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Efficacy of Preemptive Oral Pregabalin in Reduction of Acute Postoperative Pain in Patients Undergoing Total Knee Arthroplasty in a Tertiary Care Hospital in Chengalpattu District: A Double Blind Randomised Controlled Trial

Dr. Annie Sharon Priyanka[1], Dr. Krishna Prasad T.[2], Dr. Jagan G.[3], Dr. Dilip Kumar G.[4*], Dr. Srinivasan T.[5], Dr. Vanaroja S.[6], Dr. Anusha B.[7]

[1]3rd year Post Graduate, Department of Anaesthesiology, Shri Sathya Sai Medical College and Research Institute, Ammapettai, Chengalpattu District, Tamil Nadu, 603108 India.

[2]Professor, Department of Anaesthesiology, Shri Sathya Sai Medical College and Research Institute, Ammapettai, Chengalpattu District, Tamil Nadu, 603108 India.

[3]Associate Professor, Department of Anaesthesiology, Shri Sathya Sai Medical College and Research Institute, Ammapettai, Chengalpattu District, Tamil Nadu, 603108 India.

[4]Professor, Department of Anaesthesiology, Shri Sathya Sai Medical College and Research Institute, Ammapettai, Chengalpattu District, Tamil Nadu, 603108 India. *

[5]3rd year Post Graduate, Department of Anaesthesiology, Shri Sathya Sai Medical College and Research Institute, Ammapettai, Chengalpattu District, Tamil Nadu, 603108 India.

[6]3rd year Post Graduate, Department of Anaesthesiology, Shri Sathya Sai Medical College and Research Institute, Ammapettai, Chengalpattu District, Tamil Nadu, 603108 India.

[7]Professor, Department of Anaesthesiology, Shri Sathya Sai Medical College and Research Institute, Ammapettai, Chengalpattu District, Tamil Nadu, 603108 India.

Corresponding Author: Dr. Dilip Kumar G, Professor, Department of Anaesthesiology, Shri Sathya Sai Medical College and Research Institute, Ammapettai, Chengalpattu District, Tamil Nadu, 603108 India.

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KEYWORDS

Pregabalin, Total Knee Arthroplasty, Opioids, Multimodal Analgesia.

ABSTRACT:

Background: Effective postoperative pain control is essential for recovery and functional improvement after Total Knee Arthroplasty (TKA), a procedure often associated with severe pain. Although opioids are commonly used, their adverse effects—such as nausea, vomiting, sedation, and dependence—limit their use. Pregabalin, a Gabapentinoid with analgesic and antihyperalgesic properties, is emerging as a promising preemptive agent in multimodal analgesia.

Objectives: This study evaluates the efficacy of preemptive oral Pregabalin in reducing acute postoperative pain and opioid requirements in TKA patients. Secondary objectives include assessing time to first breakthrough analgesia, patient satisfaction, and adverse effects.

Methodology: A double-blind randomised controlled trial was conducted at a tertiary care hospital in Chengalpattu, Tamil Nadu. 128 patients scheduled for elective TKA were randomised into two groups: one received 150 mg oral Pregabalin 6 hours preoperatively, the other received a placebo. All patients underwent standard regional anaesthesia. Pain was assessed using the Visual Analogue Scale (VAS) at intervals of up to 48 hours postoperatively, both at rest and during movement. Secondary measures included time first to rescue analgesia, total analgesic requirement, incidence of postoperative nausea and vomiting (PONV), side effects, and patient satisfaction.

Results: VAS scores were significantly lower in the Pregabalin group at all time points ($p < 0.001$). Time to first analgesia was longer (8.5 vs. 4 hours), with reduced opioid use and lower PONV. Mild sedation and dizziness were more common but not clinically significant. Satisfaction scores were higher on postoperative days 1 and 2.

Conclusion: Preemptive Pregabalin significantly improves postoperative pain control, reduces opioid-related side effects, and enhances patient satisfaction after TKA.

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INTRODUCTION

Postoperative pain management plays a pivotal role in patient satisfaction, functional recovery, and overall surgical success. Among orthopaedic procedures, Total Knee Arthroplasty (TKA) is one of the most effective yet painful interventions, often associated with substantial postoperative discomfort. Poorly controlled pain can hinder early rehabilitation, prolong hospitalisation, and increase the risk of chronic pain, complications, and dissatisfaction. [1] To address these challenges, modern pain management has shifted toward multimodal analgesia (MMA)—a combination of analgesics targeting different pain pathways to enhance efficacy and reduce opioid reliance. Within this strategy, Gabapentinoids, particularly Pregabalin, have gained attention due to their dual action on nociceptive and neuropathic pain mechanisms. [2]

TKA involves significant bone and soft tissue manipulation, often leading to intense acute pain. Reports indicate that up to 60% of patients experience severe pain in the first 48 hours post-surgery, and 20–25% continue to suffer moderate to severe pain for months. [3] Unrelieved pain can impair mobility, cause muscle atrophy and joint stiffness, and may lead to chronic conditions such as complex regional pain syndrome. Furthermore, inadequate pain control discourages early mobilisation, increasing the risk of complications such as thromboembolism and infections. [4] Traditionally, opioids have formed the cornerstone of postoperative analgesia. However, their well-documented side effects—including nausea, sedation, constipation, respiratory depression, and dependency—have prompted a global shift toward opioid-sparing strategies, particularly under enhanced recovery after surgery (ERAS) protocols. [5] The opioid crisis has further fuelled the search for safer alternatives. [6]

Pain after TKA is complex, arising from both nociceptive (inflammatory) and neuropathic (nerve-related) components. Effective management must address both. Pregabalin, a gamma-aminobutyric acid (GABA) analog, offers a unique mechanism: it binds to the alpha-2-delta subunit of voltage-gated calcium channels in the central nervous system, inhibiting the release of excitatory neurotransmitters such as glutamate and substance P. This action reduces both peripheral and central sensitisation—key contributors to acute and chronic pain. [7], [8] Pregabalin is well-suited for preemptive analgesia, a concept involving analgesic administration before a surgical stimulus to prevent central sensitisation. It is rapidly absorbed, reaches peak plasma concentration within one hour, and has a predictable pharmacokinetic profile superior to Gabapentin. Its preemptive use has been explored in various surgeries with high pain intensity, including spinal fusion, mastectomy, and orthopaedic procedures like TKA and Total Hip Arthroplasty (THA). [9], [10]

Multiple Randomised Controlled Trials (RCTs) and meta-analyses support Pregabalin's role in reducing acute pain and opioid requirements. For instance, a meta-analysis by Li *et al.* demonstrated that Pregabalin significantly lowered resting pain scores at 24 and 48 hours postoperatively, reduced morphine use, improved early knee flexion, and minimised opioid-related side effects. However, it was associated with an increased incidence of dizziness, a known adverse effect. [11] Similarly, Wang *et al.* found that adding Pregabalin (150 mg) to a multimodal regimen improved pain control and reduced opioid needs, even when acetaminophen was added; no further benefit was observed. [12] Motififard *et al.* also reported superior pain relief and range of motion when combining preemptive Pregabalin with peri-articular injections of morphine and ketorolac. [13] Despite these findings, some researchers question the clinical significance of Pregabalin's effects. Hamilton *et al.*, in a review of 12 RCTs, found only modest reductions in pain scores (0.3–0.5 points on a 0–10 scale) and noted increased sedation, which could delay mobilisation. [14]

Importantly, Indian data are limited. Pain management practices in India differ due to varied patient demographics, sociocultural attitudes toward pain, resource constraints, and limited access to regional blocks or PCA pumps. Many patients underreport pain, and healthcare infrastructure in rural and semi-urban areas may lack the capacity for advanced pain control strategies. [15] In this context, Pregabalin offers several advantages. It is low-cost, orally administered, and does not require technical expertise or monitoring, making it particularly useful in resource-limited settings. Additionally, reducing opioid use aligns with India's public health priorities, given growing concerns around opioid misuse and limited regulation. [16]

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Chengalpattu district in Tamil Nadu—a semi-urban area with rising osteoarthritis cases and increased demand for joint replacement surgeries—represents an ideal setting for evaluating simple, scalable interventions like Pregabalin. Tertiary care centres here are witnessing a surge in TKA cases, underlining the need for evidence-based perioperative protocols. [17] This study aims to inform practical, cost-effective strategies for perioperative care in similar Indian healthcare settings. Pregabalin, with its favourable pharmacological profile and potential for integration into multimodal analgesia, may enhance outcomes for TKA patients while addressing broader public health concerns.

METHODOLOGY

A double-blinded randomised controlled trial was conducted in the teaching tertiary care hospital, for 18 months after getting Institutional Ethical Committee approval (IEC NO:875/2023) and Clinical Trial Registration (CTRI/2023/12/060814). Patients aged more than 18 years scheduled for Total Knee Arthroplasty from the Department of Orthopaedics of ASA I and II were included in the study after getting informed consent. Patients with uncontrolled systemic diseases such as diabetes mellitus or hypertension, a history of previous major knee surgeries, known psychiatric illnesses or chronic pain conditions, and contraindications to Pregabalin were excluded. This trial seeks to assess the efficacy of a single preemptive dose of oral Pregabalin (150 mg) administered six hours before surgery in patients undergoing TKA. The primary outcomes include postoperative pain scores (using the Visual Analogue Scale) and opioid consumption in the first 24–48 hours. Secondary outcomes include time to first rescue analgesic, incidence of opioid-related side effects (such as nausea and vomiting), and early functional recovery, including knee range of motion and ambulation.

Sample size calculation was based on previous studies using Epitools Software, assuming a Pregabalin efficacy rate of 10% and placebo rate of 30%, with a significance level of 10% and 80% power. A total of 128 patients were randomised into two groups (64 in each group) using computer-generated randomisation: Pregabalin Group received 150 mg Pregabalin orally, 6 hours before surgery, and Control Group received a placebo (vitamin tablet) orally, 6 hours before surgery. The study was double-blinded, ensuring that patients, caregivers, and investigators were unaware of the group assignments.

Patients underwent a thorough pre-anaesthetic check-up and standard preoperative medications were given, which included T. Alprazolam 0.5 mg and Inj. Pantoprazole 40 mg. All patients received regional anaesthesia with standard ASA monitoring (non-invasive BP, ECG, SpO2). Preloading with 15 ml/kg of Ringer's Lactate was performed before anaesthesia induction. Postoperative pain assessment using the Visual Analogue Scale (VAS) was performed at regular intervals. Breakthrough pain was managed with Inj. Paracetamol 1 g IV every 8 hours as needed. Nausea and vomiting were treated with Inj. Emeset 8 mg IV as required. Figure 1 shows the enrolment and randomisation process as per CONSORT Guidelines.

All statistical analyses were performed using SPSS software version 16.0 (IBM Bangalore). Continuous variables (e.g., age, VAS scores, time to analgesia) were summarised using mean ± standard deviation (SD) or median with interquartile range (IQR), depending on data distribution. Categorical variables (e.g., gender, ASA status, incidence of PONV, adverse effects) were presented as frequencies and percentages. Independent sample t-tests were used to compare normally distributed continuous variables between the Pregabalin and placebo groups. Mann-Whitney U tests were applied for non-normally distributed data (e.g., time to first breakthrough analgesia). Chi-square tests or Fisher’s exact tests were used for categorical variables (e.g., gender distribution, adverse effects). Repeated measures ANOVA or Friedman test was used to compare VAS scores over multiple time intervals within and between groups. A p-value < 0.05 was considered statistically significant for all comparisons. Cohen's d was calculated to measure the effect size for continuous outcomes (e.g., VAS scores). Relative Risk (RR) and 95% Confidence Intervals (CI) were used for categorical outcomes (e.g., PONV incidence).

RESULTS

The age distribution (≥ 18 years) is well balanced across the two groups. The p-value of 0.82 indicates no statistically significant difference in age distribution, supporting the randomisation process and comparability. Gender distribution (Male/Female) is similar in both groups (p=0.74), indicating successful blinding and

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randomisation without sex-based bias. ASA classification distribution is comparable across groups (p=0.76), suggesting a uniform baseline health status of participants. No significant difference in body weight distribution (<50 to ≥80 kg) (p=0.88) suggests minimal confounding by body weight in the evaluation of outcomes.

Table 1: Mean Postoperative VAS Scores between Study Groups:

Time (Hours Post-Surgery)	PREGABALIN Group (Mean ± SD)	Placebo Group (Mean ± SD)	p-Value
0–3 hours	3.5 ± 1.2	5.8 ± 1.4	<0.001
3–6 hours	3.2 ± 1.1	5.5 ± 1.5	<0.001
6–12 hours	2.8 ± 1.0	4.9 ± 1.3	<0.001
12–24 hours	2.4 ± 0.8	4.2	

Postoperative pain scores, as assessed by the Visual Analogue Scale (VAS), were significantly lower in the Pregabalin group across all time intervals (0–3, 3–6, 6–12, and 12–24 hours), irrespective of gender or ASA status. No statistically significant interaction was observed, and it is represented in Table 1. The p-values (<0.001) confirm a statistically significant improvement in pain control with Pregabalin. The time to first breakthrough analgesia (in hours) was significantly longer in the Pregabalin group (p<0.001), indicating that Pregabalin provides more prolonged pain relief (median of 8.5 hours) compared to placebo (4 hours), as depicted in Figure 2. Patients in the Pregabalin group required significantly fewer rescue analgesic doses than the placebo group within the first 24 hours (p<0.001), as shown in Table 2, confirming its opioid-sparing effect. Total paracetamol requirement was significantly lower in the Pregabalin group, affirming its role in reducing additional analgesic needs (Table 3)

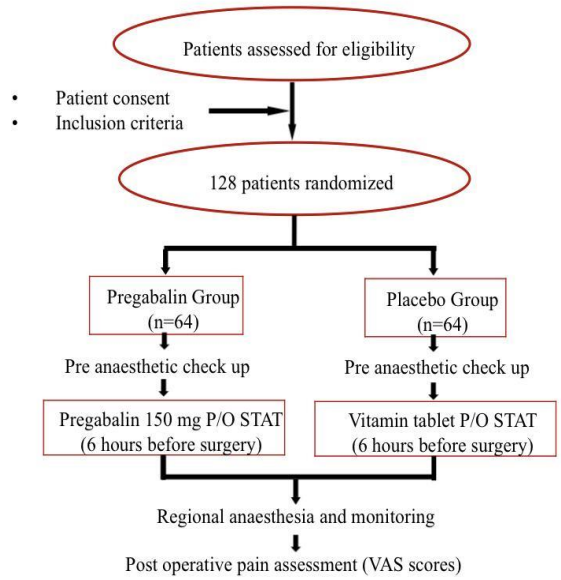
Table 2: Number of Rescue Analgesic Doses Required (First 24 Hours)

Group	Mean ± SD	Range	p-Value
PREGABALIN Group	1.1 ± 0.6	0–2 doses	
Placebo Group	2.3 ± 0.8	1–4 doses	**<0.001**

Table 3: Rescue Analgesic (Paracetamol) Consumption in 24 Hours

Group	Mean Total Dose (mg)	Standard Deviation	Range (mg)	p-Value
Pregabalin Group	1500	±500	1000–2000	
Placebo Group	2600	±800	2000–4000	**<0.001**

Figure 1: Consort Flow diagram



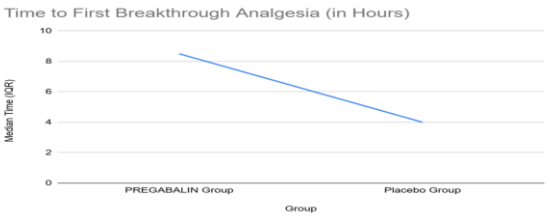


Figure 2: Time to First Breakthrough Analgesia (in Hours)

The Pregabalin group experienced significantly fewer moderate to severe PONV events compared to placebo, suggesting Pregabalin's secondary benefit in reducing opioid-related side effects. Pregabalin significantly

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reduced moderate-to-severe PONV at both 0–3 and 3–6 hours postoperatively as depicted in Figure 3, supporting its opioid-sparing and secondary antiemetic benefits. Sedation (0: Alert, 1: Drowsy, 2: Aroused with stimulation) was higher in the Pregabalin group (7.8%) but generally mild. Although statistically borderline significant (p=0.06), it did not interfere with postoperative care. Pregabalin had a higher incidence of dizziness (12.5%, p=0.04) and visual disturbance (4.7%, p=0.08), but nausea and vomiting were more frequent in the placebo group. (Table 4)

Table 4: Incidence of Adverse Effects in the Study Groups

Adverse Effect	Pregabalin Group (n=64)	Placebo Group (n=64)	p-Value
Dizziness	8 (12.5%)	2 (3.1%)	**0.04**
Nausea	6 (9.4%)	15 (23.4%)	**0.03**
Vomiting	3 (4.7%)	10 (15.6%)	**0.05**
Sedation	5 (7.8%)	1 (1.6%)	0.06
Visual Disturbance	3 (4.7%)	0 (0.0%)	0.08

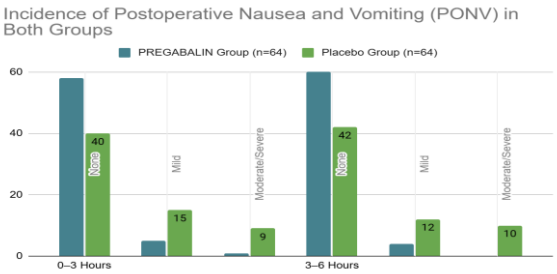

Figure 3: Incidence of Postoperative Nausea and Vomiting (PONV) in Both Groups

Significantly higher patient satisfaction scores were reported in the Pregabalin group during postoperative days 1 and 2 (p<0.001), likely due to better pain relief and fewer emetic episodes, reinforcing the overall clinical effectiveness of Pregabalin in TKA recovery. (Figure 4). All primary and secondary outcomes showed statistically and clinically significant improvements in the Pregabalin group, with large effect sizes across parameters—underscoring strong efficacy as shown in Table 5. Effect size (Cohen's d), mean differences, 95% CI, p -p-values for key outcomes: Pregabalin showed large effect sizes (Cohen's d > 1.3) across pain scores, PONV reduction, and satisfaction levels.

Table 5: Summary of Primary and Secondary Outcomes with Statistical Significance

Outcome	Mean Difference	95% Confidence Interval	p-Value	Effect Size (Cohen's d)
VAS 0–3 hrs	-2.3	(-2.8, -1.9)	<0.001	1.78 (Large)
Time to First Breakthrough (hrs)	+4.5	(3.5, 5.4)	<0.001	1.35 (Large)
Total Paracetamol Use (mg)	-1100	(-1300, -800)	<0.001	1.61 (Large)
PONV Incidence (0–3 hrs)	-29%	(-43%, -15%)	0.002	0.94 (Moderate–Large)
Patient Satisfaction Day 1 (VAS)	+13.8	(10.9, 16.7)	<0.001	2.16 (Very Large)

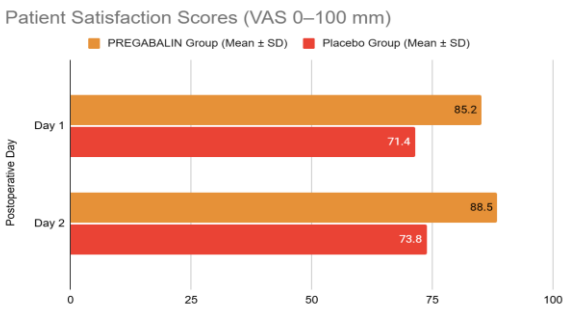

Figure 4: Patient Satisfaction Scores

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DISCUSSION

The age distribution between the Pregabalin and placebo groups was statistically comparable, ensuring that age-related differences in pain sensitivity, drug metabolism, or recovery did not confound outcomes. This alignment supports the internal validity of the findings, consistent with previous TKA studies like those by Jain *et al.* [18]. Gender distribution was also balanced, minimising the impact of sex-based differences in pain perception or analgesic response. Prior research, including that by Buvanendran *et al.*, supports Pregabalin's consistent effect across genders, reinforcing the unbiased interpretation of results. [19]. ASA physical status classification was evenly distributed, with most patients classified as ASA I or II. This parity reduces physiological variability and ensures that systemic health differences do not affect pain outcomes, aligning with findings from Bekawi *et al.* in diverse surgical populations. [20] Patient weight was similarly matched between groups. Given that pharmacokinetics and drug efficacy can vary with body weight, this comparability strengthens the reliability of the results. Despite fixed dosing, Pregabalin showed consistent analgesic efficacy across weight categories, supporting its generalizability. [21]. Visual Analogue Scale (VAS) scores were significantly lower in the Pregabalin group across all time intervals, indicating sustained analgesic benefit. This aligns with studies by Jain and Buvanendran, where Pregabalin reduced central sensitisation and lowered postoperative pain after TKA. [18, 19]

Time to first rescue analgesia was longer in the Pregabalin group, reflecting more prolonged pain relief. This delay reduces early postoperative analgesic needs, consistent with findings from Agarwal and Clarke in laparoscopic and orthopaedic surgeries. [16, 22]. Total 24-hour paracetamol consumption was significantly lower in the Pregabalin group, confirming its analgesic-sparing effect. Buvanendran and Fabritius *et al.* also documented reduced opioid and NSAID requirements with Pregabalin, reinforcing its role in multimodal pain protocols. [19, 23] Quantitative analysis of 24-hour paracetamol consumption further confirmed Pregabalin's opioid- and analgesic-sparing effects. Lower drug usage has important clinical implications, including reduced risk of hepatic side effects, fewer drug interactions, and lower treatment costs—key advantages in resource-limited healthcare settings. The Pregabalin group experienced significantly less moderate to severe PONV, especially in the first six postoperative hours. This reduction is likely due to decreased opioid use. Grant *et al.* similarly reported lower PONV incidence with Pregabalin in opioid-based protocols. Better control of PONV enhances early feeding and mobilisation, key to ERAS strategies. [24] The graded severity of PONV favoured Pregabalin, with most patients reporting no or mild symptoms and none experiencing severe nausea or vomiting in the first 6 hours. In contrast, the placebo group had notably higher rates of moderate to severe symptoms. This antiemetic advantage further supports Pregabalin's role in reducing opioid-related side effects.

Sedation was slightly higher in the Pregabalin group during the first 3 postoperative hours. Most cases were mild and resolved spontaneously. These findings, consistent with Toth's review, suggest that sedation at 150 mg is clinically manageable and does not delay recovery activities. [21] Visual disturbances occurred only in the Pregabalin group, but at a low incidence and mild severity. Symptoms such as transient blurring or diplopia resolved without intervention. Jokela *et al.* have noted similar effects at higher doses (300–600 mg), suggesting that the 150 mg dose used here maintains a favourable safety profile. [25]. Patient satisfaction scores were significantly higher in the Pregabalin group on postoperative days 1 and 2. This reflects better pain control, fewer side effects, and longer intervals before needing additional analgesics. Najam *et al.* also found improved satisfaction with preemptive Pregabalin use. [26]

A composite analysis of all major clinical endpoints—VAS scores, time to first rescue analgesia, PONV incidence, total paracetamol use, and patient satisfaction—consistently favoured the Pregabalin group. These improvements were statistically significant and clinically meaningful. Meta-analyses by Mishriky and Lam *et al.* have echoed similar findings across surgical domains. [27, 28]

CONCLUSION

In conclusion, this study confirms that a single preemptive dose of 150 mg oral Pregabalin administered six hours before Total Knee Arthroplasty significantly reduces postoperative pain, prolongs the time to first analgesic requirement, lowers PONV incidence, and enhances patient satisfaction—without severe side

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effects. These findings strongly support the incorporation of Pregabalin into multimodal analgesia strategies for TKA, paving the way for opioid-sparing protocols that are safer and more effective for diverse patient populations.

Conflicts of interest:

No potential conflict of interest relevant to this article was reported.

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