Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i3.5089

COMPARISON OF PREGABLIN VERSUS PLACEBO FOR POSTOPERATIVE PAIN IN PATIENTS UNDERGOING LOWER LIMB SURGERY

Dr Mamoona Shaikh[1*], Dr Maria Karim Narejo[2], Dr Jamil Ahmed[3], Dr Kauser Shaikh[4]

[1*]Assistant Professor, Anaesthesia Department, LUMHS, Jamshoro, Pakistan
[2]Medical Officer, MCPS Anaesthesiology, Anesthesia Department, LUMHS Jamshoro, Pakistan
[3]Associate Professor Anaesthesiology Isra University Hospital Hyderabad, Pakistan
[4]General Surgeon Shah Bhittai Hospital Hyderabad, Pakistan

[*]**Corresponding author:** Dr Mamoona Shaikh
Email: drmamoona@hotmail.com

Abstract:
Objectives: To compare the postoperative outcomes of pregablin versus placebo in patients undergoing Lower limb surgery.
Materials and Methods: In this RCT study, we enrolled a total of 100 patients, undergoing elective lower limb surgery of Tibia/femur. Patients were divided into two groups. Group I was offered Pregablin and Group II was given Placebo. Pain was assessed on VAS scale and at 2 score 4 and above IV pethidine 50 mg was given. At 24 hours pain was assessed finally and consumption of opioid was noted in the proforma by the PI.
Results: The average age of the patients was 39.08±8.81years. Mean pain score was significantly high in group II than Group I [4.7±1.39 vs. 2.52±0.99; p=0.0005]. Mean Opioid consumption was significantly high in group II as compare to group I [91.22±42.92 vs. 55.56±16.67; p=0.019].
Conclusion: Administering a single preoperative oral dose of 150 mg pregabalin has been demonstrated as an effective approach in mitigating postoperative pain among individuals undergoing lower limb surgery.

Keywords: Postoperative pain, Lower limb surgery of Tibia/femur, Opioids, pregablin

INTRODUCTION:

Acute postoperative pain is a commonly acknowledged issue affecting a majority of patients, whereas chronic postoperative pain presents as a comparatively less intricate problem.(1) Approximately 10% to 65% of patients may develop chronic pain following surgery, with 2% to 10% experiencing severe pain.(2) Postoperative pain management remains a significant challenge in surgical practice, particularly in procedures involving the lower limbs such as hip or knee replacements.(1, 3) Numerous pharmacological interventions have been investigated, among them the utilization of pregabalin, which is a gabapentinoid known for its analgesic properties.(4) Pregabalin primarily achieves its analgesic effects by binding to the α2-δ subunit of voltage-gated calcium channels within the central nervous system. This interaction results in the suppression of excitatory neurotransmitter release.(5) By modulating neuronal hyperexcitability, pregabalin attenuates nociceptive signaling, making it a promising agent for pain management in various clinical settings. Pregabalin's dual pharmacological actions make it a versatile medication in clinical practice. Whether used for the management of

neuropathic pain or as adjunctive therapy in adult partial seizures, pregabalin offers therapeutic benefits by modulating neuronal excitability and neurotransmitter release.(6) Numerous randomized controlled trials (RCTs) and meta-analyses have investigated the role of pregabalin in controlling postoperative pain across various surgical specialties. In lower limb surgery, several studies have reported favorable outcomes with pregabalin administration. For instance, a meta-analysis by Tiippana et al. (2013) demonstrated that pregabalin significantly reduced pain scores and opioid consumption following orthopedic procedures, including lower limb surgeries, compared to placebo. Indeed, numerous studies have provided evidence suggesting that drugs like pregabalin not only alleviate acute postoperative pain and reduce opioid consumption but also have the potential to mitigate the development of chronic postoperative pain (CPOP). Chronic pain following surgery is a significant clinical challenge, often characterized by persistent or recurrent pain lasting beyond the expected period of tissue healing.(7)

Postoperative pain management is a crucial aspect of patient care following lower limb surgery. Despite advancements in surgical techniques and anesthesia, many patients still experience significant pain, which can impair recovery, delay mobilization, and lead to complications such as deep vein thrombosis or pneumonia. Thus, there is a clear clinical need to identify effective strategies for managing postoperative pain in this patient population.

Objective:

To compare the postoperative outcomes of pregablin versus placebo in patients undergoing Lower limb surgery.

MATERIALS AND METHODS:

Study Design: Randomized Controlled Trial.

Study setting: Department of Anaesthesia, Liaquat University of Medical & Health sciences, Jamshoro.

Duration of the study: Duration of the study was 6 month (_____).

Inclusion Criteria:

- The patient falls under ASA physical status classification I-II.
- Patients undergoing elective lower limb surgery of Tibia/femur.
- Both gender of age 18-50 years.

Exclusion Criteria:

- Patients using narcotics assessed on history.
- Emergency surgeries like in case of open fractures.
- Contraindications for pregablin assessed on history.

Methods: The study was conducted following approval from the College of Physicians and Surgeons Pakistan and the institutional Ethical Review Committee. The principal investigator explained the study's purpose, procedure, potential risks, and benefits to eligible patients admitted to the hospital and meeting the inclusion criteria. After explaining the purpose of the study an informed consent was taken from each participant at the time of inclusion in the study. A brief history was collected, including information about age, smoking status, and history of diabetes mellitus and hypertension. Patients were randomly assigned to one of two groups using the sequentially numbered sealed opaque envelope (SNOSE) method. Patients in Group I were administered an oral dose of 150 mg pregabalin, whereas those in Group II received a visually indistinguishable placebo (capsules with similar appearance but devoid of the active ingredient). These administrations took place approximately 2 hours before anesthesia induction and were carried out by a staff nurse who was not part of the study team. No other premedication was allowed. Patients were then taken to the operating room where spinal anesthesia was equally induced using 12-15 mg of Bupivacaine 0.5% injected into the L4-L5

space with a 25-gauge needle by an anesthetist with over 2 years of experience. The surgical procedure was performed by a consultant with over 2 years of post-fellowship experience. In case of pain complaints, pain levels were assessed using the Visual Analog Scale (VAS), and if the score reached 4 or above, intravenous pethidine 50 mg was administered. Pain was reassessed at 24 hours post-surgery, and opioid consumption was recorded in the proforma by the principal investigator. Baseline characteristics such as age, gender, smoking status, and comorbid conditions including type 2 diabetes mellitus (documented history and treatment) and hypertension (documented history and treatment) were noted. The final outcome in terms of pain scores and opioid consumption was also recorded. SPSS version 26 was used for statistical analysis.

RESULTS:

A total 100 patients undergoing elective lower limb surgery of Tibia/femur were included in this study. Most of the patients were 41 to 50 years of age as shown in figure 1. The average age of the patients was 39.08±8.81years and 37.98±9.25 years in group I and group II respectively (Table 1). There were 50% male and 50% female (Table 1). Regarding diabetic and hypertension, 76% and 64% were diabetic and 50% and 38% hypertensive cases in group I and group II respectively. Similarly smoking status of the patients is also shown in Table 2. Mean pain score was significantly high in group II than Group I [4.7±1.39 vs. 2.52±0.99; p=0.0005] as shown in figure 2. There were 35 patients whose pain was observed above and equal to 4 so as per protocol we treated with IV pethidine. There were 18% (9/50) patients in group I and 52% (26/50) in group II need IV pethidine. Mean Opioid consumption was significantly high in group II as compare to group I [91.22±42.92 vs. 55.56±16.67; p=0.019] as shown in figure 3. Stratification analysis was performed and observed that mean pain score was significantly low in group I as compare to group II for all stratified confounding variables while mean opioid consumption was significantly low in group I than group II for >40 years of age, male, diabetic cases, non-smoker and those whose surgery was below and equal to 60 min as shown in table 3.

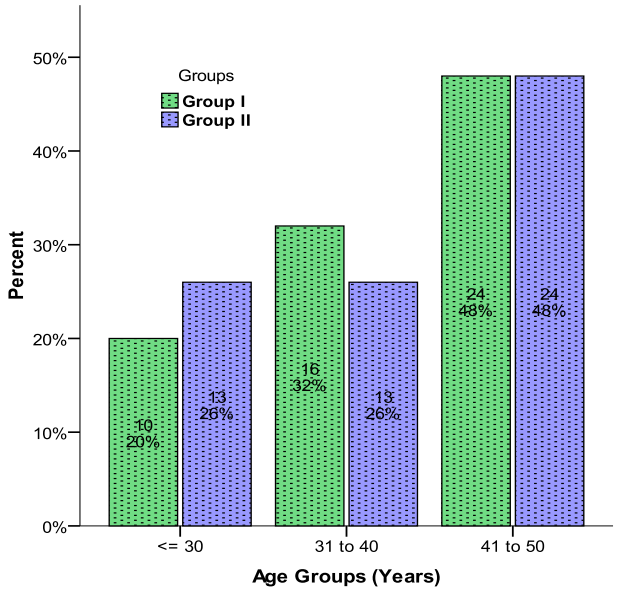

Fig 1: Gender distribution of the patients with respect to groups (n=100)

Table 1: Mean age and Duration of surgery of all enrolled Patient *(n=100)*

Variables	**Groups**	
	Group A	Group B
Age (year)	39.08±8.81	37.98±9.25
Duration of surgery (min)	67.34±14.50	72.22±16.31

Table 2: Characteristics of enrolled patients *(n=100)*

Variables	**Groups**	
	Group A	Group B
DM	38(76%)	32(64%)
Hypertension	25(50%)	19(38%)
Smoking	13(26.0%)	14(28.0%)
Gender		
Male	24(48.0%)	26(52.0%)
Female	26(52.0%)	24(48.0%)

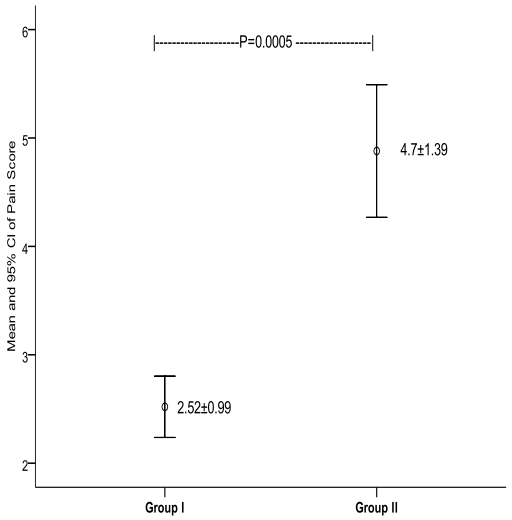

Fig 2: Comparison of mean pain score at 24 hours between groups n=100 (50 in each group)

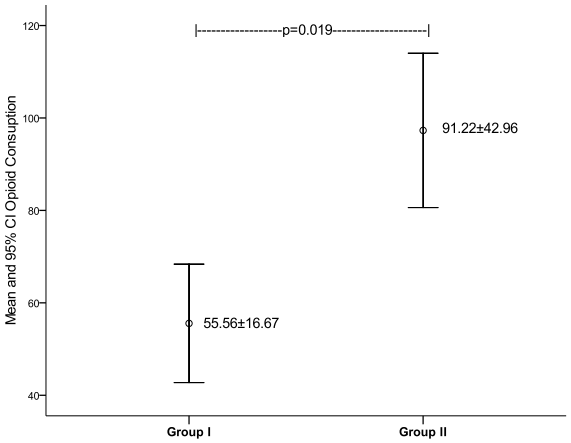

Fig 3: Comparison of mean opioid consumption between groups n=35 (9 group i and 26 in group)

Table 4: Comparison of ovulation after 8 weeks and 12 weeks in both groups (*n=500)*

		Groups			
		Group A		**Group B**	
<= 40 Years	no	Mean±SD	no	Mean±SD	P-value
Pain Score	26	2.46±0.85	26	5.46±2.23	0.00
Opioid Consumption	4	50±0.00	17	92.94±42.9	0.065
> 40 Years					
Pain Score	24	2.58±1.13	24	4.25±1.917	0.001

	Opioid Consumption	5	60±22.36	9	105.56±39.0	0.035
Gender						
Male	Pain Score	24	2.71±0.99	26	5.19±2.24	0.000
	Opioid Consumption	5	50.0±0.00	15	92±37.29	0.024
Female	Pain Score	26	2.35±0.97	24	4.54±2.04	0.000
	Opioid Consumption	4	62.5±25	11	104.5±47.19	0.119
Diabetic Mellitus						
YES	Pain Score	38	2.45±1.00	32	5±2.17	0.000
	Opioid Consumption	7	57.14±18.89	18	101.67±32.40	0.003
NO	Pain Score	12	2.75±0.96	18	4.67±2.16	0.008
	Opioid Consumption	2	50±0.00	8	87.50±58.28	0.41
Hypertension						
YES	Pain Score	25	2.56±1.19	19	4.53±2.11	0.000
	Opioid Consumption	6	58.33±20.41	9	92.22±39.22	0.076
NO	Pain Score	25	2.48±0.77	31	5.10±2.18	0.000
	Opioid Consumption	3	50±0.00	17	100±43.31	0.066
Smoking Status						
YES	Pain Score	13	2.46±0.96	13	5.71±2.05	0.000
	Opioid Consumption	2	50±0.00	10	90±39.44	0.198
NO	Pain Score	37	2.54±1.106	36	4.56±2.13	0.000
	Opioid Consumption	7	57.14±18.88	16	101.88±43.08	0.016
Duration of Surgery						
≤60 min	Pain Score	26	2.54±1.14	22	4.91±2.39	0.000
	Opioid Consumption	6	58.33±20.41	11	111.82±46.22	0.018
>60 min	Pain Score	24	2.5±0.83	28	4.86±2.01	0.000
	Opioid Consumption	3	50±0.00	15	86.67±35.18	0.097

Discussion: According to the International Association for the Study of Pain, pain is characterized as "an unpleasant sensory and emotional encounter associated with actual or potential tissue damage, or expressed in relation to such injury."(8) Postoperative pain represents a significant nociceptive stimulus associated with hyperalgesia and allodynia, which can exacerbate existing pain through the wind-up phenomenon occurring in the dorsal column of the spinal cord. Pregabalin, an FDA-approved lipophilic analogue of gamma-aminobutyric acid (GABA), stands out among commonly used analgesics due to several advantages. It not only alleviates patient anxiety but also effectively targets the neuropathic aspect of pain. Furthermore, pregabalin is reasonably priced, making it a favorable choice for managing postoperative pain. Gabapentin, a structural analog of gamma-aminobutyric acid, was initially developed as an antiepileptic medication. It functions by binding to calcium channels, thereby inhibiting calcium influx and reducing the release of excitatory neurotransmitters in both central and peripheral pain pathways.(9) This drug has demonstrated efficacy in various neuropathic pain conditions, including postherpetic neuralgia,(10) diabetic neuropathy,(11) trigeminal neuralgia,(12) neuropathic pain associated with malignancy,(13) and complex regional pain syndromes.(14) In contrast, pregabalin, a derivative of gabapentin, differs due to an amino acid substitution at the third position. Pregabalin achieves peak blood concentrations within 1 hour, with a maximum absorption rate approximately three times higher than that of gabapentin. While pregabalin also targets calcium channels like gabapentin, it exhibits a higher affinity, resulting in greater potency as an analgesic. These distinct characteristics likely contribute to an extended pain-free interval following spinal anesthesia.

The main aim of the present study was to compare the postoperative outcomes of pregablin versus placebo in patients undergoing Lower limb surgery. Usha Bafna et al.(15) undertook a study to evaluate the effects of oral gabapentin 600mg and pregabalin 150mg compared to a control group for postoperative pain relief in patients undergoing elective gynecological surgeries. Their results revealed that the preemptive administration of gabapentin and pregabalin led to a notable decrease in the requirement for postoperative rescue analgesics. Furthermore, pregabalin exhibited superior

efficacy compared to gabapentin in this regard. However, adverse effects such as nausea, hypotension, and bradycardia were noted with both drugs.(15) In our present study, the mean pain score was significantly higher in Group II compared to Group I (p=0.0005). Similar results were reported in another study, where pain intensity 12 hours after surgery was significantly lower in the pregabalin group compared to the placebo group.(16)

Furthermore, VAS scores at 12 and 24 hours after surgery were significantly lower in the pregabalin group compared to the placebo group. In our study, a higher percentage of patients in Group II required IV pethidine compared to Group I, and mean opioid consumption was significantly higher in Group II.

Several studies have demonstrated the efficacy of a single preoperative oral dose of pregabalin (150mg) in reducing postoperative pain and the consumption of opioids and NSAIDs among patients undergoing orthopedic and abdominal hysterectomy surgeries.(17-19) These investigations primarily focused on the quantitative reduction of postoperative analgesic drugs. Others studied the effects of various doses of pregabalin in gynecolaparoscopic surgeries and laparoscopic cholecystectomy, revealing a significant decrease in postoperative pain and analgesic requirement with preemptive oral pregabalin administration.(20-22)

The majority of previous research findings align with these results. For instance, Hill,(23) Agarwal et al.,(21) and Schulmeyer et al.(24) observed reduced postoperative pain severity in patients consuming pregabalin. Conversely, studies by Paech et al.,(25) Jokela et al.,(20) and Mathiesen et al.(26) found similar post-operative pain intensity between the pregabalin group and the control group. Many studies have also noted a decrease in post-operative opioid and analgesic consumption among patients receiving pregabalin.

Zhang et al.'s(27) 2011 study demonstrated a significant reduction in post-operative opioid consumption rates with pregabalin, along with a decrease in opioid-related side effects such as nausea and vomiting. Durkin et al. further illustrated the reduction of opioid consumption in patients with chronic neuropathic pain following pregabalin administration. Additionally, Post et al.(28) observed decreased opioid consumption after hip arthroplasty surgery with pregabalin usage.

CONCLUSION: A preoperative oral dose of 150 mg of pregabalin has shown effectiveness in managing postoperative pain in patients undergoing lower limb surgery. This approach notably reduces the necessity for opioids in the first 24 hours following surgery, demonstrating its opioid-sparing properties. Additionally, preemptive administration of pregabalin offers effective relief from postoperative pain, resulting in a reduced need for additional analgesics and increased patient satisfaction levels, all while maintaining stable intraoperative hemodynamics. Therefore, pregabalin presents itself as a valuable preemptive analgesic option for anesthesiologists involved in managing post-operative pain following lower limb orthopedic surgery.

References:

1. Rawal N. Current issues in postoperative pain management. European Journal of Anaesthesiology| EJA. 2016;33(3):160-71.
2. Miller RD, Eriksson L, Fleisher L, Wiener-Kronish J, Young W. Miller's Anesthesia, 2010. Churchil Livingstone, Elsevir Inc, Philadelphia, PA. 1703.
3. Joshi GP, Kehlet H. Postoperative pain management in the era of ERAS: an overview. Best Practice & Research Clinical Anaesthesiology. 2019;33(3):259-67.
4. Bansal A, Tewari A, Garg S, Gupta A. Pregabalin: Pharmacology and use in pain management. Journal of Anaesthesiology Clinical Pharmacology. 2009;25(3):321-6.
5. Sills GJ. The mechanisms of action of gabapentin and pregabalin. Current opinion in pharmacology. 2006;6(1):108-13.
6. Jabari Moghadam M. Comparison of the effect of gabapentin with pregabalin in post dural puncture headache. J Iran Soc Anesthesiol Intensive Care. 2010;31:1-6.

7. Damirchi AN, Kamali A, Azami M, Monfared ME. Comparison of the effect of apotel and pregabalin on postoperative pain among patients undergoing lower limb orthopedic surgeries. Journal of Family Medicine and Primary Care. 2019;8(7):2405-8.
8. Choudhury B, Pathak DG, Chauhan RC, Singha LC, Mondal D. Effect of intrathecal nalbuphine and magnesium sulphate used as adjuvants with bupivacaine in spinal anaesthesia for lower abdominal surgery: a comparison. Group. 2016;1000(50):43.72.
9. Ghai A, Gupta M, Hooda S, Singla D, Wadhera R. A randomized controlled trial to compare pregabalin with gabapentin for postoperative pain in abdominal hysterectomy. Saudi journal of anaesthesia. 2011;5(3):252-7.
10. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L, Group GPNS, et al. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. Jama. 1998;280(21):1837-42.
11. Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. Jama. 1998;280(21):1831-6.
12. Magnus L. Nonepileptic uses of gabapentin. Epilepsia. 1999;40:s66-s72.
13. Caraceni A, Zecca E, Martini C, De Conno F. Gabapentin as an adjuvant to opioid analgesia for neuropathic cancer pain. Journal of pain and symptom management. 1999;17(6):441-5.
14. Mellick GA, Mellick LB. Gabapentin in the management of reflex sympathetic dystrophy. Journal of pain and symptom management. 1995;4(10):265-6.
15. Bafna U, Rajarajeshwaran K, Khandelwal M, Verma AP. A comparison of effect of preemptive use of oral gabapentin and pregabalin for acute post-operative pain after surgery under spinal anesthesia. Journal of Anaesthesiology Clinical Pharmacology. 2014;30(3):373-7.
16. Alimian M, Imani F, Hassani V, Rahimzadeh P, Sharifian M, Safari S. Effects of single-dose pregabalin on postoperative pain in dacryocystorhinostomy surgery. Anesthesiology and pain medicine. 2012;2(2):72.
17. Akhavanakbari G, Entezariasl M, Isazadehfar K, Mirzarahimi T. The effects of oral pregabalin on post-operative pain of lower limb orthopedic surgery: a double-blind, placebo-controlled trial. Perspectives in clinical research. 2013;4(3):165-8.
18. Trivedi PA, Mehta M, Trivedi J. Pre emptive gabapentin versus pregabalin for post operative analgesia after abdominal hysterectomy under spinal anaesthesia. Int J Res Med. 2015;4(1):53-8.
19. Eman A, Bilir A, Beyaz SG. The effects of preoperative pregabalin on postoperative analgesia and morphine consumption after abdominal hysterectomy. Acta Med Mediterr. 2014;30(2):481-5.
20. Jokela R, Ahonen J, Tallgren M, Haanpää M, Korttila K. Premedication with pregabalin 75 or 150 mg with ibuprofen to control pain after day-case gynaecological laparoscopic surgery. British journal of anaesthesia. 2008;100(6):834-40.
21. Agarwal A, Gautam S, Gupta D, Agarwal S, Singh P, Singh U. Evaluation of a single preoperative dose of pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy. British journal of anaesthesia. 2008;101(5):700-4.
22. Jokela R, Ahonen J, Tallgren M, Haanpää M, Korttila K. A randomized controlled trial of perioperative administration of pregabalin for pain after laparoscopic hysterectomy. Pain. 2008;134(1-2):106-12.
23. Hill CM, Balkenohl M, Thomas DW, Walker R, Mathe H, Murray G. Pregabalin in patients with postoperative dental pain. European Journal of Pain. 2001;5(2):119-24.
24. Cabrera Schulmeyer MC, de la Maza J, Ovalle C, Farias C, Vives I. Analgesic effects of a single preoperative dose of pregabalin after laparoscopic sleeve gastrectomy. Obesity surgery. 2010;20:1678-81.
25. Paech MJ, Goy R, Chua S, Scott K, Christmas T, Doherty DA. A randomized, placebo-controlled trial of preoperative oral pregabalin for postoperative pain relief after minor gynecological surgery. Anesthesia & Analgesia. 2007;105(5):1449-53.

26. Mathiesen O, Rasmussen M, Dierking G, Lech K, Hilsted KL, Fomsgaard J, et al. Pregabalin and dexamethasone in combination with paracetamol for postoperative pain control after abdominal hysterectomy. A randomized clinical trial. Acta Anaesthesiologica Scandinavica. 2009;53(2):227-35.
27. Zhang J, Ho K-Y, Wang Y. Efficacy of pregabalin in acute postoperative pain: a meta-analysis. British journal of anaesthesia. 2011;106(4):454-62.
28. Post ZD, Restrepo C, Kahl LK, van de Leur T, Purtill JJ, Hozack WJ. A prospective evaluation of 2 different pain management protocols for total hip arthroplasty. The Journal of arthroplasty. 2010;25(3):410-5.