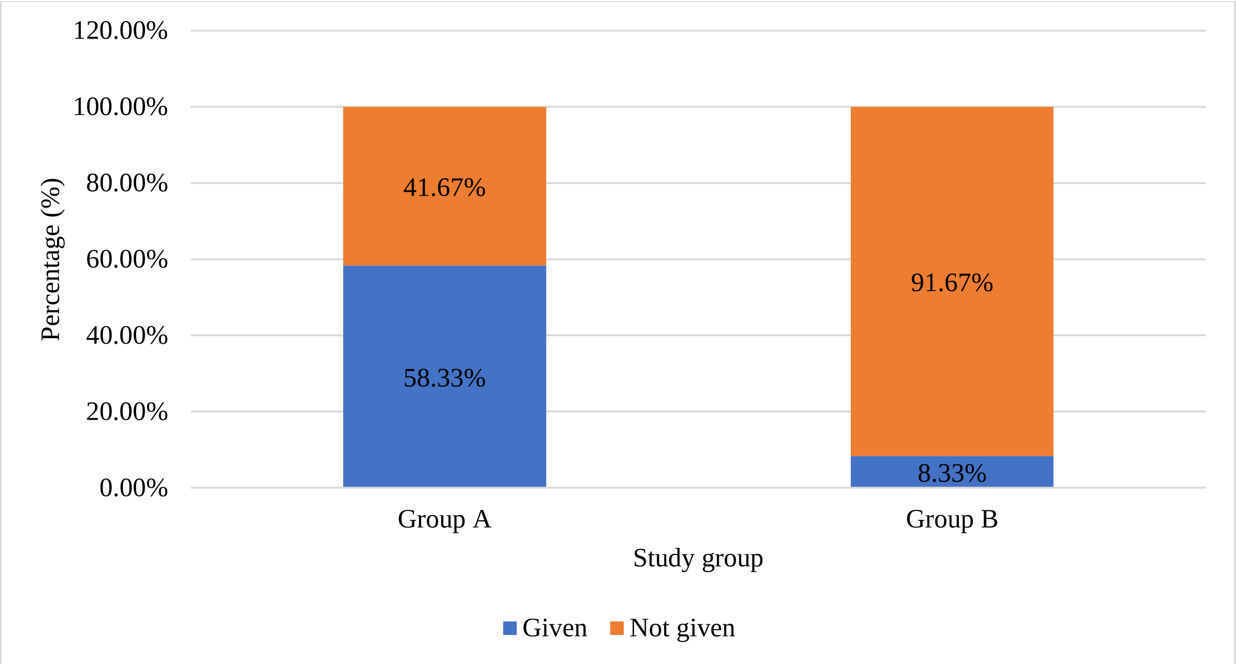

**Table 8: Comparison of Epidural bolus after 8 hours with Study group in the study population (N=48)**

| Epidural bolus after 8 hours | Study group | | Chi square value | P value |
|---|---|---|---|---|
| | Group A (N=24) | Group B (N=24) | | |
| Given | 7 (29.17%) | 18 (75.00%) | 10.10 | 0.0015 |
| Not given | 17 (70.83%) | 6 (25.00%) | | |

The difference in epidural bolus after 8hr between study groups was found to be significant with a P value of 0.0015, with majority of 18 (75.00%) participants were taken epidural bolus after 8 hours in group B where as it was only 7 (29.17%) in group A. (Table 8 & Figure 22)

**Figure 22: Grouped Bar Chart of Epidural bolus after 8hr with Study group in the study population (N=48)**

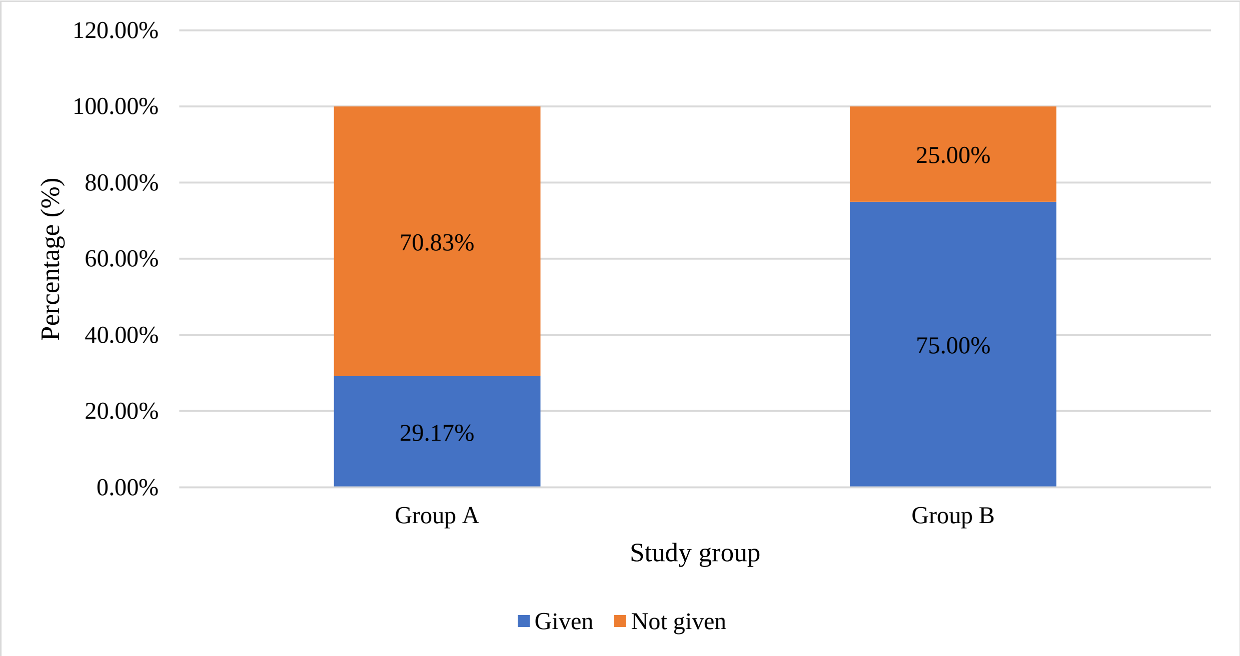

**Table 9: Comparison of Epidural bolus after 12 hours with Study group in the study population (N=48)**

| Epidural bolus after 12hr | Study group | | Chi square value | P value |
|---|---|---|---|---|
| | Group A (N=24) | Group B (N=24) | | |
| Given | 5 (20.83%) | 15 (62.50%) | 8.57 | 0.0034 |
| Not given | 19 (79.17%) | 9 (37.50%) | | |

The difference in epidural bolus after 12 hours between study groups was found to be significant with a P value of 0.0034, with majority of 15 (62.50%) participants were taken epidural bolus after 12 hours in group B where as it was only 5 (20.83%) in group A. (Table 9 & Figure 23)

**Figure 23: Grouped Bar Chart of Epidural bolus after 12hr with Study group in the study population (N=48)**

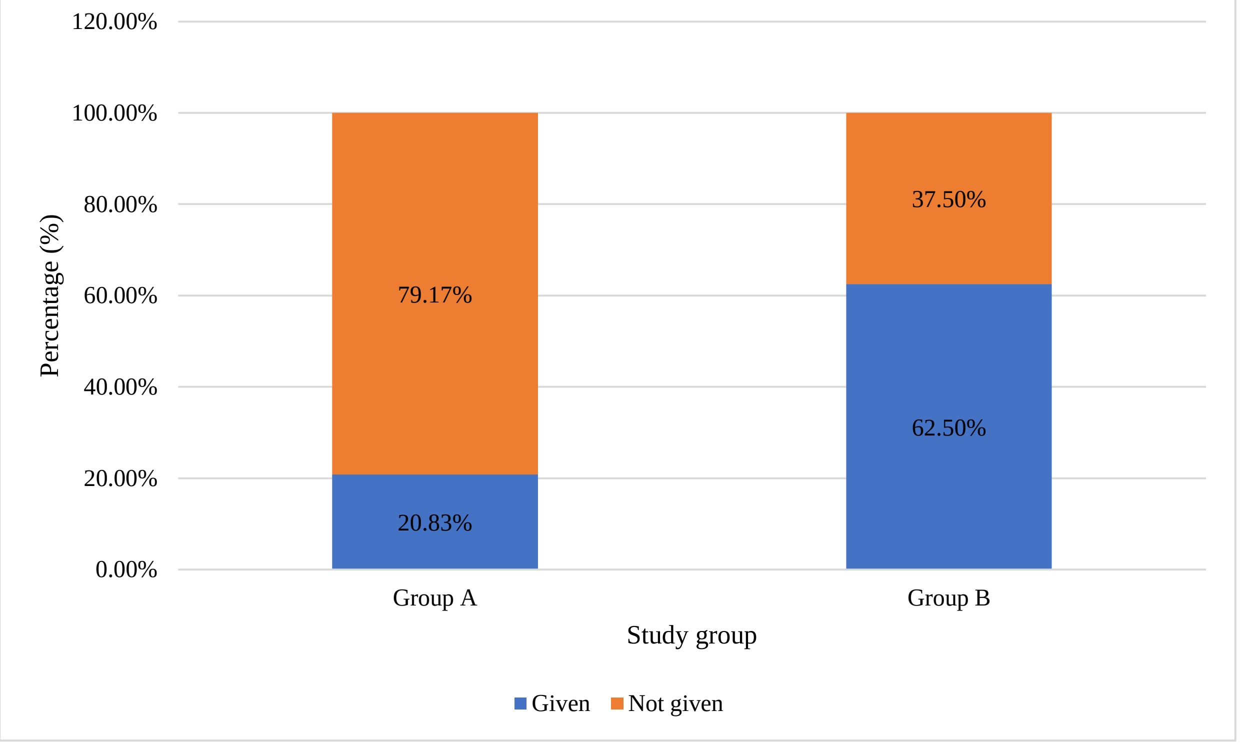

**Table 10: Comparison of Epidural bolus after 24 hours with Study group in the study population (N=48)**

| Epidural bolus after 24 hours | Study group | | Chi square value | P value |
|---|---|---|---|---|
| | Group A (N=24) | Group B (N=24) | | |
| Given | 14 (58.33%) | 23 (95.83%) | 9.55 | 0.0020 |
| Not given | 10 (41.67%) | 1 (4.17%) | | |

The difference in epidural bolus after 24hr between study groups was found to be significant with a P value of 0.0020, with majority of 23 (95.83%) participants were taken epidural bolus after 24 hours in group B where as it was only 14 (58.33%) in group A. (Table 10 & Figure 24,25)

**Figure 24: Grouped Bar Chart of Epidural bolus after 24 hours with Study group in the study population (N=48)**

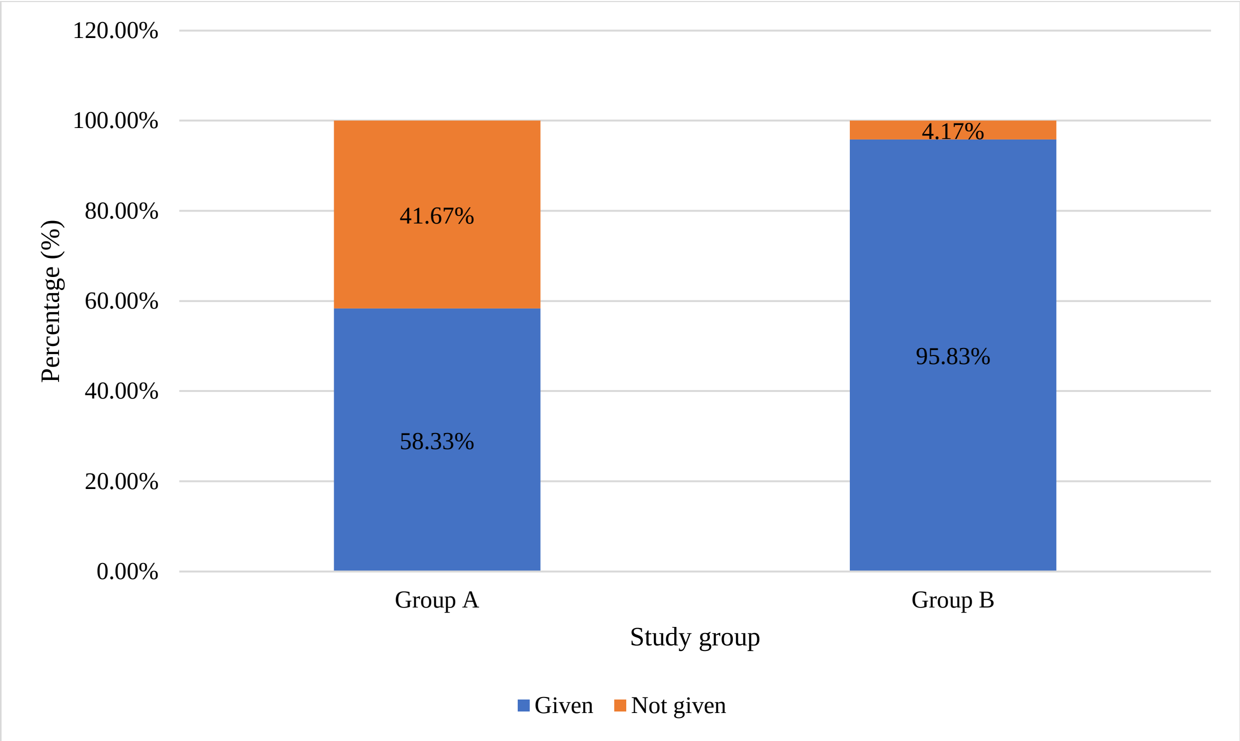

**Figure 25: Grouped Bar Chart of Epidural bolus requirement with Study group in the study population (N=48)**

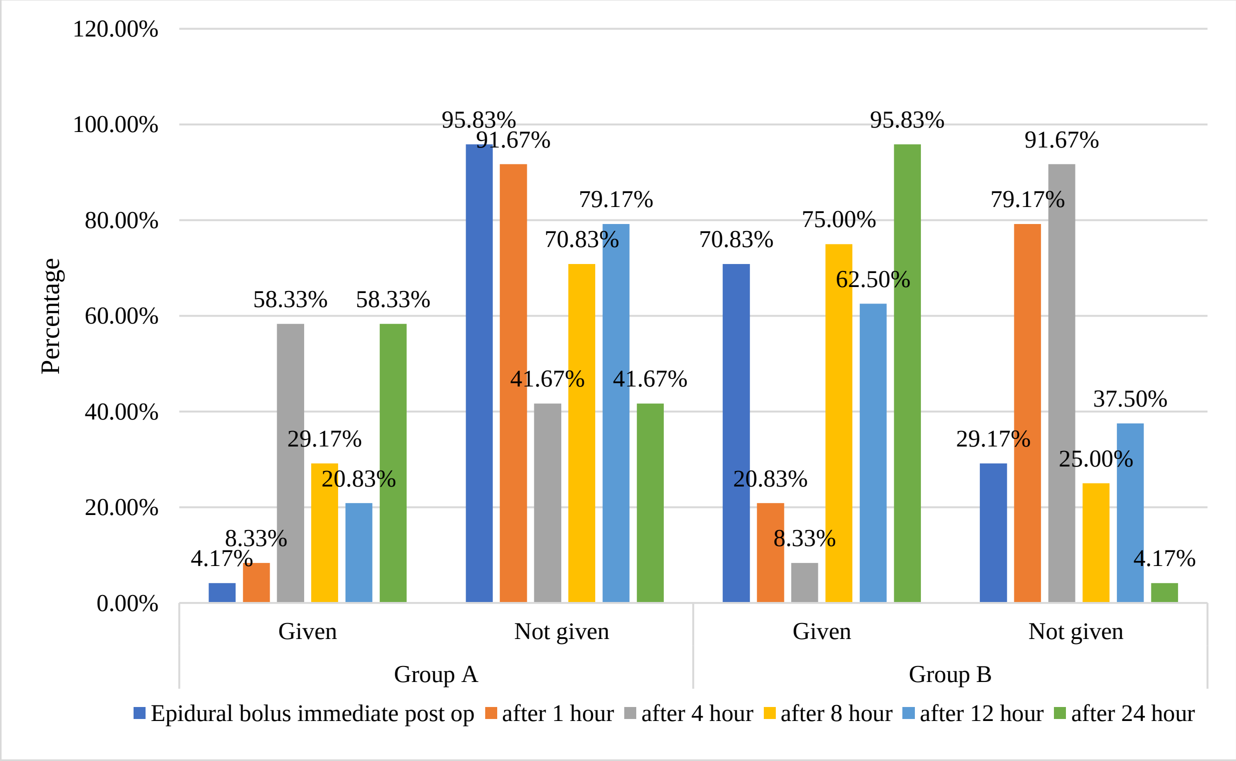

**Table 11: Comparison of Total number of epidural boluses with Study group in the study population (N=48)**

| Parameter | Study group | | Independent sample t-test P value |
|---|---|---|---|
| | Group A (N=24) Mean ± SD | Group B (N=24) Mean ± SD | |
| **Total number of epidural boluses** | 1.79 ± 0.41 | 3.33 ± 0.48 | <0.001 |

The mean total number of epidural boluses of group A was 1.79 ± 0.41 and group B was 3.33 ± 0.48, the difference in the group A total number of epidural boluses and group B was substantially significant (P Value <0.001). (Table 11 & Figure 26)

**Figure 26: Bar chart of Total number of epidural boluses with Study group in the study population (N=48)**

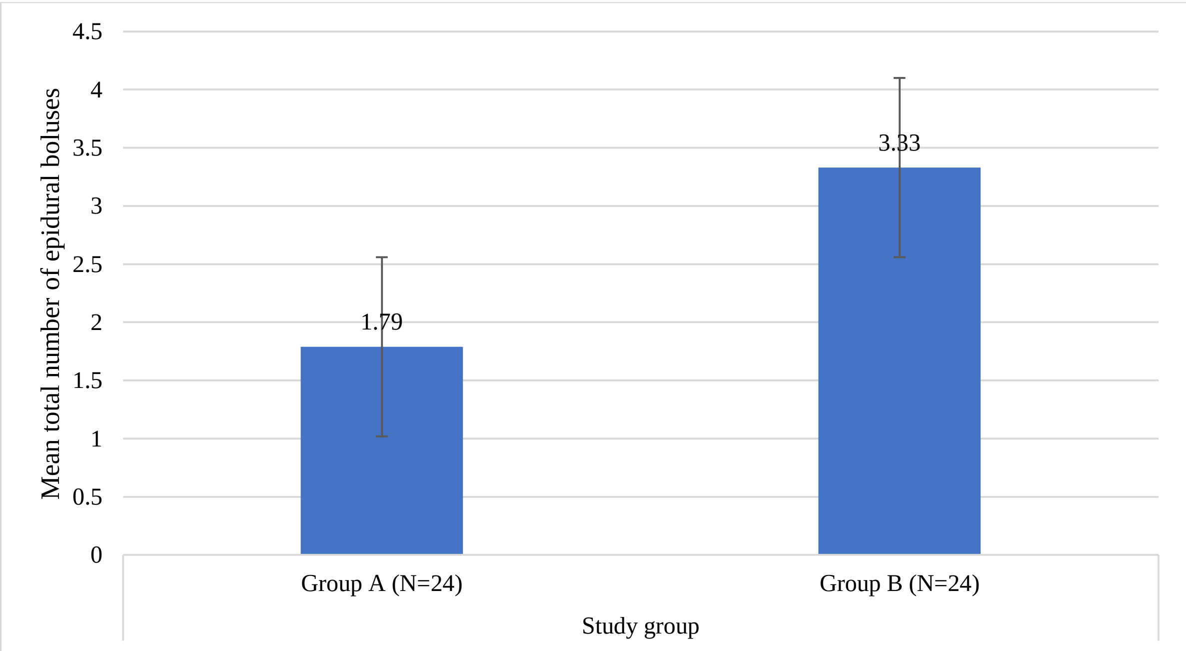

**Table 12: Comparison of Time at which 1st epidural demand bolus with Study group in the study population (N=48)**

| Time at which 1st epidural demand bolus | Study group | | Chi square value | P value |
|---|---|---|---|---|
| | Group A (N=24) | Group B (N=24) | | |
| Immediate post op | 1 (4.17%) | 17 (70.83%) | | |
| 1st hour | 2 (8.33%) | 5 (20.83%) | 31.27 | <0.001 |
| 4th hours | 14 (58.33%) | 1 (4.17%) | | |
| 8th hours | 7 (29.17%) | 1 (4.17%) | | |

The difference in time at which 1st epidural demand bolus between two study groups was found to be significant with a P value of <0.001, with majority of 17 (70.83%) participants were demanded bolus at immediate post op. (Table 12 & Figure 27)

**Figure 27: Grouped Bar Chart of Time at which 1st epidural demand bolus with Study group in the study population (N=48)**

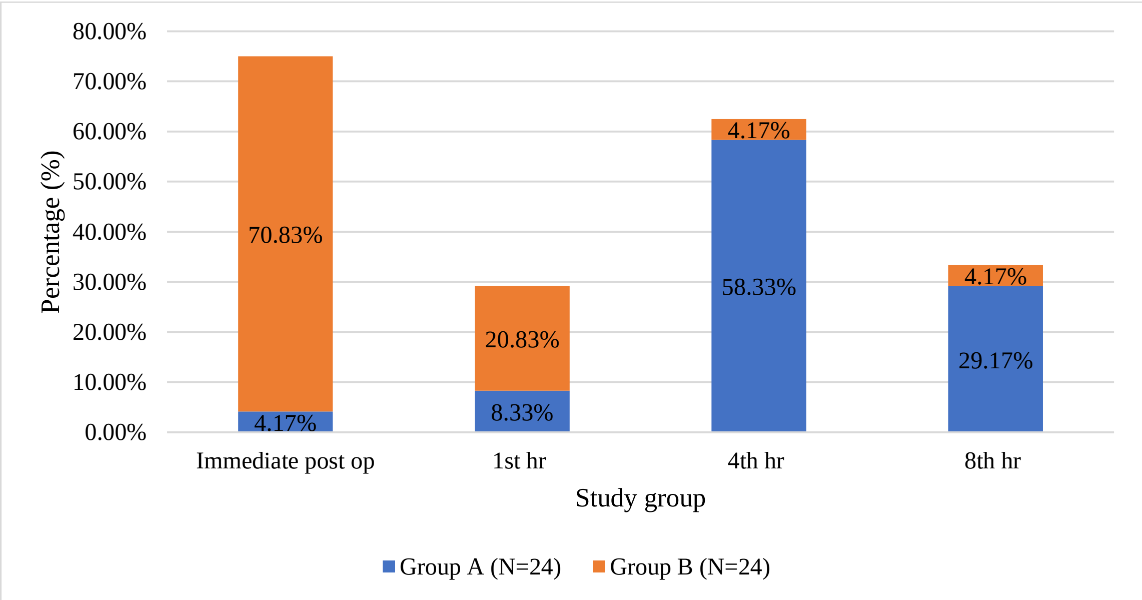

**Table 13: Comparison of Requirement of diclofenac and tramadol with Study group in the study population (N=48)**

| Requirement of diclofenac and tramadol | Study group | |
|---|---|---|
| | Group A (N=24) | Group B (N=24) |
| Diclofenac 75MG | 0 (0.00%) | 2 (8.33%) |
| Not required | 24 (100%) | 22 (91.66%) |

***Note: No statistical test is applied because cell value is zero.***

In group A, all 24 (100%) were reported no requirement of diclofenac and tramadol. In group B 2 (8.33%) were requirement of diclofenac 75mg, and remaining 22 (91.66%) were with no requirement of diclofenac and tramadol. (Table 13 & figure 28)

**Figure 28: Grouped Bar Chart of Requirement of diclofenac and tramadol with Study group in the study population (N=48)**

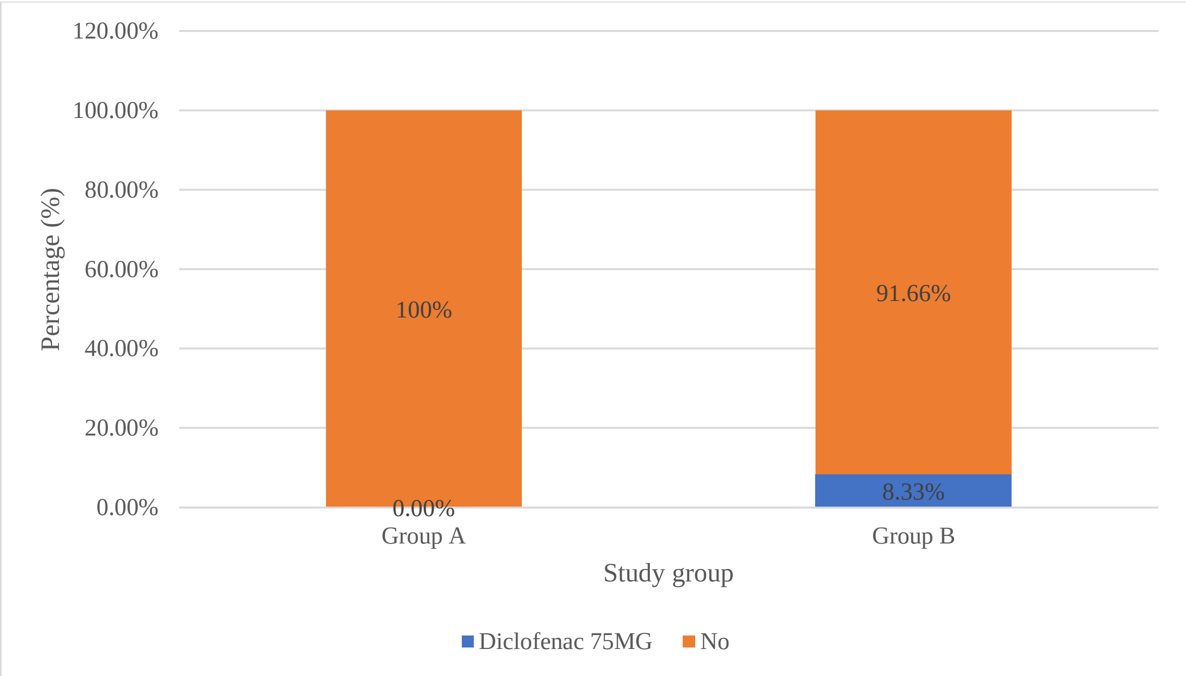

**Table 14: Comparison of Time at which 1st epidural demand bolus given with study group the Study group (N=48)**

| Parameter | Study group | | IST P Value |
|---|---|---|---|
| | Group A (N=24) | Group B (N=24) | |
| | Mean ± SD | Mean ± SD | |
| Time at which 1st epidural demand bolus given (hour) | 4.75 ± 2.40 | 0.71 ± 1.78 | <0.001 |
| Time at which 1st epidural demand bolus given (min) | 285.00 ± 144.01 | 42.50 ± 106.86 | <0.001 |

The mean time at which 1st epidural demand bolus given(hr) in group A was 4.75 ± 2.40 and in group B it was 0.71 ± 1.78, the difference in the group A time at which 1st epidural demand bolus given and group B was statistically significant (P Value <0.001). The mean time at which 1st epidural demand bolus given(min) in group A was 285.00 ± 144.01 and in group B it was 42.50 ± 106.86, the difference in the group A time at which 1st epidural demand bolus given and group B was statistically significant (P Value <0.001). (Table 14 & figure 29)

**Figure 29: Bar chart of Time at which 1st epidural demand bolus given with Study group in the study population (N=48)**

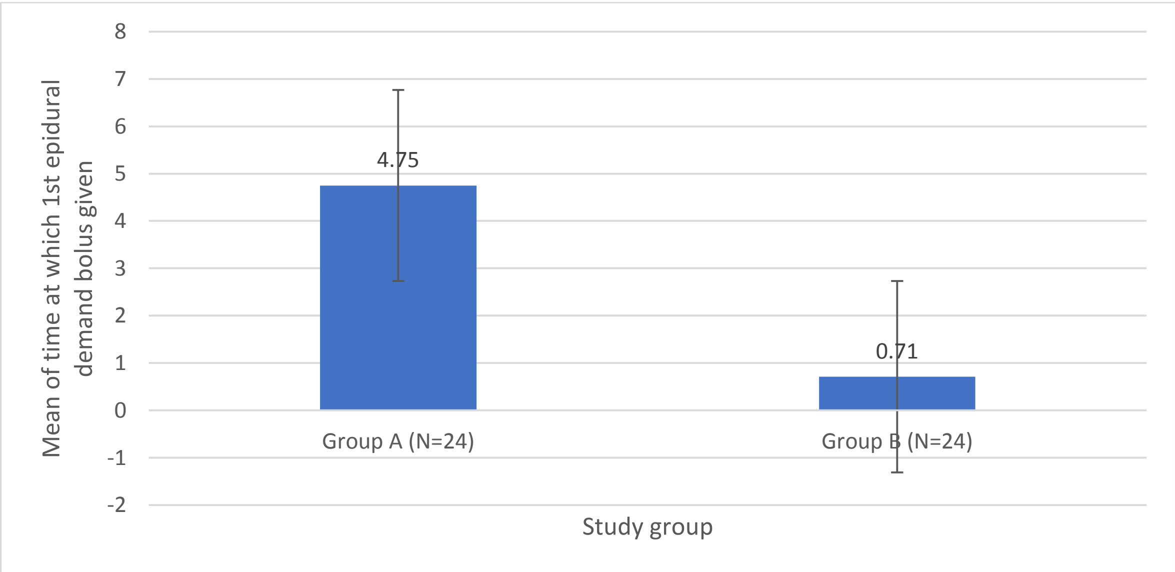

**Table 15: Comparison of Patient satisfaction with anaesthesia care in general between study group (N=48)**

| Patient satisfaction with anaesthesia care in general | Study Group | | Chi square | P value |
|---|---|---|---|---|
| | Group A (N=24) | Group B (N=24) | | |
| Very Satisfied | 10 (41.67%) | 4 (16.67%) | 9.143 | 0.027 |
| Satisfied | 10 (41.67%) | 6 (25%) | | |
| Dissatisfied | 3 (12.5%) | 11 (45.83%) | | |
| Very Dissatisfied | 1 (4.17%) | 3 (12.5%) | | |

The difference in patient satisfaction with anaesthesia care in general between two study groups was found to be significant with a P value of 0.027. Group A people were very satisfied comparing with group B (Table 15 & Figure 30)

**Figure 30: Cluster bar chart of comparison of patient satisfaction with anaesthesia care in general between study group (N=48)**

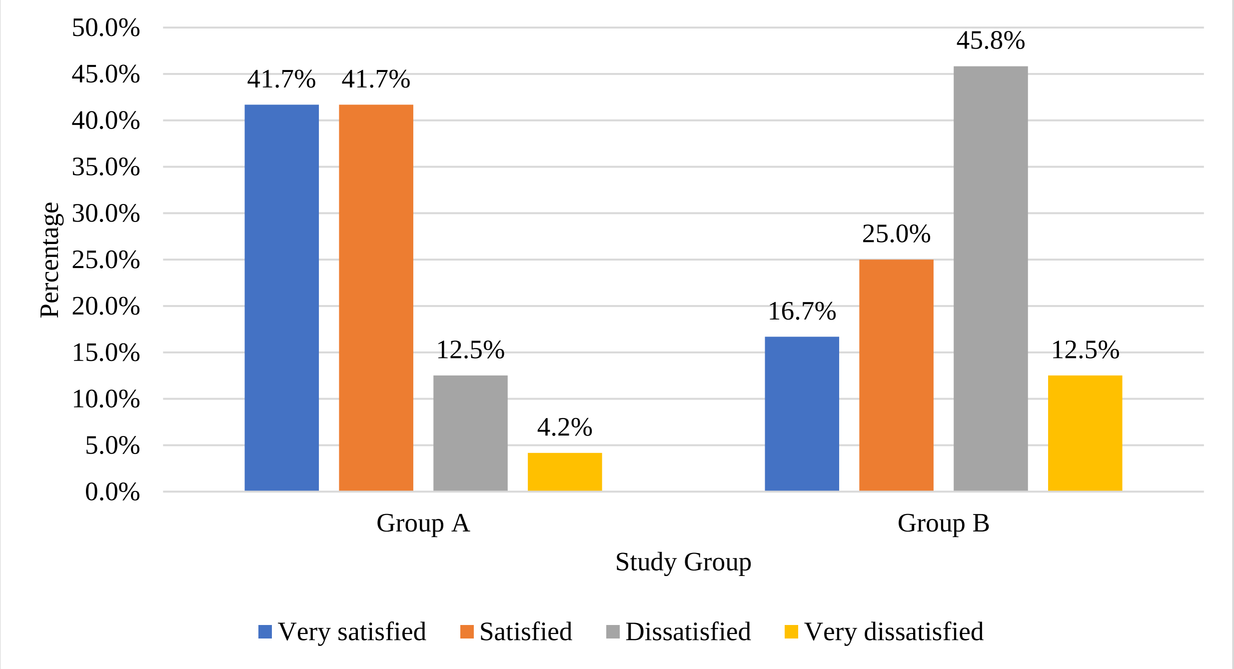

**Table 16: Descriptive analysis of Diagnosis in the study population (N=48)**

| Diagnosis | Frequency | Percentage |
|---|---|---|
| Left/right shaft of femur fracture | 27 | 56.25% |
| distal 1-3rd tibia fracture with ipsilateral fibula fracture | 5 | 10.42% |
| femoral fracture with closed IT fracture of femur | 2 | 4.17% |
| open type 3b displaced fracture of femur with displaced proximal 1-3rd tibia fracture | 1 | 2.08% |
| closed comminuted fracture of IT femur | 8 | 16.67% |
| closed displaced comminuted distal femur fracture | 4 | 8.33% |
| closed distal third spiral fracture of tibia | 1 | 2.08% |

Among the study population the majority of 27 (56.25%) people had Left/right shaft of femur fracture, 5 (10.42%) people had distal 1-3rd tibia fracture with ipsilateral fibula fracture, 8 (16.67%) people had closed comminuted fracture of IT femur, 4 (8.33%) people had closed displaced comminuted distal femur fracture and 2 (4.17%) people had femoral fracture with closed IT fracture of femur and remaining 1 (2.08%) people had open type 3b displaced fracture of femur with displaced proximal 1-3rd tibia fracture, closed distal third spiral fracture of tibia. (Table 16)

**Table 17: Descriptive analysis of Surgery in the study population (N=48)**

| Surgery | Frequency | Percentage |
|---|---|---|
| CRIF with IMIL nailing for femur fracture | 27 | 56.25% |
| CRIF with IMIL nailing of tibia with semitubular plating for fibula | 5 | 10.42% |
| CRIF with IMIL nailing for femur fracture with long PFN nailing | 2 | 4.17% |
| femur locking nail with tibia LCP nippo plating | 1 | 2.08% |
| CRIF with PFN nailing for femur | 8 | 16.67% |
| ORIF with LCP fixation of distal femur | 4 | 8.33% |
| CRIF with lcp plating for tibia | 1 | 2.08% |

Among the study population the majority of 27 (56.25%) people had CRIF with IMIL nailing for femur fracture surgery, 5 (10.42%) people had CRIF with IMIL nailing of tibia with semitubular plating for fibula surgery, 8 (16.67%) people had CRIF with PFN nailing for femur surgery, 4 (8.33%) people had ORIF with LCP fixation of distal femur surgery and 2 (4.17%) people had CRIF with IMIL nailing for femur fracture with long PFN nailing and remaining 1 (2.08%) people had femur locking nail with tibia LCP nippo plating, CRIF with lcp plating for tibia. (Table 17)

# DISCUSSION

# DISCUSSION

In contrast to mono-modal treatment, MMA uses a range of analgesic mediators and techniques under the supervision of pharmacological medications from different classes, resulting in higher pain relief with a lower medication dosage and fewer side effects. The typical MMA protocol starts during the preoperative phase continue during the operating phase, and, ideally, continues with the localized analgesic approach in the healing phase. Many of the recently established MMA regimens include pre-emptive analgesics. MMA employs a range of analgesic techniques and agents, as well as the administration of pharmacological medications from several classes, in contrast to mono-modal treatment. This leads to higher pain relief with a lower pharmaceutical dosage and fewer side effects. The usual MMA protocol begins in the preoperative phase, continues in the operating phase, and, ideally, continues with the localized analgesic approach in the healing phase. Pre-emptive analgesics are a common component of the recently adopted MMA regimens.[105]

This double-blinded randomized control experiment was conducted from January 2021 to May 2022. Based on computer-generated randomization, 48 participants between the age of 18 to 65 who were ASA grade I or II of either sex who had lower limb procedures under spinal and epidural anesthesia were divided into 2 groups as follows.

Group A: Pre-emptive MMA group received IV paracetamol 1 gm, IV diclofenac 75mg diluted in 100 ml NS, IV tramadol 50mg diluted in 100 ml NS and tab pregabalin 75mg orally, 30 mins before surgery. Group B: Placebo group received 3 pints of 100 ml NS intravenously and tab ranitidine 150 mg, 30 mins before surgery.

The current study assessed and compared the VAS, mean duration, number of epidural bolus requirements, and subject satisfaction among the groups.

**Demographic data**

This study involved 48 subjects with 24 participants each in group A and group B. There was no substantial difference in the age and proportion in gender among the two groups was insignificant (group A was 42.46 ± 17.24 vs group B was 50.88 ± 19.98yrs, p value 0.1251) (M/F: group A 87.5%/12.5% Vs group B 70.83%/ 29.1%, P value 0.2865).

**Lower orthopedic fractures**

More than 50% of the study population (56.25%) had left/right shaft of femur fracture, followed by 10.42% with distal 1-3rd tibia fracture with ipsilateral fibula fracture, 16.67% had closed comminuted fracture of IT femur, 8.33% had closed displaced comminuted distal femur fracture and 4.17% had femoral fracture with closed IT fracture of the femur and remaining 2.08% people had open type 3b displaced fracture of the femur with displaced proximal 1-3rd tibia fracture, closed distal third spiral fracture of the tibia. Most of the studies have included femur fractures, total knee and hip replacement in assessing MMA in reducing post-operative pain.[17,90]

**Type of surgery**

Among the study population the majority of 56.25% people had CRIF with IMIL nailing for femur fracture surgery, 10.42% people had CRIF with IMIL nailing of the tibia with semi-tubular plating for fibula surgery, 16.67% people had CRIF with PFN nailing for femur surgery, 8.33% people had ORIF with LCP fixation of distal femur surgery and 4.17% people had CRIF with IMIL nailing for femur fracture with long PFN nailing and remaining 2.08% people had femur locking nail with tibia LCP plating. Makkar et al study involved subjects undergoing nailing of the fractured shaft of the femur.[14] Koehler, D et al also studied the pre-emptive analgesics effect among the subject's undergoing surgery for femoral fractures.[97] However, they used ropivacaine, epinephrine, and morphine at the injection site as multimodal analgesia. They found that the combination of multimodal analgesics provided good pain control and lesser narcotics use on the initial post-surgery day.[97] Similarly, we used pre-emptive multimodal analgesics (paracetamol, diclofenac, tramadol, and pregabalin) for fracture of the lower limb were helpful in pain control and increased patient satisfaction towards anesthesia care.

**Visual Analogue Scale**

The mean VAS immediate post-op i.e., 0 hr (2hrs after giving spinal anesthesia) of group A was substantially low compared to group B (group A was 2.42 ± 0.83 VS group B was 4.42 ± 1.38, P Value <0.001). After one hour and 4 hr both the groups showed no significance (P Value 0.1246). However, at 8, 12, and 24 hr the VAS score was substantially low in group A compared to group B (P Value <0.001). Aweke, Z et al observed that the median NRS score was significantly lower in the PT group (paracetamol with tramadol) group at the fourth, sixth, and eighth hours in comparison to the paracetamol group, according to the study's numerical pain scoring.[24] A similar observation was made in the present study where pre-emptive IV paracetamol, tramadol, diclofenac, and oral pregabalin provided reduced requirements of the epidural bolus.

Further, a study by Solmaz and Kovalak[106], discovered suggestively lower VAS at the first and second hours when acetaminophen and tramadol were combined than when acetaminophen alone. Although these studies have used NRS for pain evaluation, they have found decreased pain scores when two or more drugs are added for MMA. Hence, the present study in comparison to Makkar et al[14] studies have evaluated pain through VAS and found decreased pain scores in the MMA group. However, Makkar et al[14] showed none of the individuals needed intravenous morphine after surgery (VAS greater and equal to 6). According to research by, “Passias, B” et al[88] the preventive group had statistically significant decreases in patient-reported pain levels at almost every time point. Acetaminophen, gabapentin, and celecoxib were pre-emptively administered 30–60 minutes before total joint arthroplasty, and the need for postoperative opioids was only slightly reduced. In the current study, we observed a substantial difference in the VAS score between the groups, at different intervals; immediate postoperatively, at 8hr,12hr, and 24hr.

**The demand for epidural bolus**

This study found a significant increase in the demand for epidural bolus immediate postoperatively among group B (70.83%) compared to group A (4.17%) P value of <0.001. At immediate post-op, 8 hr, 12, and 24hrs group A found expressively less need for epidural boluses compared to Group B. Hence it was found that the mean total number of epidural boluses taken in group A was substantially less compared to group B (1.79 ± 0.41 VS 3.33 ± 0.48, P Value <0.001).

The difference in time at which 1st epidural demand bolus between the two study groups was found to be substantial (P <0.001), with the most of 17 (70.83%) subjects being demanded bolus at immediate post-op.

In group A, all 24 (100%) reported no requirement for diclofenac and tramadol. In group B 2 (8.33%) patients had the requirement of diclofenac was 75mg, and the remaining 22 (91.66%) patients did not receive diclofenac and tramadol.

Hynes et al. [107] assessed the effectiveness of IV paracetamol, given as propacetamol, among patients experiencing postoperative pain in comparison to placebo and intramuscular diclofenac. They conducted double-blind, randomized research with 120 patients enduring HA under SA. In terms of total pain relief scores throughout the first five hours, they found that the paracetamol group considerably outperformed the placebo group. At both 5 and 10 hours, more subjects in the placebo group requested salvage analgesia than those in the paracetamol group.[107] Another study by Jebaraj, B et al discovered paracetamol intravenous infusion to be a safe and efficient complement to opioids after orthopedic procedures.[101] In a study by Makkar et al[14] prior to surgery, IV doses of diclofenac 75mg diluted in 10 ml, acetaminophen 1 gm, morphine 3 mg, and pregabalin 75 mg were given. The placebo group got 100 ml of intravenous saline for blinding, two boluses of 2 ml of typical saline, one bolus of 10 ml of typical saline, and a dummy pill before surgery. A preventative multimodal analgesic regimen reduces the frequency of epidural demand boluses postoperatively in the first 48 hrs in trauma subjects receiving nailing of the fractured femur's shaft. The median number of times rescue analgesics were administered is lower in the group receiving preventative analgesics. We also found a reduced need for an epidural bolus in the pre-emptive group.

Passias, B et al[88] studies in the pre-emptive employed the administration of celecoxib, acetaminophen, and gabapentin 30–60 minutes before TJA led to moderate decreases in the need for opioids post-operatively. In the current study, we observed no requirement for diclofenac and tramadol in the pre-emptive group postoperatively.

According to studies by “Paech et al.[108] Jokela et al.[109] and Mathiesen et al”.[110], the pregabalin-using group's postoperative pain intensity was comparable to that of the control group. One element that has been found in multiple trials of this medicine is decreased post-operative opioid as well as painkiller use in pregabalin group. Pregabalin, according to the author, considerably reduced the rate of postoperative opioid intake in subjects in the Zhang et al.[111] studies. Additionally, Zhang et al.[111] demonstrated how taking pregabalin can lessen some opioid adverse effects like nausea and queasiness. According to Durkin et al study, 's individuals with persistent neuropathic pain who take pregabalin use fewer opioids.[112] similarly in Kheirabadi, D et al[92] studies used pre-emptive 75mg pregabalin for lower extremity orthopedic surgeries found to decrease postoperative pain, especially within the first 24hrs of surgery, and additionally reduced opioid consumption. In addition, Omara, A et al[95] discovered that oral pregabalin significantly sped up the time it took for the sensory block to two-segment regress and enhanced sleep quality during the night following surgery. Preoperative oral pregabalin improved sleep the first night following surgery and postponed the need for postoperative analgesics. Similarly, we also used pregabalin in our study and found acceptable results. Hence in the present study, we found pregabalin one of the pre-emptive analgesics to be effective in pain control postoperatively. Although different studies have used different combinations of drugs as pre-emptive analgesics, they all reduced the additional requirement of epidural boluses and the need for analgesics in lesser time. [88,102]

**The mean time of bolus epidural demand**

The mean time at which 1st epidural demand bolus was given(hr) in group A was 4.75 ± 2.40 and in group B it was 0.71 ± 1.78, the difference in the group A time at which 1st epidural demand bolus was given and group B was noteworthy (P Value <0.001).

The mean time at which 1st epidural demand bolus was given at 285.00 ± 144.0(min) in group A and in group B it was 42.50 ± 106.86(min), the difference in the group A time at which 1st epidural demand bolus was given and group B was substantial (P Value <0.001). Aweke, Z e al[24] discovered that the paracetamol group had a lower mean time to first analgesic request (88± 21 min) than the PD group (103± 23) min, p = 0.001) and the PT group (144.05± 14.72 min, p 0.001). Sebastian, B et al.[25] and Entezariasl, M et al[102] found that the pre-emptive group (pregabalin 150 mg) required significantly more time for rescue analgesia (VAS score >3) than the control group.

**Patient Satisfaction**

With a P value of .027, it was determined that there was a significant difference between the two research groups' patient satisfaction with anaesthetic care overall. Group A people were very satisfied compared with group B. Similarly a study by Kheirabadi, D et al[92] and Sebastian, B et al.[25] found increased patient satisfaction scores in the pre-emptive group.

According to a study done in “Connecticut,” multimodal analgesics only have lesser adverse effects like nausea, sedation, pruritis, queasiness, and constipation in addition to providing better pain relief. Studies have shown that combining multimodal analgesia with a rehabilitation program can result in a quicker recovery, a shorter stay in the hospital, and a shorter convalescence period.[15] Similarly in the present study, the preemptive multimodal analgesics were found to have the least side effects they expressed more satisfaction towards anesthesia care in general.

# LIMITATION

## LIMITATIONS

1. The current study has some drawbacks, including the involvement of different anesthetists and surgeons and the inability to control confounding factors like incision size.
2. Intraoperative hemodynamics were not compared between the two groups.
3. Patient-controlled analgesia pumps could have been used instead of giving a direct epidural bolus.
4. Did not record any analgesia was given priorly before shifting to operation theatre.

# CONCLUSION

# CONCLUSIONS

In patients undergoing lower extremity orthopaedic surgeries, an analgesic drug combination of IV paracetamol 1g, IV diclofenac 75mg, IV tramadol 50mg, and tab pregabalin 75mg orally, 30 minutes prior to surgery decreased the need for epidural boluses and increased the time required to receive 1st analgesic compared to placebo group. The preemptive analgesic appeared to be more effective since the patients were satisfied.

# SUMMARY

# SUMMARY

This double-blinded randomized control experiment was conducted in Sri Devaraj Urs Medical College, Tamaka, Kolar, from January 2021 to May 2022. Based on computer-generated randomization, 48 participants between the ages of 18 and 65 who were underwent lower limb procedures under spinal with epidural anesthesia and met the inclusion criteria were divided into two groups.

Group A: Preemptive multimodal group received IV paracetamol 1 g, IV diclofenac 75mg diluted in 100 ml NS, IV tramadol 50mg diluted in 100 ml NS, and tab pregabalin 75mg orally, 30 mins before surgery.

Group B: the placebo group received 3 pints of 100 ml NS intravenously and tab ranitidine 150 mg, 30 mins before surgery.

The current study assessed and compared the VAS score, mean duration, number of epidural bolus requirements, and patient satisfaction among the groups.

This study involved 48 subjects with 24 participants each in group. No significant difference was found in age and proportion in gender among the 2 groups was insignificant. More than half of the study population (56.25%) Left/right shaft of femur fracture.

In comparison to group B, group A's mean VAS score was significantly lower immediately post-surgery, P Value <0.001. After 1hr and 4 hr both the groups showed no significance (P Value 0.1246). However, at 8, 12 and 24 hr the VAS score was suggestively low equated to group B (P Value <0.001).

This study found a significant increase in the demand for epidural bolus immediate postoperatively in group B (70.83%) compared to group A (4.17%) P the value of <0.001. At immediate post-op , 8 hr, 12 and 24hrs group A found significantly less need of epidural boluses compared to Group B. Hence it was found that the mean total number of epidural boluses taken in group A was significantly less compared to group B (1.79 ± 0.41 VS 3.33 ± 0.48, P Value <0.001).

With a P value of 0.001, it was determined that there was a substantial difference between the two study groups in the timing of the first epidural demand bolus, with the majority of 17 participants (70.83%) from group B receiving it immediately after surgery. In group A, all 100% reported no requirement for diclofenac and tramadol. In group B, 8.33% required diclofenac 75 mg of, and the remaining 91.66% had no requirement of diclofenac and tramadol. The mean time at which 1st epidural demand bolus was given(min) in group A was statistically significant (P Value <0.001). With a P value of 0.027, it was determined that there was a significant difference between the two study groups' perceptions of patient satisfaction with anaesthesia care overall. Group A people were very satisfied compared with group B.

The study results found the MMA group with a lesser requirement for epidural boluses and the time required to receive 1$^{st}$ epidural bolus was more in the pre-emptive multimodal analgesia group.

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# BIBLIOGRAPHY


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# ANNEXURES

## ANNEXURE - I

## PROFORMA

### EFFECT OF PREEMPTIVE MULTIMODAL ANALGESIA REGIMEN ON POST OPERATIVE EPIDURAL DEMAND BOLUSES IN LOWER LIMB ORTHOPAEDIC SURGERIES

**Investigators:** Dr Mathew George/ Dr Kiran.N

1. Name of the patient: 2. Age/Sex:

3. IP No: 4. ASA grade:

- **General physical examination:**

Pulse rate: respiratory rate: BP: Temperature:

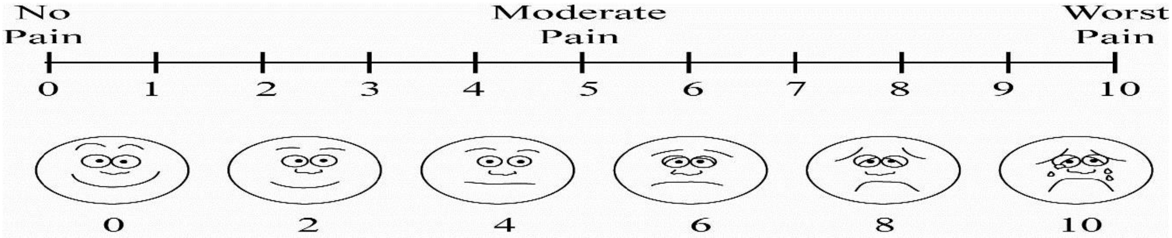
- **Systemic examination:**

**RS - CVS - CNS - P/A –**

- **Diagnosis:**
- **Surgery:**

- **Group A:** Preemptive multimodal group receives intravenous IV paracetamol 1 g, IV diclofenac 75mg diluted in 100ml NS, IV tramadol 50mg diluted in 100ml NS and tab pregabalin 75mg orally, 30 mins before surgery.
- **Group B:** Placebo group receives 3 pints of 100ml NS intravenously and tab rantac150 mg, 30 mins before surgery.

- **VAS - VISUAL ANALOGUE SCALE** (for pain)




Group: _________

| TIME | Visual analogue scale | Epidural boluses |
|---|---|---|
| Immediate post op | | |
| 1hr | | |
| 4hr | | |
| 8hr | | |
| 12hr | | |
| 24hr | | |

Time at which 1st epidural demand bolus is given ……………………

Total number of epidural bolus received ………….

Requirement of diclofenac 75mg and tramadol 50 mg ………………

Patient satisfaction with anesthesia care in general after 24 hrs : ……………………………….

(Very Satisfied, Satisfied, Dissatisfied, Very Dissatisfied)

## ANNEXURE- II

## PATIENT INFORMATION SHEET

**STUDY TITLE: EFFECT OF PREEMPTIVE MULTIMODAL ANALGESIA REGIMEN ON POST OPERATIVE EPIDURAL DEMAND BOLUSES IN LOWER LIMB ORTHOPAEDIC SURGERIES**

**Investigators: Dr Mathew George/ Dr Kiran.N**

**Study location:** R.L.Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar.

**Details -** Patients undergoing lower limb orthopaedic surgeries under combined spinal epidural anaesthesia were selected. This study aims to reduce the number of epidural demand boluses post operatively in preemptive multimodal analgesia group. Patient and the attenders will be completely explained about the procedure being done i.e. giving pre-emptive multimodal analgesia regimen 30 mins preoperatively, regimens include paracetamol 1 g IV, Diclofenac 75 mg IV, Tramadol 50 mg IV, oral pregabalin 75 mg. Placebo group will receive 3 pints of normal saline and tab ranitidine 150 mg,30mins preoperatively. Requirement of post-operative epidural boluses and rescue analgesics will also be explained. Multimodal analgesics will be avoided in the patients associated with head injury, known hypersensitivity to the drug, morbid obesity, renal impairment and psychiatric patients.

Please read the information and discuss with your family members. You can ask any question regarding the study. If you agree to participate in the study, then relevant information and history will be taken. This information collected will be used only for dissertation and publication.

All information collected from you will be kept confidential and will not be disclosed to any outsider. Your identity will not be revealed. There is no compulsion to agree to this study. The care you will get will not change if you don’t wish to participate. There will not be any monetary benefits/incentives for taking part in this study. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

For further information contact
Dr Mathew George
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## ANNEXURE- III

## INFORMED CONSENT FORM

**Name of the institution:** SRI DEVARAJ URS MEDICAL COLLEGE

**Name of the principal investigator:** Dr. Mathew George
**Name of the guide:** Dr. Kiran.N
**Name of the subject/participant:**

STUDY: EFFECT OF PREEMPTIVE MULTIMODAL ANALGESIA REGIMEN ON POST-OPERATIVE EPIDURAL DEMAND BOLUSES IN LOWER LIMB ORTHOPAEDIC SURGERIES.
Date:

I, _______________________________________________ aged ____________, after being explained in my own vernacular language about the purpose of the study and the risks and complications of the procedure, hereby give my valid written informed consent without any force or prejudice for using preemptive multimodal analgesia regimen in lower limb orthopaedic surgeries under combined spinal epidural anaesthesia. The nature and risks involved have been explained to me to my satisfaction. I have been explained in detail about the study being conducted. I have read the patient information sheet and I have had the opportunity to ask any question. Any question that I have asked, have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research. I hereby give consent to provide my history, undergo physical examination, undergo the procedure, undergo investigations and provide its results and documents etc. to the doctor / institute etc. For academic and scientific purpose, the operation / procedure, etc. may be video graphed or photographed. All the data may be published or used for any academic purpose. I will not hold the doctors / institute etc. responsible for any untoward consequences during the procedure / study. I am aware that there won't be any monetary benefits for taking part in this study. A copy of this Informed Consent Form and Patient Information Sheet has been provided to the participant.

_______________ _________________

(Signature & Name of Pt. Attendant) (Signature/Thumb impression & Name of Patient/Guardian)
(Relation with patient)

Witness 1:
Witness 2:

___________________
(Signature & Name of Research person /doctor)

# KEY TO MASTER CHART

| | |
|---|---|
| Sl No | Serial Number |
| UHID | Unique Health Identification Number |
| Group A | Pre-emptive Multimodal Analgesia Group |
| Group B | Placebo Group |
| VAS | Visual Analogue Scale |
| M | Male |
| F | Female |
| Hr | Hour |
| IT | Intertrochanteric |
| CRIF | Closed reduction-internal fixation |
| PFN | Proximal Femoral Nail |
| IMIL | Intramedullary interlocking nail |
| mg | Milligram |
| LCP | Locking Compression Plate |
| op | Operative |

## Coding:

| Variable name | Code |
|---|---|
| Epidural bolus immediate post op | Not given = 0, Given = 1 |
| Epidural bolus after 1hr | Not given = 0, Given = 1 |
| Epidural bolus after 4hr | Not given = 0, Given = 1 |
| Epidural bolus after 8hr | Not given = 0, Given = 1 |
| Epidural bolus after 12hr | Not given = 0, Given = 1 |
| Epidural bolus after 24hr | Not given = 0, Given = 1 |

# MASTER CHART

| SL NO | GROUP | AGE | SEX | UHID | DIAGNOSIS | SURGERY | VAS IMMEDIATE POST OP 0HR | VAS after 1hr | VAS after 4hr | VAS after 8hr | VAS after 12 hr | VAS after 24hr | epidural bolus requirement immediate postoperatively 0hr | epidural bolus requirement at 1hr | epidural bolus requirement at 4hr | epidural bolus requirement at 8hr | epidural bolus requirement at 12hr | epidural bolus requirement at 24hr | total number of epidural boluses given | Time at which 1st epidural bolus given | Requirement of diclofenac and tramadol | Patient satisfaction with anesthesia care in general |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Group A | 40 | F | 943963 | distal 1-3rd right tibia fracture with ipsilateral fibula fracture | CRIF with IMIL nailing of tibia with semi tubular plating for fibula | 2 | 3 | 2 | 4 | 2 | 3 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 8th hr | No | Very Satisfied |
| 2 | Group A | 19 | M | 950263 | Right shaft of femur fracture | CRIF with IMIL nailing for femur fracture | 2 | 3 | 4 | 2 | 3 | 4 | 0 | 0 | 1 | 0 | 0 | 1 | 2 | 4th hr | No | Satisfied |
| 3 | Group A | 30 | M | 883577 | Left shaft of femur fracture | CRIF with IMIL nailing for femur fracture | 2 | 3 | 4 | 2 | 3 | 4 | 0 | 0 | 1 | 0 | 0 | 1 | 2 | 4th hr | No | Very Satisfied |
| 4 | Group A | 62 | F | 941079 | closed displaced comminuted distal femur fracture | ORIF with LCP fixation of distal femur | 1 | 2 | 2 | 4 | 3 | 5 | 0 | 0 | 0 | 1 | 0 | 1 | 2 | 8th hr | No | Very Satisfied |
| 5 | Group A | 47 | M | 951831 | Left shaft of femur fracture | CRIF with IMIL nailing for femur fracture | 1 | 2 | 2 | 5 | 2 | 3 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 8th hr | No | Satisfied |
| 6 | Group A | 31 | M | 953598 | femoral fracture with closed IT fracture of femur | CRIF with IMIL nailing for femur fracture with long PFN nailing | 5 | 1 | 2 | 3 | 3 | 4 | 1 | 0 | 0 | 0 | 0 | 1 | 2 | Immediate post op | No | Very Satisfied |
| 7 | Group A | 40 | M | 902036 | Left shaft of femur fracture | CRIF with IMIL nailing for femur fracture | 2 | 3 | 4 | 2 | 5 | 3 | 0 | 0 | 1 | 0 | 1 | 0 | 2 | 4th hr | No | Satisfied |
| 8 | Group A | 18 | M | 934637 | open type 3b displaced fracture of right femur with displaced proximal 1-3rd tibia fracture | femur locking nail with tibia LCP nippo plating | 3 | 3 | 4 | 2 | 3 | 4 | 0 | 0 | 1 | 0 | 0 | 1 | 2 | 4th hr | No | Very Satisfied |
| 9 | Group A | 28 | M | 933692 | Right shaft femur fracture | CRIF with IMIL nailing for femur fracture | 2 | 3 | 4 | 2 | 3 | 4 | 0 | 0 | 1 | 0 | 0 | 1 | 2 | 4th hr | No | Very Satisfied |
| 10 | Group A | 25 | M | 907785 | femoral fracture with closed IT fracture of femur | CRIF with IMIL nailing for femur fracture with long PFN nailing | 2 | 3 | 4 | 3 | 2 | 4 | 0 | 0 | 1 | 0 | 0 | 1 | 2 | 4th hr | No | Very Satisfied |
| 11 | Group A | 38 | M | 894968 | Left Shaft of femur fracture | CRIF with IMIL nailing for femur fracture | 2 | 3 | 4 | 3 | 5 | 3 | 0 | 0 | 1 | 0 | 1 | 0 | 2 | 4th hr | No | Very Satisfied |
| 12 | Group A | 65 | M | 898563 | distal 1-3rd right tibia fracture with ipsilateral fibula fracture | CRIF with IMIL nailing of tibia with semi tubular plating for fibula | 2 | 3 | 4 | 3 | 3 | 5 | 0 | 0 | 1 | 0 | 0 | 1 | 2 | 4th hr | No | Satisfied |
| 13 | Group A | 49 | M | 894354 | closed comminuted fracture of IT femur | CRIF with PFN nailing for femur | 3 | 3 | 5 | 3 | 5 | 3 | 0 | 0 | 1 | 0 | 1 | 0 | 2 | 4th hr | No | Very Satisfied |
| 14 | Group A | 30 | M | 918364 | Left shaft of femur fracture | CRIF with IMIL nailing for femur fracture | 2 | 4 | 3 | 3 | 5 | 3 | 0 | 1 | 0 | 0 | 1 | 0 | 2 | 1st hr | No | Satisfied |
| 15 | Group A | 50 | M | 89166 | closed comminuted fracture of IT femur | CRIF with PFN nailing for femur | 3 | 3 | 4 | 2 | 3 | 3 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 4th hr | No | Very Satisfied |
| 16 | Group A | 29 | M | 40522 | Left shaft of femur fracture | CRIF with IMIL nailing for femur fracture | 3 | 3 | 4 | 3 | 4 | 2 | 0 | 0 | 1 | 0 | 1 | 0 | 2 | 4th hr | No | Dissatisfied |
| 17 | Group A | 60 | M | 41900 | closed comminuted fracture of IT femur | CRIF with PFN nailing for femur | 2 | 3 | 3 | 4 | 2 | 3 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 8th hr | No | Satisfied |
| 18 | Group A | 47 | M | 469874 | closed comminuted fracture of IT femur | CRIF with PFN nailing for femur | 2 | 3 | 3 | 4 | 3 | 3 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 8th hr | No | Satisfied |
| 19 | Group A | 40 | M | 51399 | distal 1-3rd right tibia fracture with ipsilateral fibula fracture | CRIF with IMIL nailing of tibia with semi tubular plating for fibula | 3 | 4 | 3 | 3 | 3 | 4 | 0 | 1 | 0 | 0 | 0 | 1 | 2 | 1st hr | No | Satisfied |
| 20 | Group A | 65 | F | 50811 | closed comminuted fracture of IT femur | CRIF with PFN nailing for femur | 3 | 3 | 4 | 3 | 3 | 5 | 0 | 0 | 1 | 0 | 0 | 1 | 2 | 4th hr | No | Satisfied |
| 21 | Group A | 50 | M | 55155 | distal 1-3rd right tibia fracture with ipsilateral fibula fracture | CRIF with IMIL nailing of tibia with semi tubular plating for fibula | 3 | 3 | 4 | 2 | 3 | 4 | 0 | 0 | 1 | 0 | 0 | 1 | 2 | 4th hr | No | satisfied |
| 22 | Group A | 25 | M | 54063 | Right shaft of femur fracture | CRIF with IMIL nailing for femur fracture | 3 | 3 | 4 | 3 | 3 | 4 | 0 | 0 | 1 | 0 | 0 | 1 | 2 | 4th hr | No | Very Dissatisfied |
| 23 | Group A | 49 | M | 65899 | Left shaft of femur fracture | CRIF with IMIL nailing for femur fracture | 3 | 3 | 2 | 5 | 3 | 4 | 0 | 0 | 0 | 1 | 0 | 1 | 2 | 8th hr | No | Dissatisfied |
| 24 | Group A | 62 | M | 68047 | Left shaft of femur fracture | CRIF with IMIL nailing for femur fracture | 2 | 3 | 2 | 4 | 2 | 4 | 0 | 0 | 0 | 1 | 0 | 1 | 2 | 8th hr | No | Dissatisfied |
| 25 | Group B | 43 | M | 66143 | Right shaft of femur fracture | CRIF with IMIL nailing for femur fracture | 6 | 2 | 3 | 3 | 6 | 5 | 1 | 0 | 0 | 0 | 1 | 1 | 3 | Immediate post op | No | Satisfied |
| 26 | Group B | 50 | M | 63402 | Right shaft of femur fracture | CRIF with IMIL nailing for femur fracture | 3 | 5 | 3 | 7 | 6 | 5 | 0 | 1 | 0 | 1 | 1 | 1 | 4 | 1st hr | No | Very Satisfied |
| 27 | Group B | 35 | M | 62478 | Right shaft of femur fracture | CRIF with IMIL nailing for femur fracture | 2 | 3 | 7 | 3 | 6 | 5 | 0 | 0 | 1 | 0 | 1 | 1 | 3 | 4th hr | No | Satisfied |
| 28 | Group B | 30 | F | 52373 | closed comminuted fracture of IT femur | CRIF with PFN nailing for femur | 3 | 5 | 2 | 3 | 5 | 6 | 0 | 1 | 0 | 0 | 1 | 1 | 3 | 1st hr | No | Satisfied |
| 29 | Group B | 65 | M | 55441 | closed comminuted fracture of IT femur | CRIF with PFN nailing for femur | 2 | 3 | 3 | 6 | 5 | 5 | 0 | 0 | 0 | 1 | 1 | 1 | 3 | 8th hr | No | Dissatisfied |
| 30 | Group B | 65 | F | 55651 | closed displaced comminuted distal femur fracture | ORIF with LCP fixation of distal femur | 3 | 5 | 3 | 6 | 3 | 7 | 0 | 1 | 0 | 1 | 0 | 1 | 3 | 1st hr | No | Satisfied |
| 31 | Group B | 49 | M | 61325 | left shaft of femur fracture | CRIF with IMIL nailing for femur fracture | 5 | 2 | 3 | 4 | 5 | 5 | 1 | 0 | 0 | 1 | 1 | 1 | 4 | Immediate post op | Diclofenac 75 mg | Very Satisfied |
| 32 | Group B | 23 | M | 61630 | Left shaft femur fracture | CRIF with IMIL nailing for femur fracture | 6 | 2 | 3 | 5 | 3 | 5 | 1 | 0 | 0 | 1 | 0 | 1 | 3 | Immediate post op | No | Very Dissatisfied |
| 33 | Group B | 36 | M | 61755 | Right shaft of femur fracture | CRIF with IMIL nailing for femur fracture | 5 | 2 | 3 | 6 | 3 | 4 | 1 | 0 | 0 | 1 | 0 | 1 | 3 | Immediate post op | No | Satisfied |
| 34 | Group B | 60 | M | 60611 | Right shaft of femur fracture | CRIF with IMIL nailing for femur fracture | 6 | 3 | 3 | 6 | 4 | 5 | 1 | 0 | 0 | 1 | 1 | 1 | 4 | Immediate post op | No | Very Satisfied |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 35 | Group B | 59 | M | 66851 | closed comminuted fracture of IT femur | CRIF with PFN nailing for femur | 2 | 6 | 2 | 3 | 6 | 6 | 0 | 1 | 0 | 0 | 1 | 1 | 3 | 1st hr | No | Dissatisfied |
| 36 | Group B | 65 | M | 937247 | closed displaced comminuted distal femur fracture | ORIF with LCP fixation of distal femur | 6 | 3 | 3 | 5 | 3 | 5 | 1 | 0 | 0 | 1 | 0 | 1 | 3 | Immediate post op | No | Satisfied |
| 37 | Group B | 64 | F | 936099 | Right shaft of femur fracture | CRIF with IMIL nailing for femur fracture | 5 | 3 | 4 | 6 | 4 | 3 | 1 | 0 | 1 | 1 | 1 | 0 | 4 | Immediate post op | No | Dissatisfied |
| 38 | Group B | 60 | F | 934618 | Left shaft of femur fracture | CRIF with IMIL nailing for femur fracture | 3 | 6 | 3 | 4 | 2 | 4 | 0 | 1 | 0 | 1 | 0 | 1 | 3 | 1st hr | No | Dissatisfied |
| 39 | Group B | 6 0 | M | 901818 | Left shaft of femur fracture | CRIF with IMIL nailing for femur fracture | 4 | 3 | 3 | 6 | 6 | 5 | 1 | 0 | 0 | 1 | 1 | 1 | 4 | Immediate post op | Diclofenac 75 mg | Dissatisfied |
| 40 | Group B | 31 | M | 931771 | closed displaced comminuted distal femur fracture | ORIF with LCP fixation of distal femur | 6 | 3 | 3 | 3 | 6 | 5 | 1 | 0 | 0 | 0 | 1 | 1 | 3 | Immediate post op | No | Dissatisfied |
| 41 | Group B | 65 | M | 929311 | Right shaft of femur fracture | CRIF with IMIL nailing for femur fracture | 4 | 3 | 3 | 3 | 6 | 5 | 1 | 0 | 0 | 0 | 1 | 1 | 3 | Immediate post op | No | Very satisfied |
| 42 | Group B | 33 | M | 930047 | closed distal third spiral fracture of tibia | CRIF with LCP plating for tibia | 5 | 3 | 3 | 5 | 7 | 5 | 1 | 0 | 0 | 1 | 1 | 1 | 4 | Immediate post op | No | Dissatisfied |
| 43 | Group B | 65 | F | 928331 | Right proximal femur fracture | CRIF with IMIL nailing for femur fracture | 5 | 3 | 3 | 5 | 6 | 5 | 1 | 0 | 0 | 1 | 1 | 1 | 4 | Immediate post op | No | Dissatisfied |
| 44 | Group B | 60 | F | 929531 | Right proximal femur fracture | CRIF with IMIL nailing for femur fracture | 5 | 3 | 3 | 4 | 2 | 4 | 1 | 0 | 0 | 1 | 0 | 1 | 3 | Immediate post op | No | Very Dissatisfied |
| 45 | Group B | 47 | M | 909255 | left distal femur fracture | CRIF with IMIL nailing for femur fracture | 5 | 3 | 3 | 6 | 3 | 6 | 1 | 0 | 0 | 1 | 0 | 1 | 3 | Immediate post op | No | Dissatisfied |
| 46 | Group B | 54 | M | 86082 | Left shaft of femur fracture | CRIF with IMIL nailing for femur fracture | 5 | 3 | 3 | 5 | 3 | 6 | 1 | 0 | 0 | 1 | 0 | 1 | 3 | Immediate post op | No | Dissatisfied |
| 47 | Group B | 65 | F | 76724 | Right proximal femur fracture | CRIF with IMIL nailing for femur fracture | 6 | 3 | 3 | 5 | 4 | 5 | 1 | 0 | 0 | 1 | 1 | 1 | 4 | Immediate post op | No | Very Dissatisfied |
| 48 | Group B | 57 | M | 79978 | distal 1-3rd right tibia fracture with ipsilateral fibula fracture | CRIF with IMIL nailing of tibia with semi tubular plating for fibula | 4 | 3 | 3 | 6 | 2 | 6 | 1 | 0 | 0 | 1 | 0 | 1 | 3 | Immediate post op | No | Dissatisfied |