Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/20887
DOI URL: http://dx.doi.org/10.21474/IJAR01/20887

RESEARCH ARTICLE

PRE-EMPTIVE ANALGESIA WITH PREGABALIN IN ELECTIVE LOWER LIMB ORTHOPAEDIC SURGERIES: A RANDOMIZED CONTROLLED TRIAL

Satva Thangarasu and Ashish Bangari

Manuscript Info

Manuscript History
Received: 24 March 2025
Final Accepted: 27 April 2025
Published:May 2025

Key words:-
Pre-emptiveanalgesia, pregabalin, postoperative pain, orthopaedic surgery, central sensitization

Abstract

Background: Postoperative pain in orthopaedic surgeries, particularly lower limb procedures, is severe and can delay rehabilitation. Pre-emptive analgesia aims to prevent central sensitization by administering analgesics before surgical injury.

Objective: To evaluate the efficacy of pre-emptive pregabalin in reducing postoperative pain and opioid consumption in elective lower limb orthopaedic surgeries.

Methods: A randomized, double-blind, placebo-controlled trial enrolled 60 patients undergoing elective lower limb orthopaedic surgeries. Patients received pregabalin (150 mg) or placebo one hour before surgery. Primary outcome was postoperative pain score (Visual Analog Scale, VAS) at 24 hours; secondary outcomes included opioid consumption and adverseeffects.

Results:
ThetimetofirstepiduraltopupforPregabalingroupis11.2±5.3hourswhen compared to 4.67±5.3 hours for control group ($p<0.05$). The total number of top upfor pregabalin group is 0.96±0.41 when compared to control group 1.7±0.7 ($p<0.05$). The total number of rescue morphine for pregabalin group is 0.47±0.6 whencompared to control group 1.57 ± 0.67 ($p< 0.05$).

Conclusion: Pre-emptive pregabalin reduces postoperative pain and opioid requirements in lower limb orthopaedic surgeries, supporting its use in multimodal analgesia.

Introduction:-

Postoperative pain following orthopaedic surgeries, particularly lower limb procedures, is often severe, contributing to delayed rehabilitation, prolonged hospital stays, and increased risk of chronic pain [1]. The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage [2]. Surgical tissue injury triggers peripheral and central sensitization, amplifying pain through heightened responsiveness of nociceptive neurons and reduced pain thresholds [3]. Peripheral sensitization results from inflammatory mediators lowering the threshold of nociceptors, while central sensitization enhances dorsal horn neuron excitability, leading to hyperalgesia and allodynia [4].

Pre-emptive analgesia, administered before surgical incision, aims to block nociceptive input, preventing or reducing sensitization [5]. Unlike postoperative analgesia, pre-emptive strategies may mitigate the establishment of pain hypersensitivity, potentially reducing analgesic requirements and improving outcomes [6]. Various agents, including non-steroidal anti-inflammatory drugs, opioids, and local anaesthetics, have been studied, with mixed results on efficacy. Pregabalin, a gabapentinoid, binds to the α2δ subunit of voltage-gated calcium channels, reducing neurotransmitter release and attenuating neuropathic and postoperative pain. Clinical studies suggest pregabalin decreases postoperative opioid use and preoperative anxiety without significant side effects [7].Given the high pain burden in lower limb orthopaedic surgeries and the potential of pregabalin to modulate pain pathways, this study evaluated the efficacy of pre-emptive pregabalin in reducing postoperative pain and opioid consumption compared to placebo in patients undergoing elective lower limb orthopaedic procedures.

Materials and Methods:

This prospective, randomized, double-blind controlled study was conducted from May 2017 to May 2018 at MIOT Hospital, Chennai, in accordance with the institutional ethical committee guidelines. Sixty patients scheduled for elective lower limb orthopaedic surgery, aged 19–60 years and classified as ASA physical status I or II, were enrolled. Patients undergoing emergency surgery; those with pre-existing neurological, liver, renal, or psychiatric disorders; local lumbar infections; coagulation disorders; allergies to gabapentinoids; ASA classes III–V; chronic pain medication users; or those refusing consent were excluded.

Patients were randomly allocated into two groups (n = 30 each) using computer-generated random numbers in a double-blind fashion. Group P received 300 mg pregabalin, while Group C received a placebo.Sample size calculation was performed using nMaster 2.0 software and, based on previous study data, indicated that 28 patients per group were required to achieve 90% power with a 1% type I error. To compensate for an anticipated 10% attrition rate, 30 patients were enrolled in each group. The calculation was based on the formula for two means with equal variances:$n = [(Z\alpha/2 + Z\beta)^2 \times 2\sigma^2] / d^2$; where Zα/2 is the critical value for the desired confidence level, Zβ is the critical value for the desired power, σ^2 represents the pooled variance, and d is the detectable mean difference.

Preoperative Preparation and Consent

All enrolled patients underwent a comprehensive preoperative evaluation including clinical examination, routine biochemical tests, electrocardiography, and chest X-ray. Eligible patients, identified per the selection criteria, received an explanation of the anaesthesia procedure in their vernacular language, and written informed consent was obtained.

Randomization and Drug Administration Sixty patients scheduled for elective lower limb orthopaedic surgery were randomized in a double-blind manner into two groups (n = 30 each) using a computer-generated table. Group P received a 300 mg capsule of pregabalin (MAXGALIN, Sun Pharma) and Group C received an identical placebo tablet 90 minutes before anaesthesia. No additional premedication was administered.

Anaesthetic Technique Upon arrival in the operating room, baseline vitals (heart rate, systolic/diastolic blood pressure, mean arterial pressure, and respiratory rate) were recorded. An 18G IV cannula was placed, and patients were preloaded with crystalloids (10 ml/kg). Under strict asepsis and with patients in the sitting position, the epidural space was identified at the L2–L3 or L3–L4 interspace using a 16G Tuohy needle and the loss-of-resistance technique. An 18G catheter was threaded cephalad (3–4 cm inside) and a test dose (3 cc of 1.5% lignocaine with adrenaline 5 µg/ml) administered. Spinal anaesthesia was then performed in the same interspace with 3 cc of 0.5% hyperbaric bupivacaine. Cases exceeding 125 minutes or those requiring intraoperative epidural supplementation were excluded.

Intraoperative Management

Continuous monitoring was performed every 5 minutes using ECG, NIBP, pulse oximetry, and urine output, with supplemental oxygen (4–5 L/min via a face mask) and IV midazolam (0.05 mg/kg) for anxiolysis. Motor block was assessed using the modified Bromage score, and sensory block was evaluated with a spirit swab (at 5 and 10 minutes). Hypotension (>20% drop from baseline) was managed with IV fluids and ephedrine (3 mg increments), bradycardia (<50 bpm) with IV atropine (0.3 mg), and respiratory depression (RR <8/min) was recorded.

Postoperative Monitoring and Analgesia

Patients were observed in the recovery room for 60 minutes before being transferred to the ward. Postoperative assessments included continuous monitoring of vitals and evaluation of pain intensity using the visual analogue scale (VAS) at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 hours. Sedation levels were recorded using the Ramsay sedation scale at designated intervals (1, 2, 4, 6, 8, 12, 16, and 24 hours). When VAS reached ≥4, an epidural top-up (6 ml of 0.125% bupivacaine with 2 µg/ml fentanyl) was administered; persistent pain was treated with rescue IM morphine (4 mg). All patients additionally received IV paracetamol (1 g thrice daily). Postoperative pain management was continued with an epidural infusion of 0.125% bupivacaine with fentanyl (2 µg/ml at 4–6 ml/hr),

and patients were monitored for adverse events, including hypotension, bradycardia, and respiratory depression. Additional postoperative care included haemoglobin and haematocrit measurement at 24 hours, drain removal after 48 hours, and twice-daily screening for deep vein thrombosis with prophylaxis provided by enoxaparin 40 mg SC daily until discharge.

Statistical Analysis Continuous data are presented as mean ± SD and categorical data as percentages. Group comparisons were performed using Student's t-test for continuous variables and the chi-square test for categorical variables. A two-tailed p-value <0.05 was considered statistically significant. Data analysis was performed using SPSS version 17.0.

Results:

In this randomized controlled trial, 60 ASA I–II patients (aged 20–60 years) undergoing elective lower limb orthopaedic surgery with combined spinal–epidural anaesthesia were randomized to receive pregabalin 300 mg (Group P, n=30) or placebo (Group C, n=30) 90 minutes preoperatively. Baseline characteristics, including age (38.17 ± 8.89 vs. 40.10 ± 10.69 years; p=0.45), sex (86.67% vs. 70.00% male; p=0.2092), ASA status (56.7% vs. 70% ASA I; p=0.426), BMI, and surgical duration (105.27 ± 7.86 vs. 104.87 ± 8.02 min; p=0.8460), were comparable, with no prior surgery at the same site.

Intraoperative parameters, including motor block onset (Bromage score 3) and sensory block levels at 5 and 10 minutes, showed no significant differences (p>0.88). Postoperatively, Group P demonstrated significantly lower visual analogue scale (VAS) pain scores at most time points (1–24 h; p<0.05), except at 12 h, where Group C had lower scores (2.1 ± 0.84 vs. 3.2 ± 0.92; p<0.001) due to additional rescue analgesia. Group P required fewer epidural top-ups (0.96 ± 0.41 vs. 1.7 ± 0.70; p<0.0001) and had a prolonged time to first top-up (11.2 ± 5.3 vs. 4.67 ± 1.9 h; p<0.001). Rescue morphine use was significantly lower in Group P (0.47 ± 0.62 vs. 1.57 ± 0.67 doses; p<0.0001), with 60% requiring no morphine compared to 6.7% in Group C.

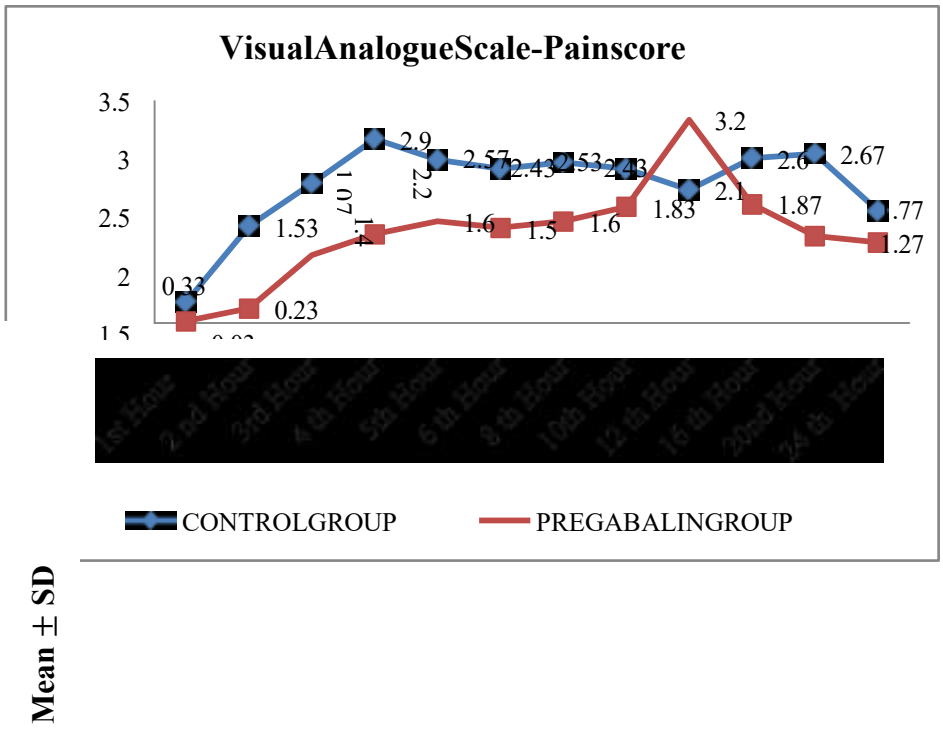


Figure 1: Pain score comparing control and pregabalin group

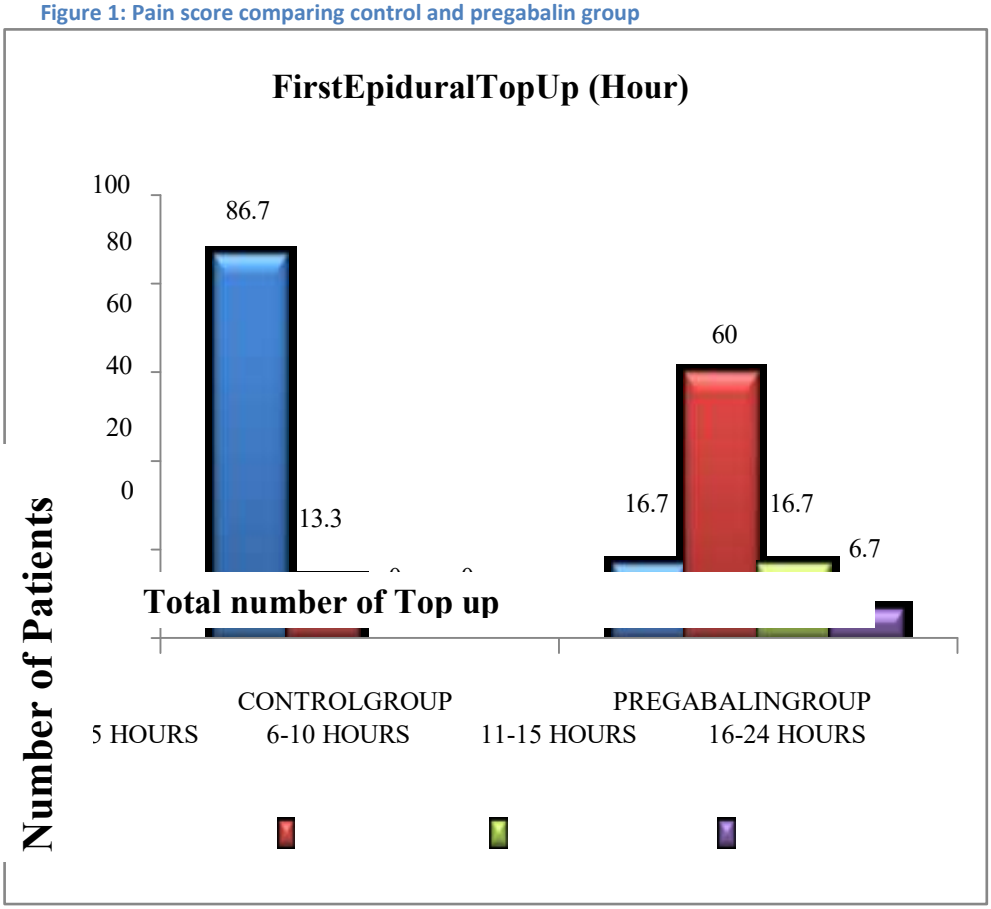
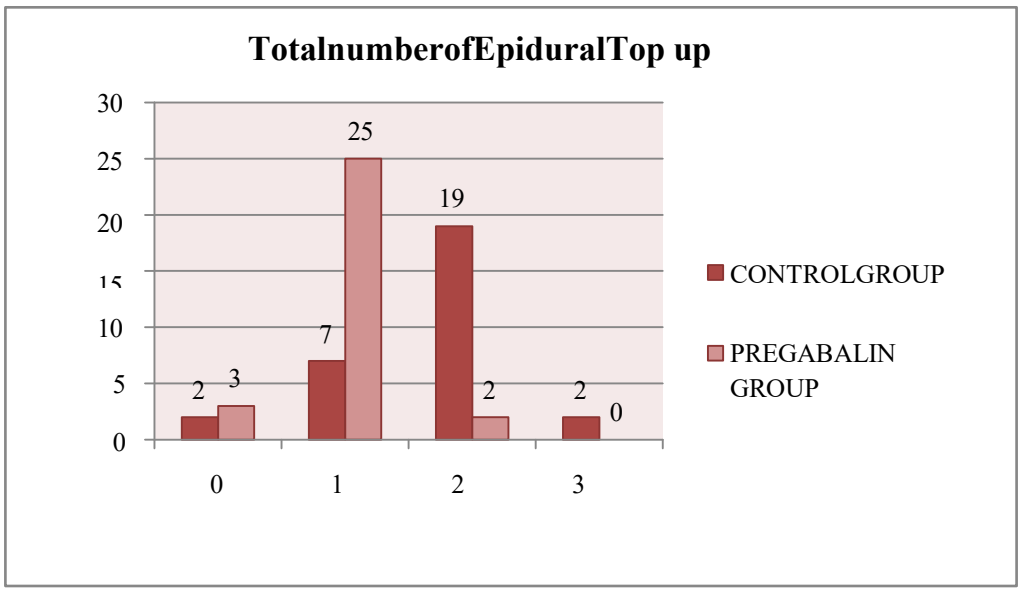


Figure 2: Time to the first epidural top-up in control and pregabalin group

Figure 3: Total number of epidural top-up in control and pregabalin group



These findings indicate that preoperative pregabalin significantly enhances postoperative analgesia, reducing pain intensity and the need for supplemental analgesics, thus improving patient outcomes in orthopaedic surgery.

Discussion:

Historically, pain management received limited attention until initiatives such as Dr. James Campbell's 1995 proposal to include pain as a vital sign and the U.S. declaration of the "Decade of Pain Control and Research" in 2000 refocused efforts on effective pain treatment [8]. Despite these efforts, acute postoperative pain after surgical procedures—especially in orthopaedic cases—remains a significant challenge, with poorly managed pain contributing to persistent pain syndromes in up to 50% of patients.

Multimodal analgesia, which combines agents like local anaesthetics, opioids, NSAIDs, and other adjuvants, is now widely employed to harness synergistic effects for better pain control. Among pre-emptive strategies, pregabalin has gained interest due to its improved pharmacokinetic profile compared to gabapentin. Its enhanced lipid solubility, rapid absorption (achieving peak plasma concentrations within one hour), and high-affinity binding to calcium channels contribute to a prolonged pain-free interval following spinal anaesthesia.

Clinical studies corroborate these benefits. For instance, Buvanendran et al. demonstrated that administering pregabalin (300 mg) preoperatively can reduce postoperative opioid use and improve early rehabilitation outcomes in total knee replacement patients [9]. Similarly, Jain et al. observed significant reductions in morphine consumption in patients receiving pregabalin. Studies conducted in the Indian population have also shown that pregabalin not only prolongs the time to rescue analgesia but may improve overall patient satisfaction without compromising intraoperative haemodynamics. However, contrasting evidence exists; for example, studies by Mathieson et al. and Micheal et al [10] did not find significant differences in pain scores or opioid consumption with pregabalin, underscoring the variability in outcomes across different surgical contexts.

Overall, while pregabalin shows promise as an effective pre-emptive analgesic in orthopaedic surgery, these mixed findings highlight the need for further research to optimize dosing strategies and integrate it into a comprehensive, multimodal pain management protocol.

Limitations of the Study:

This study has notable limitations. Pregabalin was administered 1.5 hours preoperatively, consistent with its rapid absorption (WHO report), but optimal timing for pre-emptive analgesia is unclear, as 2–8 hours may be needed for effective CSF concentrations (Buvanendran et al.). A 300 mg dose was used, yet doses from 75 mg to 600 mg require further study for optimization. The additive effects of morphine and pregabalin confounded sedation and pain control assessments. Range of motion of the traumatized limb was not evaluated. Hospital stay duration was not compared, despite potential prolongation from pregabalin's side effects (dizziness, vomiting, blurred vision, and headache). Patient satisfaction scores were not recorded.

Conclusion

Preoperative administration of pregabalin 300 mg, given 90 minutes before surgery as pre-emptive analgesia, effectively reduces postoperative pain scores and significantly decreases the need for postoperative analgesics in lower limb orthopaedic surgeries, with no major adverse effects observed.

Results:

	Pregabalin group	Control group	p value
Timetofirstepiduraltopup	11.2±5.3	4.67±1.9	<0.001
Totalnumberofepiduraltop-up	0.96±0.41	1.7±0.7	<0.001
Meanrescue Morphine	0.47±0.6	1.57±0.6	<0.001

References:

1. Paul A, Afzal M, Bandyopadhyay K, Mishra A, Mookerjee S. Pre-emptive analgesia: Recent trends and evidences. Indian Journal of Pain. 2013; 27(3):114.
2. Jorgen B, Dahl & Henrik kehlet. Postoperative pain and its management. In: Wall and Melzack's (eds). Text book of pain. Fifth edition. England: Elsevier. 2006: 637.
3. MSGold, MJCaterina.MolecularBiologyoftheNociceptorTransduction.In: Allan I.Basbaum (ed). Science

of pain. Elsevier. 2009; 44.

4. Igor Kissin. Preemptive Analgesia. The Journal of the American Society of Anesthesiologists. 2000; 93:1138–43
5. Li Z, Taylor CP, Weber M, Piechan J, Prior F, Bian F, et al. Pregabalin is a potent and selective ligand for α2δ- 1 and α2δ-2 calcium channel subunits. European Journal of Pharmacology. 2011; 667(1–3):80–90.
6. International Association for the Studyof Pain. IASP Terminology. [Cited 2018 Jun 11]. Available from: https://www.iasp-pain.org/Education/Content.aspx? Item Number=1698
7. Medford N, Critchley HD. Conjoint activity of anterior insular and anterior cingulate cortex: awareness and response. Brain Structure & Function. 2010;214(5–6):535–49
8. CampbellJN.APS1995Presidentialaddress.TheJournalofpain.1996;5(1) p:85-88
8. Buvanendran A, Kroin JS, Della Valle CJ, Kari M, Moric M, Tuman KJ. Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial. Anesthesia Analgesia. 2010;110(1):199–207
9. Urban MK, Labib KM, Reid SC, Goon AK, Rotundo V, Cammisa FP, et al. Pregabalin Did Not Improve Pain Management After Spinal Fusions. The Musculoskeletal Journal of Hospital for Special Surgery. 2018 Feb; 14(1):41–6.