Original Article

The Possible Preventive Role of Pregabalin in Postmastectomy Pain Syndrome: A Double-Blinded Randomized Controlled Trial

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Abstract

Context. Chronic postmastectomy pain syndrome (PMPS) has a considerable negative impact on the quality of life of breast cancer patients.

Objective. The objective of this study was to assess the possible preventive role of perioperative pregabalin in PMPS.

Methods. This randomized controlled study included 200 patients with breast cancer scheduled for elective breast cancer surgery. They were randomly assigned to one of two treatment groups. The pregabalin group received 75 mg of pregabalin twice daily for seven days and the control group received oral equivalent placebo capsules. The primary outcome was development of neuropathic PMPS. Neuropathic pain was assessed using the Grading System for Neuropathic Pain. Secondary outcome measures were safety and Visual Analogue Scale scores.

Results. Neuropathic pain was significantly less frequent in the pregabalin group compared to the control group at four weeks ($P = 0.005$), 12 weeks ($P = 0.002$), and 24 weeks ($P < 0.001$) postoperatively. PMPS was diagnosed in 11 patients (11%) of the pregabalin group and 29 patients (29%) of the control group ($P < 0.001$, relative risk: 0.26, 95% CI: 0.12−0.56). At the three follow-up time points, Visual Analogue Scale scores during the first three postoperative weeks were comparable in both groups while they were significantly lower in the pregabalin group at 4, 12, and 24 weeks. These two groups were comparable in the frequency of adverse events ($P = 0.552$).

Conclusion. Perioperative oral pregabalin 75 mg twice daily, starting at the morning of surgery and continued for one week, could reduce the frequency of postmastectomy pain syndrome. J Pain Symptom Manage 2019;57:1−9. © *2018 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words

Postmastectomy pain syndrome, pregabalin, grading system for neuropathic pain, VAS score

Introduction

One of the significant postsurgical complications that have a considerable negative impact on the quality of life of breast cancer patients is the chronic postmastectomy pain syndrome (PMPS). It is a chronic postsurgical neuropathic pain that follows breast cancer procedures, in the absence of evident infection or tumor recurrence and lasting more than three months after surgery.[1,2] The delineation between acute and chronic postsurgical pain ranges from two to three months up to one year. The International Association for Study of Pain defined the chronic pain as that persists beyond the usual time of healing.[3]

The prevalence of PMPS is exceedingly variable ranging from 10% to 40%.[4−6] The underlying

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pathophysiological mechanisms of PMPS are highly complicated and entangle both peripheral and central sensitization.[7] It is mainly a result of injury to the peripheral nerves in the axilla or the chest wall during the dissection of axillary lymph nodes.[4] Other neuropathic PMPS could be due to paraneoplastic syndromes, complex regional pain syndrome, chemotherapy-induced neuropathy or radiation plexopathy, and lymphedema.[8]

Different pharmacological tools have been in use for either prevention or treatment of such refractory pain syndrome with variable efficacy. Anticonvulsants such as gabapentinoids have been evaluated to treat both acute and chronic PMPS with proven effectiveness.[9, 10] Pregabalin is an orally administered gamma-aminobutyric acid analog that has similar pharmacology to its prodrug gabapentin and has anticonvulsant, anxiolytic, analgesic, and sleep-modifying action.[11] Its efficacy has been proven in many neuropathic pain syndromes such as diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia.[12, 13]

The rationale of this study was to assess the efficacy of the early perioperative use of pregabalin on the incidence of PMPS within six months of follow-up.

Patients and Methods

This parallel-group double-blind, randomized controlled trial was conducted in the National Cancer Institute, Cairo University, Cairo, Egypt, during the period from December 2015 to March 2017. The study adopted the principles of the Declaration of Helsinki and following the Medical Research Involving Human Subjects Act (WMO) and was approved by institutional review board (no: 201516004.2) and registered at the Pan African Clinical Trials Registry, PACTR201705002266194. The purpose of the study was explained in clear Arabic to all participants before enrollment into the study, and an informed consent form was signed by and obtained from all of those enrolled.

We recruited patients eligible for elective breast cancer surgery (either modified radical mastectomy or conservative breast surgery) combined with axillary dissection attending the center at age 18−60 years and American Society of Anesthesiologists physical status I, II, or III.

Exclusion criteria included 1) history of allergy to pregabalin, gabapentin, NSAIDs, or morphine; 2) pregnancy or lactation; 3) morbid obesity or major medical disorders; 4) patients with preexisting pain that necessitates morphine at a daily dose of 30 mg or more (or equivalent opioids); 5) history of pregabalin or gabapentin intake in the preceding three months; 6) history of drug abuse; 7) expected another breast surgery in the subsequent period; and 8) neuropsychiatric disorders.

Randomization and Blinding

A computer-generated random numbers list was used for the allocation of the participants. Block randomization with a block size of 4 was used with 1:1 ratio of pregabalin and control groups. The allocation sequence was concealed from the researchers enrolling and assessing participants. Participants were randomly allocated to the pregabalin group and the control group. The pregabalin group received pregabalin (Lyrica, Pfizer, NY) 75 mg with a sip of water one hour before induction of anesthesia and repeated 12 hourly for seven days. The control group received placebo capsules at the same time points with the same steps. Both pregabalin and placebo capsules were supplied to patients by nurses blinded to the study. Neither the researcher allocating the participants nor the assessing person knew the decoding of the groups in its relation to the allocation sequence. Data were collected by a junior pain resident blinded to the study protocol.

Procedures

The same procedures were applied to all patients. Standard monitors were applied to the patients. Midazolam (preoperative sedation) 0.02 mg/kg IV then propofol 1.5−2 mg/kg, fentanyl 2−3 μg/kg, and atracurium 0.5 mg/kg IV were given for induction of general anesthesia. All patients received paracetamol 1 gm by IV drip, ketorolac 30 mg IV drip, and morphine sulfate 0.1 mg/kg. Anesthesia was maintained by sevoflurane 2%−3% in O_2/air mixture with reinjection of atracurium 0.1 mg/kg every 30 minutes. After extubation and recovery, the patients were transferred to the postanesthesia care unit, and when they fulfilled discharge criteria, they were transferred to ordinary wards. Postoperative analgesia was scheduled to keep the patient Visual Analogue Scale (VAS) <40 mm using patient-controlled analgesia during hospitalization period as follows: a disposable silicon balloon pump (Accufuser) was used. It contained morphine 0.2 mg/mL, 8 mg ondansetron, and 180 mg ketorolac. The infusion rate was 5 mL/hour, and the lockout interval was 15 minutes. The hourly delivered morphine dose was 1−1.8 mg, and the pump was sufficient for about 60 hours according to patient response. Additional morphine doses of 3−5 mg IV/IM were available for all patients to ensure good analgesia (VAS < 40 mm). On discharge, pain killers in form of oral/parenteral paracetamol, NSAIDs, and tramadol HCl were prescribed according to patient preference and drugs availability for the rest of the first postoperative week. Patients were evaluated at the follow-up visits 4, 12, and 24 weeks postoperatively. All data were collected by a junior pain clinic physician who was blinded to the study groups.

Outcome Measures

The primary outcome measure was the proportion of patients who developed neuropathic PMPS at different follow-up times. We defined postmastectomy neuropathic pain as pain involving the anterior aspect of the chest, axilla, and/or upper arm with the classical features of neuropathic pain including numbness, tingling, burning, shooting, stinging, or stabbing pains, and hyperesthesia.[7] If this type of pain persisted continuously or intermittently for more than three months, it was considered PMPS.[14] Neuropathic pain was evaluated according to the Grading System for Neuropathic Pain (GSNP).[15] Positive neuropathic cases are those with GSNP 3 (probable) or GSNP 4 (definite), that is, GSNP ≥3 (Fig. 1). GSNP is as follows: Grade 1 (likely), Grade 2 (possible), Grade 3 (probable), and Grade 4 (definite).

Secondary outcome measures were as follows:

- VAS scores: a horizontal 100 mm version is used with 0 left-end indicating no pain and 100 mm right-end indicating worst imaginable pain. Both dynamic (VAS-D) and at-rest (VAS-R) average daily VAS were measured on Days 1 and 2 (hospital stay period) by the ward nurse. Then, the average daily VAS values were further assessed either by phone or on follow-up visits on Days 3, 4, 5, 6, and 7. The average VAS values at the end of Weeks 2, 3, 4, 12, and 24 were assessed by a junior pain physician who was blinded to the study design.
- Average daily drug consumption
  - During hospital stay: total daily morphine and ketorolac consumption (mg) on Days 1 and 2.
  - After discharge: daily oral paracetamol (g), ketorolac (mg), and tramadol HCl (mg) on Days 3, 4, 5, and 6.
- The frequency of side effects during the period of drug administration including nausea, vomiting, sedation, dizziness, myalgia, myoclonus, asterixis, and blurred vision.

Patients who developed postmastectomy neuropathic pain were treated by pregabalin 75–300 mg/day and amitriptyline 10–25 mg/day. Analgesics such as paracetamol, NSAIDs, tramadol HCl 100–400 mg/day, and oxycodone 20–60 mg/day were added if required according to pain severity.

Sample Size Justification and Statistical Analysis

As there was no study that addressed the same research question in these cases, we calculated the sample size according to a preliminary analysis of the first 60 patients (30 in each group) as a pilot to detect the proportion of PMPS in each group. PMPS affected 10% of the pregabalin group and 30% of the control group. Based on these findings, 82 patients were needed to elicit the difference between groups at an alpha error of 0.05 and a power of 0.9. One hundred patients were recruited in each group to guard for any dropouts.

Statistical analysis was done using IBM© SPSS© Statistics Version 22 (IBM© Corp., Armonk, NY). Numerical data were expressed as mean and SD. Qualitative data were expressed as frequency and percentage.

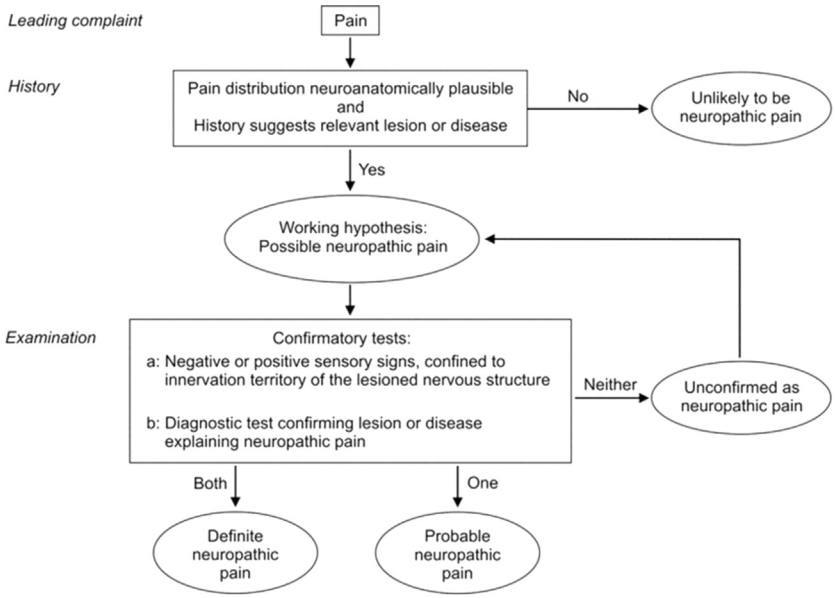

Fig. 1. GSNP flowchart. GSNP = Grading System for Neuropathic Pain.

Chi-square test (Fisher's exact test) was used to examine the relationship between qualitative variables. For quantitative data, the comparison between two groups was made using independent sample t-test or Mann-Whitney test. Relative risk (RR) with 95% CI was used for risk estimation. Study outcomes were evaluated according to the intention-to-treat analysis principle. A *P*-value of < 0.05 was considered significant.

Results

All patients fulfilling the eligibility criteria ($n = 243$) were asked to participate in the study. Thirteen subjects refused to participate, and 30 were excluded for different reasons. Enrolled subjects ($n = 200$) were randomized to the pregabalin group and the control group, 100 in each group. Nineteen patients were lost to follow-up (eight in the pregabalin group: two at the fourth week, three at the 12th week, and three at the 24th week vs. 11 in the control group: three at the fourth week, three at the 12th week, and five at the 24th week). The dispositions of these subjects are shown in Fig. 2.

Baseline Characteristics

Two-hundred patients were included in the intention-to-treat analysis, 100 in each group. At inclusion, there was no statistically significant differences between the two groups regarding the age, ASA-physical status, and type of breast surgery. Besides, there was no significant difference ($P = 0.063$) in the operative duration between both groups and duration of hospital stay (Table 1).

VAS Values and Drug Consumption

VAS values at different follow-up time points during the first three postoperative weeks were comparable in the pregabalin and control groups (although values were lower in the pregabalin group). Similarly, there was no significant difference in drug consumption in the two groups (Tables 2 and 3).

Neuropathic Pain and PMPS

Neuropathic pain was encountered in significantly higher proportion of patients of the control group compared to the pregabalin group at four weeks ($P = 0.005$), 12 weeks ($P = 0.002$), and 24 weeks ($P < 0.001$) postoperatively. PMPS was diagnosed in 11 patients (11%) of the pregabalin group and 29 patients (29%) of the control group ($P < 0.001$, RR: 0.26, 95% CI: 0.12−0.56). At the three follow-up time points, VAS scores were significantly lower in the pregabalin group (Table 4).

Adverse Events

There was no significant difference ($P = 0.552$) between the two groups as regards the frequency of adverse events. Detailed adverse events are shown in Table 5.

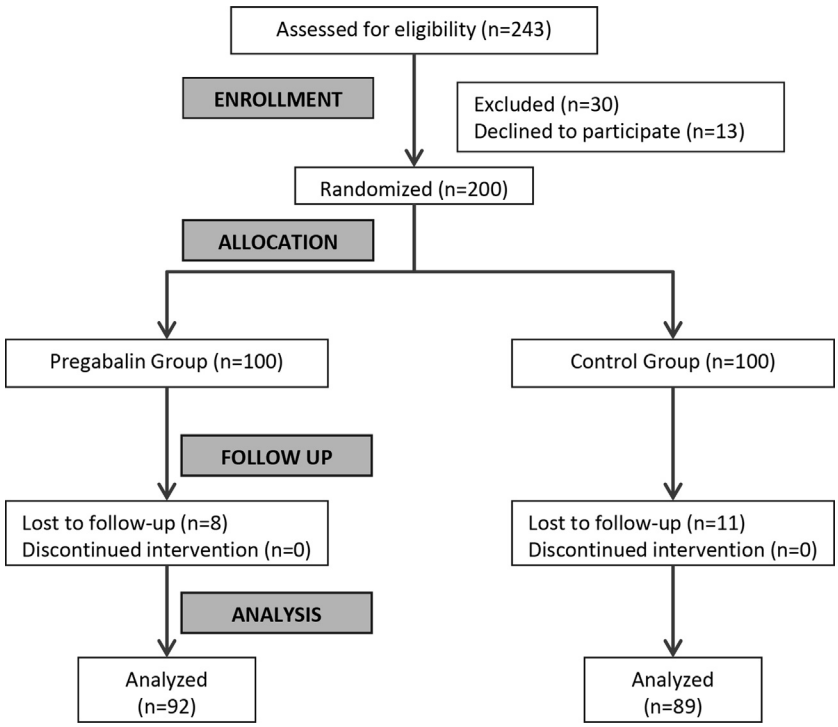

Fig. 2. CONSORT flowchart.

Table 1
Baseline Characteristics

Baseline Characteristics	Pregabalin Group	Control Group	*P*-Value
Intention to Treat sample	$n = 100$	$n = 100$	
Age (yrs)	49.8 ± 11.6	51.0 ± 8.4	0.403
ASA-physical status			
ASA-I	41 (41%)	45 (45%)	0.696
ASA-II	49 (49%)	48 (48%)	
ASA-III	10 (10%)	7 (7%)	
Type of breast surgery			
Modified radical mastectomy	63 (63%)	66 (66%)	0.658
Conservative breast surgery	37 (37%)	34 (34%)	
Duration of surgery (min)	115 ± 25	112 ± 21	0.359
Duration of hospital stay (hours)	57 ± 5.3	61 ± 6	

Data are presented as mean ± SD or no. (%).

Discussion

The present study showed a statistically and clinically significant reduction in the emergence of neuropathic PMPS by using a moderate dose of pregabalin for one week after breast cancer surgery. Pregabalin reduced the risk of PMPS with an RR of 0.26 (95% CI: 0.12−0.56). Generally, pain intensity measured by VAS scores was significantly lower (better analgesia) in the pregabalin group at all time points (4, 12, 24 weeks).

Approximately 10% of patients undergoing different surgical maneuvers are liable to develop chronic postsurgical pain (CPSP), particularly breast surgeries and limb reconstruction procedures.[16] Both anesthetic and surgical techniques could be modified to reduce the prevalence of early as well as chronic postsurgical pain through using evidence-based programs of the so-called "preventative analgesia."[4, 16, 17] The incidence is much higher after procedures with significant nerve damage or transection like amputation (50%−80%), mastectomy (20%−40%), and thoracotomy (30%−50%).[4, 5, 18] Neuropathic pain is characteristic of PMPS and usually presents as shooting, burning, dull aching, or dysesthetic character in the surgical scar, chest wall, upper arm, shoulder, axilla, as well as phantom breast dysesthesia and paresthesia.[7]

Several drugs, particularly anticonvulsants and antidepressants used originally as adjuvants in WHO step ladder analgesic system, are now implemented as cardinal components of multimodal analgesia for postoperative pain and infective[19] or traumatic[20] neuropathies.

Recently, a revised consensus statement from the Canadian Pain Society has recommended preventive analgesic standards based on evidence base−related efficacy, safety, and ease of use. Gabapentinoids including pregabalin, tricyclic antidepressant, and selective serotonin reuptake inhibitors are classified as first-line treatment for chronic postsurgical neuropathic syndromes.[18, 21, 22] The preventive analgesic role of gabapentinoid and pregabalin has been extended to include similar neuropathic pain states such as postspinal cord injury, post-traumatic peripheral neuropathy,[20] and failed back surgery syndrome.[23] The growing indications of gabapentinoids including pregabalin in this aspect are attributed to their role in central sensitization processes in all pain stages.[21]

In the current work, pregabalin 75 mg has been given one hour before induction of anesthesia to get peak plasma level during the period of surgery.[24] Perioperative pregabalin dosage is still a conflicting issue, whether lower dosage 75−150 mg/day[25] that was preferred in our work or higher regimen tried by other researchers.[24] The authors selected the average dose regimen (150 mg/day) for fear of patients' intolerance of drug side effects in the early postoperative

Table 2
Average VAS Values in the First Three Weeks in Both Groups

	Pregabalin Group		Control Group		*P*-Value	
	$n = 100$		$n = 100$			
ITT Sample	VAS-R	VAS-D	VAS-R	VAS-D	VAS-R	VAS-D
Assessment points						
Day 1	33 ± 17	35 ± 13	35 ± 19	37 ± 17	0.216	0.17
Day 2	30 ± 15	31 ± 11	33 ± 16	33 ± 15	0.086	0.14
Day 3	27 ± 11	29 ± 13	28 ± 13	30 ± 16	0.121	0.31
Day 4	25 ± 10	24 ± 12	27 ± 14	27 ± 15	0.123	0.06
Day 5	21 ± 11	23 ± 11	23 ± 13	25 ± 11	0.121	0.10
Day 6	18 ± 10	20 ± 9	20 ± 11	22 ± 13	0.090	0.10
Day 7	17 ± 11	17 ± 8	19 ± 11	23 ± 11	0.100	>0.99
Week 2	23 ± 17		24 ± 13			0.32
Week 3	24 ± 15		27 ± 17			0.09

VAS = Visual Analogue Scale.
Data are represented as mean ± SD. *P*-value <0.05 is considered statistically significant.

Table 3
Daily Drugs Consumption

ITT sample	Pregabalin Group $n = 100$	Control Group $n = 100$	*P*-Value
Morphine (mg)			
Day 1	9.7 ± 3.8	11.2 ± 4.1	0.99
Day 2	8.4 ± 2.7	8.8 ± 3.5	0.82
Ketorolac (mg)			
Day 1	29.1 ± 11.4	33.6 ± 12.3	0.99
Day 2	25.2 ± 8.1	26.4 ± 10.5	0.82
Day 3	22 ± 12	26 ± 12	0.99
Day 4	16 ± 11	18 ± 11	0.90
Day 5	13 ± 12	14 ± 11	0.73
Day 6	10 ± 11	12 ± 10	0.91
Tramadol HCl (mg)			
Day 3	180 ± 57	220 ± 58	>0.99
Day 4	170 ± 53	190 ± 55	0.99
Day 5	145 ± 52	160 ± 53	0.98
Day 6	116 ± 50	128 ± 52	0.95
Paracetamol (g)			
Day 3	1.2 ± 0.5	1.4 ± 0.6	0.99
Day 4	0.9 ± 0.5	1.2 ± 0.5	0.99
Day 5	0.8 ± 0.5	0.9 ± 0.5	0.92
Day 6	0.5 ± 0.5	0.6 ± 0.5	0.92

Data are represented as mean ± SD. *P*-value <0.05 is considered statistically significant.

period, namely confusion and sedation that may result in early patients' discontinuation of the drug. Our concept of using an average daily dose of pregabalin 150 mg coincides with the results of Hetta et al.[9] The sole affinity of pregabalin to N-type calcium channels that reduce sensitization of pain and the lack of its affinity to L-type calcium channels of blood vessels and the heart[26] make it a suitable anticonvulsant for the operative scenario. In our work, pregabalin is given for seven days to cover the postoperative hyperexcitability and excitatory neuroplasticity of the dorsal horn neurons that persist for five to six days after surgery.[27]

In the current work, pregabalin efficacy in reducing the incidence of PMPS was proved, together with a significant reduction of VAS in the follow-up period after breast cancer surgery for up to six months. Our results coincide with the work of Buvanendran et al.[28] who found that the occurrence of chronic pain was less common in the pregabalin group than in the control group. However, they used the high pregabalin dose of 300 mg on the morning of knee surgery followed by 150 mg twice daily for 10 days, then 50 mg twice daily for four days. Hetta et al.[9] had stratified that pregabalin in a daily dose of 150 mg was necessary to obtain analgesia after mastectomy. Pregabalin benefits were settled in other works[18,21,23,25,29] but doubted in other trial and meta-analysis.[30,31]

Our results of pregabalin efficacy in PMPS after breast cancer surgery are comparable with those in other previous studies.[6] There were positive results of the use of gabapentin in controlling acute postmastectomy pain. If used in sufficient doses and for enough time, it might reduce PMPS.[18] The role of gabapentinoids and pregabalin in controlling acute postmastectomy pain (together with acute postsurgical pain), especially the severe form, is proven to reduce the emergence of both nociceptive and neuropathic components of postsurgical pain.[10]

According to Eipe et al.,[32] the emergence of CPSP is related to the type of surgery and the extent of tissue damage. Mastectomies may be linked with pronociceptive mechanisms (axillary dissection and nerve injury lead to acute hyperalgesia and neuropathic pain, i.e., Model 1).[32] The risk of CPSP after breast cancer surgical trauma was higher among patients being of younger age and underwent axillary lymph node dissection, that is, Model 1.[32,33] It has been postulated that preoperative pain and poorly controlled postoperative pain (during the first 72 hours after surgery) are predominant risk criteria for emerging CPSP, that is, pain predicts pain.[34–36] Hence, proper control of acute postoperative pain, especially in the first 24 hours after surgery, is of utmost importance and every 10% increase in the period of acute postoperative pain may be associated with CPSP up to 30%.[37,38]

Table 4
Visual Analogue Scale Score and Proportion of Patients With Neuropathic Pain and PMPS During Follow-Up Visits in the Two Studied Groups

ITT sample	Pregabalin Group $n = 100$	Control Group $n = 100$	*P*-Value	RR (95% CI)
Visual Analogue Score				
Four weeks	29 ± 14	35 ± 14	0.001	
Twelve weeks	25 ± 12	34 ± 14	0.007	
Twenty-four weeks	27 ± 18	35 ± 21	0.002	
Probable neuropathic pain on GSNP ≥ Grade 3				
Four weeks	15 (15%)	32 (32%)	0.005	0.38 (0.19–0.75)
Twelve weeks	14 (14%)	32 (32%)	0.002	0.35 (0.17–0.70)
Twenty-four weeks	13 (13%)	35 (35%)	<0.001	0.28 (0.14–0.57)
PMPS at 12 weeks	11 (11%)	29 (29%)	<0.001	0.26 (0.12–0.56)

PMPS = postmastectomy pain syndrome; RR = relative risk; GSNP = Grading System for Neuropathic Pain.

Table 5
Adverse Events in the Two Studied Groups

Adverse Events	Pregabalin Group $n = 100$	Control Group $n = 100$	*P*-Value
Sedation	3 (3%)	1 (1%)	0.621
Nausea and vomiting	2 (2%)	3 (3%)	1.000
Myalgia	2 (2%)	1 (1%)	1.000
Dizziness	1 (1%)	3 (3%)	0.621
Blurred vision	1 (1%)	0 (0%)	1.000
Total no. of patients with adverse events	7 (7%)	5 (5%)	0.552

Persistent and severe postsurgical pain necessitates the use of analgesics including opioids which in turn enhance the risk of developing chronic pain.[39] This could be explained by—together with severe tissue trauma and nerve injury accompanying severe persistent postsurgical pain—opioid-induced hyperalgesia especially with high doses and prolonged use.[40–42] The release of chemokines, procytokines, and neutrophils due to pain and inflammation of surgical trauma accounts for peripheral and central sensitization with hyperalgesia, hyperpathia, and allodynia. Secondary hyperalgesia that precedes central sensitization is of cardinal participation in chronic pain development, and analgesics including opioids are of little value in its treatment and thence prevention of CPSP.[39]

The results of previous trials regarding the role of gabapentinoids and pregabalin in reducing PMPS emergence are inconclusive whether beneficial[18,32,43] or not.[44] An interesting meta-analysis was published by Rai et al.[44] They concluded that gabapentin (and to a less extent pregabalin) is efficient for acute postoperative analgesia and opioid sparing. However, their role in preventing CPSP is inconclusive. A paramount limitation of this meta-analysis is the limited sample size (only 12 RCTs: eight for gabapentin and four regarding pregabalin).

Furthermore, many cardinal differences exist between the current work and the work by Rai et al. First, we relied on multimodal analgesia for both in-hospital (patient-controlled analgesia) and postdischarge analgesia. Second, the duration of pregabalin therapy was extended to cover the whole first perioperative week to overcome dorsal root ganglia neuroplasticity (this was considered only in 2/4 of pregabalin RCTs and 2/8 of gabapentin RCTs). In addition, the authors in this trial ensured good control of acute postoperative pain (VAS $\leq$ 40 mm) to nullify its impact on CPSP transition. In addition, surgical interventions were different (axillary dissection plus modified radical mastectomy or reconstructive surgery in this work vs. lumpectomy and mastectomy in Rai meta-analysis). Finally, the follow-up period was extended in this study up to 24 weeks versus 12 weeks in Rai meta-analysis. The pregabalin-associated opioid-sparing effect that reduces the probability of opioid-induced hyperalgesia is another reason for different results in the present study.

For estimating the emergence of neuropathic PMPS, we used the GSNP.[15] This system has been developed by neurology and pain experts for both clinical and research purposes. It is based on the fact that identification of neuropathic pain relies on detecting the lesion or disease process of the underlying neuroanatomical peripheral or central somatosensory nervous system. Physical examination for neuropathic findings is mandatory, and level of diagnosis is either probable or definite.[15]

The results of our study showed that both groups were comparable regarding the incidence of sedation, nausea and vomiting, myalgia, dizziness, and blurred vision. In addition, all these adverse effects were self-limited and transient for few hours. It is well known that sedation and dizziness are the most common side effects of pregabalin. However, these side effects occur at the higher dose of pregabalin.[28, 30]

The advantage of this study is being an assessor-blinded randomized controlled trial with enough sample size. Moreover, it offers the benefit of being the first head-to-head comparison using a randomized controlled trial design. Nonetheless, one limitation of the study is that the period of postoperative follow-up needs to be longer, for example, for 12 months, another one is that the outcomes were assessed by a junior pain clinic physician. Finally, we recommend a wide-scale multicenter trials and/or meta-analysis to verify the currently available data. Stratification of guidelines both to prevent and to treat PMPS is required. An explicit algorithm for medical and interventional tools has to be specified.

In conclusion, the perioperative oral use of pregabalin 75 mg twice daily, starting at the morning of surgery and continued for one week, can reduce the emergence of PMPS after breast cancer surgery for six months' follow-up period.

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