Analgesic efficacy of preoperative administration of low-dose pregabalin in patients undergoing breast cancer surgery

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Abstract

Background: Effective acute pain management with modest adverse effects is important to early recovery and mobilization in patients undergoing breast cancer surgery. The pathologic mechanisms include nociceptive and neuropathic pathway. Administration of different types of analgesics may provide synergistic effects to reduce postoperative pain. ***Objectives:*** To investigate the analgesic efficacy and opioid-sparing effects of a single low-dose pregabalin in this patients undergoing breast cancer surgery. ***Methods:*** Thirty-two ASA status I-II patients undergoing modified radical mastectomy or mastectomy with axillary lymph node dissection, were recruited and allocated into 2 groups in this prospective, randomized placebo controlled, double-blind study to either receive oral pregabalin 75 mg or a matching placebo 1 hour before surgery. Postoperative pain (static and dynamic) was assessed by numeric verbal rating scale (NRS) (0 = pain and 10 = worst imaginable pain). NRS scores for pain, patient-controlled morphine consumption and side effects were recorded at postoperative care unit (PACU), 6 hour, 12 hour, 24 hour, and 48 hour after surgery. ***Results:*** Comparing with the placebo group, NRS pain scores at rest were significantly lower in the pregabalin group at 12 hour and 24 hour after surgery (0 vs 1, p=0.019 and 0 vs 1, p=0.013), whereas NRS pain scores on movement were similar. Cumulative patient-controlled morphine consumption and side effects were comparable between both groups. ***Conclusion:*** Preoperative administration of pregabalin 75 mg improved postoperative pain at rest 12 hour and 24 hour after breast cancer surgery without increasing side effects.

Keywords: *pregabalin, postoperative pain, mastectomy, breast cancer*

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ประสิทธิผลของยา pregabalin ขนาดต่ำในการระงับปวดหลังการผ่าตัดมะเร็งเต้านม

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บทคัดย่อ

บทนำ: ความปวดภายหลังการผ่าตัดเต้านมมีสาเหตุจากการบาดเจ็บของเนื้อเยื่อและจากระบบประสาทที่ทำงานผิดปกติ ดังนั้นการที่ผู้ป่วยได้รับยาระงับปวดที่ครอบคลุมทุกสาเหตุ จึงมีความสำคัญอย่างยิ่งสำหรับการระงับปวดที่มีประสิทธิภาพเพื่อให้ผู้ป่วยสามารถฟื้นตัวได้โดยเร็วที่สุด ***วัตถุประสงค์:*** เพื่อศึกษาประสิทธิผลของยา pregabalin ขนาดต่ำ ในการระงับปวดหลังการผ่าตัดมะเร็งเต้านม รวมทั้งศึกษาผลข้างเคียงจากยา ***วิธีการศึกษา:*** เป็นการศึกษาเปรียบเทียบกับกลุ่มควบคุม มีตัวควบคุมแบบปกปิดสองด้านในผู้ป่วยหญิงจำนวน 32 ราย ASA I-II ที่มารับการผ่าตัดรักษามะเร็งเต้านม โดยถูกสุ่มเป็น 2 กลุ่ม คือ กลุ่มทดลองจะได้รับยา pregabalin 75 มก. รับประทาน 1 ชม. ก่อนผ่าตัด และกลุ่มควบคุมได้รับยาหลอก รับประทานแบบเดียวกัน จากนั้นจะมีการประเมินระดับความปวดหลังผ่าตัดโดยใช้ numeric rating scale ปริมาณมอร์ฟีนสะสมที่ได้รับ และผลข้างเคียงจากยา ที่ห้องพักฟื้น ที่ 6 ชม. ที่ 12 ชม. ที่ 24 ชม. และที่ 48 ชม. หลังการผ่าตัด ***ผลการศึกษา:*** กลุ่มทดลองมีระดับความปวดหลังผ่าตัดขณะพักน้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติที่ 12 ชม. และ ที่ 24 ชม. หลังการผ่าตัด (0 vs 1, p=0.019 และ 0 vs 1, p=0.013 ตามลำดับ) ส่วนระดับความปวดขณะเคลื่อนไหว ปริมาณมอร์ฟีนสะสมและผลข้างเคียงไม่ต่างกันทั้ง 2 กลุ่ม ***สรุป:*** การใช้ pregabalin 75 มก. รับประทานก่อนผ่าตัด สามารถลดระดับความปวดหลังผ่าตัดขณะพักได้ โดยไม่เพิ่มอุบัติการณ์ของผลข้างเคียง

คำสำคัญ: *พรีกาบาลิน, การระงับปวดหลังผ่าตัด, การผ่าตัดเต้านม, มะเร็งเต้านม*

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Introduction

The successful pain management following breast cancer surgery remains challenging. The pathologic mechanisms include nerve injury related to surgical technique resulting in different types of sensory disturbances.[1] Nearly 60% of breast surgery patients experienced severe acute postoperative pain.[2] Acute postoperative pain severity, preoperative breast pain, and axillary lymph node dissection are associated with the development of chronic post-mastectomy pain.[3-8] Published studies reported estimates of the prevalence of post-mastectomy pain syndrome range between 10% and 60%, with about 5% to 10% of severe or disabling pain.[1,2,5,6,9]

Multimodal analgesia is the pain management technique, which involves administration of different types of analgesic drugs that may contain synergistic effects to maximize postoperative pain relief and decrease analgesia-related adverse effects. The use of pregabalin combined with other analgesics for improving postoperative pain has been established in a variety of surgical populations.[10-21] Binding of the drug to the presynaptic $\alpha 2\delta$ subunit of voltage-gated calcium channels reduces the release of excitatory neuropeptides.[22,23] This mechanism provides antihyperalgesic and antiallodynic properties by decreasing the hyperexcitability of dorsal horn neurons affected from tissue damage.

Regarding the safety of pregabalin in acute pain management, two recent meta-analyses reported administration of high-dose pregabalin (100-300 mg/day) during perioperative period provided additional analgesia, but at cost of adverse effects such as sedation, dizziness, and visual disturbance.[24,25] It is important to find the lowest optimum dose to avoid the common dose-dependent undesirable effects.[26] However, the evidence to support the role of low-dose pregabalin is limited and inconclusive.[10,13,21,26,28] To our knowledge, there are no studies addressing the analgesic effect of a single low-dose pregabalin to reduce pain after breast cancer surgery. Therefore, this study was designed to evaluate the analgesic efficacy of a single 75 mg of pregabalin given preoperatively in patients undergoing modified radical mastectomy or primary mastectomy with axillary lymph node dissection.

Methods

The study design was approved by the institutional Ethics Committee and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all patients scheduled for modified radical mastectomy or primary mastectomy with axillary lymph node dissection at King Chulalongkorn Memorial Hospital. Eligible criteria were women aged 20-65 years, ASA physical status I-II, and BMI less than 35 kg/m^2. Exclusion criteria included previous breast surgery, reconstructive surgery or bilateral surgery, a history of allergy or contradiction to any of the study medications, severe neurological or psychiatric disorder, alcohol or drug abuse, impaired renal function, pregnancy or lactation, patients with other chronic pain syndromes or current therapy with gabapentinoids or any opioids.

In this prospective, double-blinded placebo controlled trial, patients meeting the inclusion criteria

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during pre-anesthetic assessment randomly allocated into 2 groups by using a computer-generated random number table. According to their assigned study group, patients in the control group received placebo and those in the pregabalin group received 75 mg pregabalin at 1 hour before surgery. To ensure blinding, study medications were prepared in identical capsules, packed and sealed in opaque containers with labeled randomization number by the hospital pharmacy.

During preoperative visit, all patients were trained to rate their pain on a numeric verbal rating scale (NRS) and were instructed to the use of patient-controlled analgesia. No other premedication was given before anesthesia.

All patients received standard anesthesia care in the operating theatre. General anesthesia was induced with propofol 1.5-2 mg/kg, followed by cisatracurium 0.15-0.2 mg/kg to facilitate orotracheal intubation. During the operation, anesthesia was maintained using 50% nitrous oxide in oxygen, desflurane, and intravenous morphine sulfate 0.1 mg/kg. The amount of intravenous agent and volatile agent were titrated by the attending anesthesiologist who was blinded to the randomization. At the end of surgery, residual neuromuscular blockade was antagonized with neostigmine 0.05 mg/kg and atropine 0.02 mg/kg. All patients were transferred to post-anesthesia care unit (PACU) after extubation. The total amount of morphine and propofol were recorded. In the PACU, patient received intravenous morphine via patient-controlled analgesia (PCA) device with patient activated dose of 1 mg, lockout interval of 6 minutes, with 4-hour maximum limit of 30 mg, without basal morphine infusion rate.

Primary outcome was postoperative pain severity. The NRS pain scores (0 = no pain and 10 = worst imaginable pain) were assessed on arrival of the patient to the PACU (0), 6 hour, 12 hour, 24 hour, and 48 hour after operation. The pain was assessed at rest and on movement (mobilization of the ipsilateral arm of surgery). Secondary outcomes were cumulative PCA morphine consumption (recorded at 6 hour, 12 hour, 24 hour, and 48 hour postoperatively) and incidence of adverse effects including postoperative nausea and vomiting (PONV), sedation, respiratory depression, and pruritus. All side effects were assessed by visits of the blind investigator at 0, 6 hour, 12 hour, 24 hour, and 48 hour postoperatively. PONV was assessed by using four-point ordinal scale (0, no nausea or vomiting; 1, mild nausea; 2, moderate nausea; and 3, severe nausea with vomiting). Ondansetron 8 mg was given to PONV of grade >2 as the rescue antiemetic. Levels of sedation were assessed on four-point scale (0, awake; 1, mild sedation; 2 sleepy but arousal; 3, very sleepy). Pruritus were graded on four-point verbal scale (0, no pruritus; 1, mild pruritus; 2, moderate pruritus; and 3, severe pruritus). Respiratory depression was defined as respiratory rate <8 /min and oxygen saturation <90% without oxygen supplementation.

Sample size was calculated on the basis of our preliminary study on the amount of total morphine required in the first 48 hours after breast cancer

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surgery. To reduce opioid requirement for 33% in the treatment group and for the results to be of statistical significance with $\alpha = 0.05$ and $\beta = 0.90$, 12 patients in each group were required. Therefore, we recruited 32 patients to prevent 30% dropouts.

Statistical analysis

Descriptive data were analyzed with unpaired t-test. The NRS pain score, postoperative morphine PCA consumption were analyzed with Mann-Whitney U test. The incidence of side effects was analyzed using Mann-Whitney U-test. Per protocol and intention to treat were used to analyze the missing data. The statistical analysis was performed using the package SPSS 17.0 (SPSS Inc., Chicago, IL, USA). $P<0.05$ was considered statistically significance.

Results

A total 32 of patients were assessed for eligibility and included in this study. However, two patients were later considered dropouts from the study after initial randomization. One patient received additional analgesics apart from the study protocol and the other one refused to take study drugs. Therefore, 30 patients (14 in the placebo group and 16 in the pregabalin group) were included in the final analyses.

Patient demographics and preoperative data were similar between the two groups. Likewise, duration of surgery and the number of patients who underwent modified radical mastectomy versus mastectomy with axillary lymph node dissection among the groups were comparable.

The NRS pain scores during postoperative period are demonstrated in Table 1 and 2. Compared with the placebo group, NRS pain scores at rest were significantly lower in the pregabalin group at 12 hour ($p = 0.019$) and 24 hour postoperatively ($p= 0.013$); however, NRS pain scores on movement were comparable between both groups. Postoperative PCA morphine consumption did not differ between both groups (Table 3). Incidence and severity of PONV and sedation were also similar between the two groups. There was no incidence of respiratory depression or pruritus in this study. The overall patient satisfaction with anesthesia and postoperative pain management was equal in both groups.

Table 1. NRS pain scores at rest

Postoperative period	Placebo (n=14)	Pregabalin (n=16)	P–value
6 hour	2 (0-7)	2 (0-8)	0.75
12 hour	1 (0-7)	0 (0-2)	0.019*
24 hour	1 (0-3)	0 (0-2)	0.013*
48 hour	0 (0-3)	0 (0-1)	0.26

Values are presented as median (min-max). * $P<0.05$

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Table 2. NRS pain scores during movement

Postoperative period	Placebo (n=14)	Pregabalin (n=16)	P–value
PACU	4 (0-10)	7 (0-7)	0.51
6 hour	3.5 (0-10)	4 (0-8)	0.988
12 hour	3 (0-8)	2 (0-6)	0.15
24 hour	1.5 (0-5)	2 (0-10)	0.85
48 hour	0 (0-7)	0 (0-2)	0.73

Values are presented as median (min-max).

Table 3. Post-operative cumulative morphine PCA consumption (mg)

Postoperative period	Placebo (n=14)	Pregabalin (n=16)	P–value
6 hour	4 (0-10)	4 (0-15)	0.265
12 hour	5 (0-12)	5.5 (0-16)	0.466
24 hour	8.5 (0-23)	6 (0-30)	0.203
48 hour	9.5 (0-43)	6 (0-30)	0.159

Values are presented as median (min-max).

Discussion

We observed that multimodal analgesia of preoperative single-dose of pregabalin 75 mg provided superior analgesia on pain at rest over the placebo group at 12 and 24 hour postoperatively without significant opioid-sparing effects following breast cancer surgery or increasing side effects. Nevertheless, the above-mentioned analgesic benefit did not result in improving the dynamic pain com ponent.

The present study investigated pregabalin given as a premedication for preventive analgesia. This concept is based on the assumption that complete blocking of any pain signals from the surgical wound from the time of incision until final wound healing might be the only way to prevent central neural sensitization.[27] Several published studies evaluated the efficacy of preemptive pregabalin in acute post-surgical pain; however, only a few used a single low dose preoperatively. Our results were in favor of a single low-dose pregabalin in decreasing postoperative pain at rest. These findings also correlated with previous literature that emphasized single dose 75 mg given preoperatively in some different clinical settings such as septoplasty, laparoscopic hysterectomy, and percutaneous nephrolithotomy.[28-30]

On the contrary, White and colleagues evaluated the effect of pregabalin in a dose-ranging study of a single-dose preoperative pregabalin 75 mg to 300 mg compared with placebo in patients undergoing otolaryngologic surgery, general surgery, plastic surgery and urologic surgery.[26] Their findings on

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pain after surgery were comparable in all groups until postoperative day 7. In another study using a low-dose pregabalin before minor gynecologic surgery, Paech and colleagues also found no significant difference between groups for pain experienced and fentanyl requirement, along with higher incidence of side effects in the pregabalin group.[23]

The inconsistent findings of the analgesic effects of pregabalin in the perioperative period are probably due to several confounding factors including the use of multimodal analgesic regimens, the procedure-specific analgesic response, the timing of drug administration, as well as quality of design. Recent meta-analysis, assessed the postsurgical analgesic efficacy and adverse events after administration of pregabalin under different surgical categories.[31-32] Lam DMH, et al. found that 2 hour VAS pain scores were decreased in all procedures; however, the effect size varied greatly. Sedation was increased in cardiothoracic, spinal and miscellaneous procedures, but not in gynecologic, laparoscopic cholecystectomy, or ENT procedures.[33] They concluded consideration for pregabalin use in postoperative pain should be procedure-specific.

It is essential to find the lowest optimum dose of pregabalin to avoid common dose-dependent side effects, particularly dizziness and drowsiness, which could be troublesome.[26] Our findings did not show any significant increased incidence of any adverse effects including sedation, visual disturbance, dizziness, respiratory depression, pruritus or PONV. This is probably due to the single low-dose of pregabalin used in the present study.

The limitation in our study is that we did not assess the pain in early postoperative period as frequent or evaluate the dose-response. Further studies are suggested to investigate the optimal dose, the duration of pregabalin continuation, and additional benefits beyond acute postoperative period.

Conclusion

Administration a single dose of 75-mg pregabalin preoperatively provides better analgesia in patients undergoing breast cancer surgery without increasing adverse events. However, the benefit is only limited to the static pain component.

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