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ORIGINAL ARTICLE

Efficacy of Pregabalin Versus Gabapentin as Preemptive Analgesia in Patients Undergoing Modified Radical Mastectomy: a Randomized Controlled Trial

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Abstract

Introduction: Postoperative pain after modified radical mastectomy (MRM) increases morbidity, opioid use, and recovery time. Gabapentinoids may reduce central sensitization when administered before surgical injury. This study compared pregabalin and gabapentin as preemptive analgesics in patients undergoing MRM.

Patients and Methods: This double-blind randomized controlled trial was conducted at Ngoerah Hospital, Denpasar. Forty-two patients scheduled for elective MRM were allocated to oral pregabalin 150 mg (n = 21) or oral gabapentin 900 mg (n = 21), administered two hours before surgery. The primary outcome was Visual Analogue Scale (VAS) pain score at 12, 24, and 48 hours postoperatively. Secondary outcomes were time to first rescue analgesia and cumulative opioid consumption during the first 24 postoperative hours. Between-group comparisons used the independent t-test or Mann-Whitney U test, as appropriate.

Results: Pregabalin produced lower VAS scores than gabapentin at 12 hours (2.18 +/- 0.65 vs 2.65 +/- 0.74; p = 0.034), 24 hours (2.27 +/- 0.66 vs 2.71 +/- 0.63; p = 0.030), and 48 hours (1.90 +/- 0.65 vs 2.36 +/- 0.71; p = 0.033). Time to first rescue analgesia was longer with pregabalin (232.69 +/- 19.88 vs 219.88 +/- 17.81 minutes; p = 0.034), and 24-hour opioid consumption was lower (240 [145] vs 360 [155] micrograms fentanyl equivalent; p = 0.034). No adverse hemodynamic.

Conclusion: Preoperative oral pregabalin 150 mg provided statistically superior analgesia and reduced opioid consumption compared with gabapentin 900 mg after MRM. However, the absolute differences in pain scores and rescue-analgesia time were modest; therefore, safety monitoring and larger studies are warranted

Keywords: Analgesia; Gabapentin; Mastectomy, Modified radical; Postoperative pain; Pregabalin.

Introduction

Postoperative pain is common after breast-cancer surgery and remains clinically important after modified radical mastectomy (MRM). The prevalence of post-mastectomy pain has been reported to range from 25% to 60% among women undergoing the procedure.[1] Recent evidence on pain after mastectomy has shown that approximately 68.9% of women experience moderate-to-severe acute postoperative pain, while 22.1% develop subacute pain.[2] These findings indicate a substantial

postoperative pain burden and highlight the need for effective preemptive analgesic strategies in breast surgery.

The pathophysiology of postoperative pain involves complex interactions between the immune and nervous systems, leading to peripheral and central sensitization. In mastectomy, neuropathic pain may occur due to injury to the intercostobrachial nerve or smaller peripheral branches in the axillary region, causing sensory disturbance and persistent pain. Because MRM-related pain has both nociceptive and neuropathic components, optimal analgesic management is essential to prevent pain chronification and enhance postoperative recovery.[3]

Gabapentinoids, particularly pregabalin and gabapentin, are commonly used as preemptive analgesic agents because they attenuate central sensitization by modulating calcium channel activity at the $\alpha_2\delta$ subunit. Although both drugs share a similar mechanism of action, their pharmacokinetic differences may influence clinical efficacy.[4] Meta-analyses have shown that both agents can reduce postoperative pain and opioid consumption.[5] However, direct comparative evidence between pregabalin and gabapentin in patients undergoing MRM remains limited, particularly in Indonesia.[6]

Therefore, this study aimed to evaluate the comparative efficacy of preoperative oral pregabalin 150 mg and gabapentin 900 mg in patients undergoing MRM. The evaluated outcomes included postoperative pain intensity measured using visual analogue scale (VAS) at 12, 24, and 48 hours after surgery, time to first rescue analgesia, and total opioid consumption within the first 24 postoperative hours.

Patients and Methods

This double-blind randomized controlled trial was conducted at Ngoerah Hospital, Denpasar, Bali, Indonesia, between August and October 2025. Ethical approval was obtained from the Health Research Ethics Committee of Universitas Udayana Faculty of Medicine/Ngoerah Hospital (approval number: 1423/UN14.2.2.VII.14/LT/2025). Written informed consent was obtained from all participants before enrollment.

The target population consisted of patients scheduled for elective MRM under general anesthesia. Participants were recruited consecutively according to predefined eligibility criteria. The inclusion criteria were female patients aged 30–65 years, American Society of Anesthesiologists (ASA) physical status I–II, and body mass index (BMI) of 18–30 kg/m². Patients with chronic pain disorders, current anticonvulsant or antidepressant use, hepatic or renal impairment, or a history of allergy to the study drugs were excluded.

The sample size was calculated using the formula for comparison of two independent means, with a two-sided alpha of 0.05 ($Z\alpha$ = 1.96) and 90% power ($Z\beta$ = 1.28). Calculations were based on postoperative VAS scores, time to first rescue analgesia, and total postoperative opioid consumption. The estimated sample sizes were 16, 3, and 19 participants per group, respectively. The largest estimate was selected as the basis for sample size determination. After accounting for an anticipated 10% dropout rate, the minimum required sample size was 21 participants per group, resulting in 42 participants in total.

Randomization was performed using a computer-generated random number table by an independent statistician. Allocation

concealment was maintained using sequentially numbered, sealed, opaque envelopes. The randomization list was kept by an independent hospital pharmacist and remained inaccessible to the recruiting investigators, anesthesiologists, and outcome assessors throughout the study.

Pregabalin and gabapentin were prepared by the hospital pharmacist through over-encapsulation into identical opaque gelatin capsules. Therefore, the study drugs were indistinguishable to participants, anesthesiologists, and outcome assessors. The randomization code could only be broken in the event of a severe allergic reaction or other clinical emergency requiring immediate drug identification.

Both study drugs were administered orally with a small amount of water two hours before anesthesia induction. Group P1 received gabapentin 900 mg, while Group P2 received pregabalin 150 mg. All patients underwent standardized general anesthesia consisting of preoxygenation, propofol induction, sevoflurane maintenance in an oxygen–air mixture, and muscle relaxation with atracurium. Intraoperative analgesia was provided using fentanyl 2 μg/kg, followed by standard postoperative care in the recovery unit.

Postoperative pain intensity was assessed using the VAS at 12, 24, and 48 hours after surgery. All participants received intravenous paracetamol 1 g every 8 hours and intravenous ketorolac 30 mg every 8 hours as scheduled analgesia. Time to first rescue analgesia was defined as the interval from the end of surgery to the first request for supplemental analgesia. Rescue analgesia was administered as intravenous ketorolac 30 mg. Total opioid consumption during the first 24 postoperative hours was calculated in micrograms of fentanyl equivalents. All outcomes were assessed by trained blinded assessors.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 29.0 (IBM Corp., Armonk, NY, USA). Data distribution was assessed using the Shapiro–Wilk test. Normally distributed continuous variables were presented as mean ± standard deviation, while non-normally distributed variables were presented as median and interquartile range. Between-group comparisons were performed using the independent-samples t-test, Mann–Whitney U test, Chi-square test, or Fisher's exact test, as appropriate. A p-value of <0.05 was considered statistically significant.

Results

A total of 42 eligible patients were included and randomly allocated into two equal groups, with 21 patients in each group. All participants completed the study according to the protocol, with no dropouts or protocol deviations. Baseline demographic and clinical characteristics, including age, BMI, and ASA physical status, were comparable between groups, with no significant intergroup differences ($p > 0.05$) (Table 1).

Postoperative VAS scores were significantly lower in the pregabalin group than in the gabapentin group at 12 hours (2.18 ± 0.65 vs 2.65 ± 0.74), 24 hours (2.27 ± 0.66 vs 2.71 ± 0.63), and 48 hours (1.90 ± 0.65 vs 2.36 ± 0.71) after surgery (all $p <0.05$) (Table 2). This finding indicates superior postoperative analgesic control in the pregabalin group, with pain levels progressively declining over time in both groups, though more

pronounced in the pregabalin cohort. The mean trend of postoperative pain reduction in both groups is presented in Figure 1, illustrating the consistently lower VAS scores among patients treated with pregabalin.

The time to first rescue analgesia was significantly longer in the pregabalin group than in the gabapentin group (232.69 ± 19.88 vs 219.88 ± 17.81 minutes; p = 0.034) (Table 3). Total opioid consumption during the first 24 postoperative hours was also significantly lower in the pregabalin group than in the gabapentin group (240 [145] µg vs 360 [155] µg fentanyl equivalent; p = 0.034) (Table 4). This reduction reflects the opioid-sparing effect of pregabalin when used as a preemptive analgesic adjunct.

Table 1. Demographic Characteristics

Characteristics	Preemptive Analgesia						p-value
	Gabapentin 900 mg (n = 21)			Pregabalin 150 mg (n = 21)			
	N,%	Average	SD	N,%	Average	SD	
Age (year)		51.75	7.27		50.43	8.46	0.434*)
ASA							
I	1 (4.8)			3 (14.3)			0.757**)
II	20 (95.2)			18 (85.7)			
BMI (kg/m^2)		23.21	3.56		23.54	3.44	0.108*)

*) Independent t-Test; **) chi-square test; ASA: American Society of Anesthesiologists physical status classification; BMI: body mass index

Table 2. Comparison of Postoperative VAS scores

Time after surgery	Preemptive Analgesia				p-value
	Gabapentin 900 mg (n = 21)		Pregabalin 150 mg (n = 21)		
	Average	SD	Average	SD	
12 hours	2.65	0.74	2.18	0.65	0.034*)
24 hours	2.71	0.63	2.27	0.66	0.030*)
48 hours	2.36	0.71	1.90	0.65	0.033*)

*) Independent t-Test

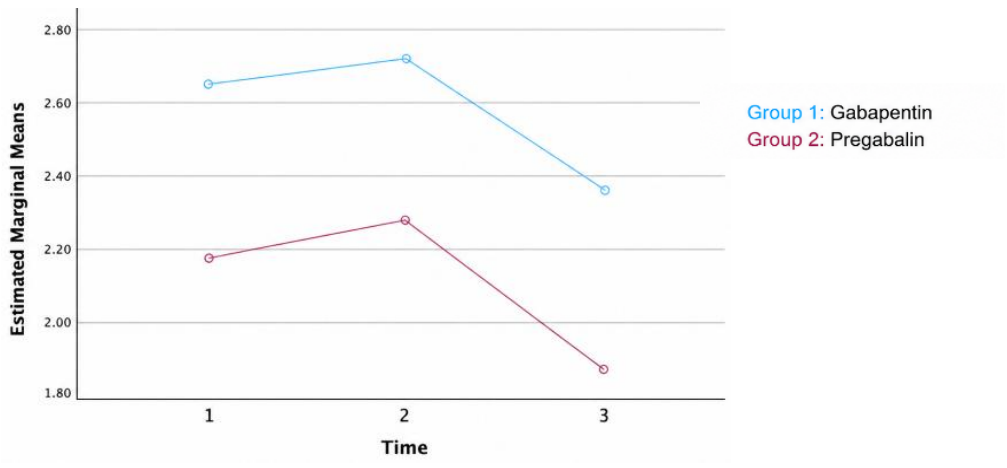

Figure 1. Visual Analog Scale (VAS) scores at 12, 24, and 48 hours postoperatively between the two groups.

Overall, the pregabalin group showed better analgesic efficacy, longer duration of analgesia, and reduced postoperative opioid requirements compared to the gabapentin group, without any reported adverse hemodynamic events.

Discussion

This study showed that preoperative oral pregabalin 150 mg provided better postoperative analgesic outcomes than gabapentin 900 mg in patients undergoing MRM. Patients who received pregabalin had lower postoperative VAS scores at 12, 24, and 48 hours, a longer time to first rescue analgesia, and lower opioid consumption during the first 24 postoperative hours. These findings suggest that pregabalin may be more effective than gabapentin as a preemptive analgesic adjunct in this surgical population.

The lower postoperative pain scores in the pregabalin group may be explained by the pharmacologic properties of gabapentinoids. These agents bind to the $\alpha_2\delta$ subunit of presynaptic voltage-gated calcium channels, reducing calcium influx and suppressing the release of excitatory neurotransmitters such as glutamate, norepinephrine, and substance P.[7] This mechanism decreases neuronal hyperexcitability in the dorsal horn and attenuates central sensitization, which is particularly relevant in MRM because postoperative pain may involve both nociceptive and neuropathic components. Compared with gabapentin, pregabalin has greater $\alpha_2\delta$-subunit affinity, more predictable absorption, higher bioavailability, and a more rapid onset of action, which may contribute to more consistent analgesic effects.[1,5]

The present findings are consistent with previous evidence showing that preemptive gabapentinoids can reduce postoperative pain and analgesic requirements across several surgical settings.[8,9] In breast surgery, pregabalin has also been associated with reduced acute postoperative pain and improved analgesic outcomes.

Table 3. Comparison of Total Opioid Consumption

Variable	Preemptive Analgesia				p-value
	Gabapentin 900 mg (n = 21)		Pregabalin 150 mg (n = 21)		
	Median	IQR	Median	IQR	
Fentanyl (μg)	360	155	240	145	0.034*)

*) Mann-Whitney U test

Table 4. Comparison of Time to First Rescue Analgesia

Variable	Preemptive Analgesia				p-value
	Gabapentin 900 mg (n = 21)		Pregabalin 150 mg (n = 21)		
	Average	SD	Average	SD	
Time (minutes)	219.88	17.81	232.69	19.88	0.034*)

*) Independent T-test

These findings support the role of pregabalin as part of multimodal analgesia, particularly in procedures associated with moderate-to-severe postoperative pain and potential neuropathic mechanisms.

The longer time to first rescue analgesia in the pregabalin group suggests a more sustained analgesic effect. Pregabalin has linear pharmacokinetics and high bioavailability of approximately 90%, resulting in more predictable plasma concentrations.[10,11] In contrast, gabapentin has saturable intestinal absorption at higher doses, which may lead to more variable clinical effects. This pharmacokinetic difference may explain why pregabalin produced a longer duration of analgesia despite both drugs acting through a similar mechanism.[12]

The prolonged analgesic duration observed in this study corresponds with how pregabalin reduces the hyperexcitability of neuronal membranes and delays the recurrence of nociceptive transmission following tissue injury. Inhibition of calcium channel–mediated neurotransmitter release leads to decreased sensitization of pain pathways, prolonging the analgesic effect beyond the early postoperative phase.[13]

Total opioid requirement during the first 24 postoperative hours was significantly lower in the pregabalin group than in the gabapentin group, indicating a stronger opioid-sparing effect of pregabalin. Pregabalin reduces the central sensitization that amplifies pain signaling and indirectly minimizes opioid requirements. Jiang et al. (2018) also found that gabapentinoids, when used as preemptive analgesics, effectively decreased total perioperative opioid consumption.

The reduction in opioid use is clinically important because it reduces the incidence of opioid-related side effects such as nausea, vomiting, sedation, and respiratory depression. The findings align with Routray et al. (2018) and Khetarpal et al. (2016), who reported that pregabalin use led to better postoperative pain relief with fewer opioid-related complications. Additionally, a recent study supported that preoperative pregabalin minimized opioid dependency and improved recovery quality.[14,15]

Pregabalin and gabapentin are GABA analogues in terms of structure; however, their pharmacologic effects are not mediated through direct interaction with GABA receptors. Their primary mechanism involves binding to the $\alpha_2\delta$ subunit of voltage-gated calcium channels, thereby suppressing neurotransmitter release and decreasing neuronal excitability. Pregabalin's stronger receptor affinity enhances its ability to prevent central sensitization and postoperative hyperalgesia. Moreover, Chincholkar (2020) described that gabapentinoids stabilize neuronal membranes and inhibit ectopic discharge from injured nerves, contributing to their analgesic and antihyperalgesic properties.[7]

The results of this study are consistent with Routray et al. (2018), which concluded that pregabalin administration before surgery significantly reduced postoperative pain intensity and opioid requirements compared with gabapentin. Khetarpal et al. (2016) also reported that pregabalin was more effective in providing postoperative analgesia in patients undergoing abdominal surgery. Likewise, Hetta et al. (2016) demonstrated similar findings in gynecologic surgery, where pregabalin resulted in lower pain scores and fewer analgesic demands.[6,14,15]

Furthermore, Jiang et al. (2018) found that pregabalin provided prolonged analgesia and a greater reduction in opioid consumption compared to gabapentin, supporting the analgesic superiority of pregabalin. These consistent results across multiple studies validate the effectiveness of pregabalin as a preemptive analgesic in various surgical populations, including breast, gynecologic, and orthopedic surgery.[16]

From a clinical perspective, preoperative pregabalin offers several advantages: effective pain reduction, prolonged analgesia, and lower opioid use, which together contribute to improved patient satisfaction and recovery. These findings are in line with multimodal analgesic concepts that emphasize opioid-sparing approaches to reduce postoperative complications and enhance early mobilization.[17] The current study supports incorporating pregabalin into multimodal pain management strategies for surgeries associated with moderate to severe postoperative pain.

Although the differences in VAS scores between groups were statistically significant, the absolute magnitude of these differences (approximately 0.4–0.5 points on a 0–10 scale) was relatively small and may fall below the minimal clinically important difference (MCID) commonly reported for acute postoperative pain, which ranges from approximately 1.0 to 1.3 points. This suggests that while pregabalin demonstrated statistically superior analgesic control compared with gabapentin, the clinical relevance of this difference for individual patient comfort may be modest. The more clinically meaningful findings of this study may instead lie in the secondary outcomes, namely the prolonged time to first rescue analgesia and the reduction in total opioid consumption, both of which carry direct implications for opioid-sparing strategies and recovery quality. Nevertheless, the absolute difference in time to first rescue analgesia (approximately 13 minutes) was itself relatively modest, and although statistically significant, its practical impact on patient comfort or clinical decision-making may be limited. Similarly, the magnitude of opioid-sparing observed should be interpreted with caution given the modest absolute difference in consumption between groups.

This study has several noteworthy limitations. The modest sample size (21 patients per group) and single-center setting may limit the statistical power to detect smaller treatment effects and reduce the generalizability. Furthermore, although statistically significant, the absolute differences observed in VAS scores and time to first rescue analgesia were relatively modest in clinical terms, and these results should therefore be interpreted with caution rather than as definitive evidence of clinical superiority. This study also did not assess chronic postsurgical pain or broader quality-of-recovery outcomes, both of which are clinically relevant endpoints following mastectomy and warrant evaluation in future studies with longer follow-up. In addition, serum concentrations of the investigated drugs were not evaluated, and adverse effects such as dizziness and somnolence were not systematically documented. The findings of this study may also have limited applicability to centers that routinely employ regional analgesic techniques (e.g., paravertebral or pectoral nerve blocks) or opioid-free anesthesia strategies for modified radical mastectomy, as the comparative benefit of gabapentinoids in

such settings remains unclear. Therefore, further multicenter studies involving larger populations, longer follow-up duration, and comparison across different anesthetic and analgesic protocols are needed to confirm these results and clarify the broader clinical applicability of pregabalin as a preemptive analgesic.

Conclusion

Preoperative oral pregabalin 150 mg was associated with lower postoperative pain scores, longer time to first rescue analgesia, and reduced opioid consumption compared with gabapentin 900 mg in patients undergoing modified radical mastectomy. These findings suggest that pregabalin may be a useful component of multimodal analgesia for postoperative pain management in this surgical population. However, given the modest absolute differences in pain scores and rescue analgesia timing, its clinical benefit should be interpreted with caution.

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Conflict of Interest

The author(s) report no conflict of interest.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author's Contributions

Conceptualisation: Y.J.P, M.S.P.A. Methodology: Y.J.P, I.P.P.S, I.P.K. Investigation: I.P.P.S, M.S.P.A. Data curation: Y.J.P, I.P.P.S. Formal analysis: Y.J.P. Writing – original draft: Y.J.P. Writing – review & editing: Y.J.P, M.S.P.A. Supervision: I.P.P.S, I.P.K. All authors approved the final manuscript.

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