

## Prospective Study

# Does a Single Preoperative Dose of Pregabalin Have Opioid-Sparing Effects Following Mastectomy?

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### Abstract

**Background:** Pregabalin, an antiepileptic and chronic pain medication, has been recently found to be useful for reducing acute postoperative pain when administered preoperatively. Although various dose regimens have been tried in different surgical settings, the minimum effective dose is not established. We aimed to evaluate the analgesic efficacy of a single dose pregabalin in patients undergoing mastectomy and axillary dissection.

**Methods:** Sixty women scheduled for mastectomy and axillary dissection were randomized to receive either pregabalin 150 mg or placebo orally 1h before surgery. The intraoperative and postoperative management was standardized. Postoperative pain was assessed at rest and on movement for 12h using the visual analog scale (VAS). Morphine was administered if VAS exceeded 30. Primary outcomes were severity of postoperative pain and postoperative morphine requirement. Secondary outcomes were incidence and severity of side effects such as postoperative nausea and vomiting (PONV), headache, sedation and respiratory depression if any.

**Results:** Fifty-seven patients completed the study. Postoperative morphine consumption was significantly less ( $5.90 \pm 3.4$  vs.  $12.0 \pm 2.4$  mg;  $P < 0.001$ ) and median [IQR] time to first analgesic was significantly longer (90 [40-120] vs. 10 [10-70]min;  $P < 0.001$ ) in the pregabalin group than in the placebo group. The incidence of side effects was similar in the two groups.

**Conclusion:** A single dose of 150 mg pregabalin administered 1h prior to surgery resulted in a substantial reduction in postoperative pain and overall morphine consumption after mastectomy and axillary dissection without significant side effects.

**Keywords:** Pregabalin; Postoperative analgesia; Mastectomy

### Introduction

Gabapentinoids are anti-convulsants with membrane stabilizing and anti-nociceptive effects. These drugs bind to the presynaptic voltage-dependent calcium channel. The ant nociceptive effect is believed to be related to the reduction of the  $Ca^{2+}$  influx at presynaptic terminals in hyper-excited neurons, which may lead to the reduction of the release of several excitatory neurotransmitters, including glutamate, norepinephrine, and substance P [1]. Thus, gabapentinoids appear to reduce the hyper excitability of dorsal horn neurons that is induced by tissue damage [2].

The analgesic effect of gabapentin has been well established in various surgical populations and was described in multiple systemic reviews [3,4]. Pregabalin appears to be a better option when compared with gabapentin, as it exhibits greater analgesic efficacy and better pharmacokinetic profile. The side-effects profile of pregabalin is also promising; in addition it has no effect on arterial pressure or heart rate [5]. Pregabalin demonstrates highly predictable and linear pharmacokinetics, a profile that makes it easy to use in clinical practice. It is rapidly and extensively absorbed after oral dosing in the fasted state, with maximal plasma concentration occurring at 1h after single or multiple doses. It can be started at an effective dose of 150 mg/day [6], the dose of pregabalin used in the present study. Furthermore, the oral bioavailabil-

ity of pregabalin is high at  $\geq 90\%$  and is independent of dose [7].

The objective of the present study was to investigate the effect of a single dose of 150 mg oral pregabalin on postoperative morphine consumption and pain after unilateral mastectomy and axillary dissection.

## Materials and Methods

After approval of the Institutional Ethics Committee and written informed consent, this randomized, double-blind and placebo controlled study was conducted in women undergoing mastectomy with axillary dissection in the Medical Research Institute Hospital of Alexandria University between Jan, 2012 and Nov, 2012. Sixty ASA I-II women aged 24-73 years were enrolled in the study. Patients were not included if they had known allergy to opioids or pregabalin, a history of drug or alcohol abuse, impaired kidney or liver function, had a body mass index more than 40, chronic intake of analgesics, intake of non-steroidal anti-inflammatory drug or paracetamol 24H prior to operation.

Before surgery, all patients were instructed in the use of visual analog scale (0, no pain; 100, worst unbearable pain).

On the day of surgery, patients were randomly assigned to receive pregabalin 150mg (Lyrica, Pfizer, Egypt) (pregabalin group) or an identical-looking placebo (placebo group) orally 1h before surgery (n= 30 per group). Randomization assignments were based on computer-generated codes that were maintained in sequentially numbered opaque envelopes until just before use. Personnel involved in patient management and data collection were unaware of the group assignment.

No sedative premedication other than pregabalin or placebo was given. Anesthesia was induced with propofol 2 mg/kg, morphine 0.1 mg/kg and cisatracurium 0.1 mg/kg. The trachea was intubated and controlled ventilation began. Anesthesia was maintained with isoflurane (1.2%) end tidal concentration in 100% oxygen.

Rescue analgesic (morphine 0.05 mg/kg I.V.) was administered during the procedure in the event of hypertension or tachycardia exceeding 20% of the baseline after ensuring adequate muscle relaxation and anesthesia. Intravenous ondansetron 4mg was given 30 min before the end of surgery. Isoflurane was discontinued at the end of surgery. Emergence times (min) from discontinuation of anesthesia to spontaneous breathing, hand pressing, tracheal extubation, and recalling date of birth were assessed at 1- min intervals. The duration of anesthesia and surgery were also recorded.

After satisfactory recovery, the patients were transferred to the post-anesthesia care unit (PACU). Pain was assessed every

30 min for the first 2h and then at two hourly intervals for the next 10 h (i.e. until 12h post-op). Pain was assessed at rest and on movement (supine to sitting position) using VAS. Morphine in the dose of 0.5 mg/kg was administered in case VAS exceeded 30. Total morphine consumption during this 12h period was recorded. No other analgesic was administered during the study period.

We specifically evaluated the potential side effects of pregabalin, including nausea, vomiting, headache and sedation.

The severity of PONV was graded on a 4-point scale (0, no nausea or vomiting; 1 mild nausea; 2 moderate nausea; and 3 severe nausea with vomiting). Rescue antiemetic ondansetron 4 mg i.v. was given to all patients with PONV of grade  $\geq 2$ . The Ramsay sedation score (awake levels: 1 restless; 2 tranquil; 3 responds to commands; a sleep levels were dependent on patient's response to a light glabellar tap; 4 brisk response; 5 sluggish response; and 6, no response) was used to assess sedation[8]. Patients with a sedation score of  $\geq 4$  were considered as sedated.

Respiratory depression was defined as ventilatory frequency  $\leq 8$  bpm and oxygen saturation  $< 90\%$  without oxygen supplementation.

Calculation of sample size was based on the presumption that a sample size of 25 patients per group was needed to detect at least 20% decrease in postoperative morphine consumption at a significant level of 5% and power of 90%. To take care of any drop outs, we enrolled 30 patients in each group. Data were checked for normality prior to analysis. Continuous data were expressed as mean (SD) and non-parametric data as median and interquartile range. The demographic data in the two groups were compared using two samples Student t-test. The morphine consumption in the two groups was analyzed using independent t-test. Pain scores in the two groups were analyzed using Mann-Whitney U-test. The incidence of side effects was compared using Fisher's exact test. All analyses were performed using SPSS v 11.0 for Windows (SPSS Inc., Chicago IL) and a  $p < 0.05$  was considered significant.

## Results

Sixty patients were included in the study; however three were subsequently excluded two in the pregabalin and one in the placebo group. In the pregabalin group, two patients were re-operated due to bleeding 3h after the primary operation and received medication other than prescribed in the study protocol. In the placebo group, one patient had paracetamol the morning before surgery. Thus data from 57 patients, 28 in the pregabalin group and 29 in the placebo group were included and analyzed.

Patient demographics, duration of surgery and intraoperative dose of morphine were similar in both groups (Table 1).

Variable	Groups	
	Placebo (n=29)	Pregabalin (n=28)
Age (year)	56 (5.1)	52 (7.6)
Weight (kg)	88 (0.7)	86 (0.5)
Height (cm)	165 (4.2)	163 (6.6)
Duration of surgery (min)	105 (11.2)	115 (10.3)
Intraoperative morphine (mg)	11.7 (4.7)	12.4 (6.6)

**Table 1:** Patient characteristics values are mean (SD) or numbers. No significant differences between groups by student's t-test.

The times from the end of anesthesia to spontaneous breathing, following verbal commands (hand grip), tracheal extubation, and orientation were similar in both groups (Table 2).

Time to (min)	Placebo (n=29)	Pregabalin (n=28)
Spontaneous breathing	6.7 (3.1)	6.2 (3.6)
Following commands (hand grip)	10.2 (1.8)	9.4 (2.5)
Tracheal extubation	11.1 (2.3)	10.5 (2.8)
State birth date	13.9 (3.3)	12.6 (2.2)

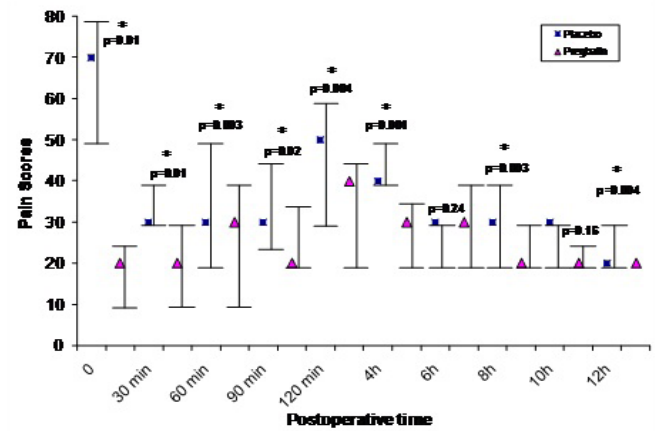
**Table 2:** Emergence and intermediate recovery times after discontinuation of anesthesia. Values are mean (SD). No significant differences between groups by student's t-test.

Postoperative morphine consumption was 48% less in pregabalin group than placebo group, which was statistically significant. Also, time to first rescue analgesia was significantly longer in pregabalin group (Table 3).

Variable	Groups	
	Placebo (n=29)	Pregabalin (n=28)
Time to first rescue morphine (min) [median (IQR)]	10.0 (10-70)	90 (40-120)
Total morphine administered (mg) [mean (SD)]	12.04 (2.4)	5.90 (3.4)

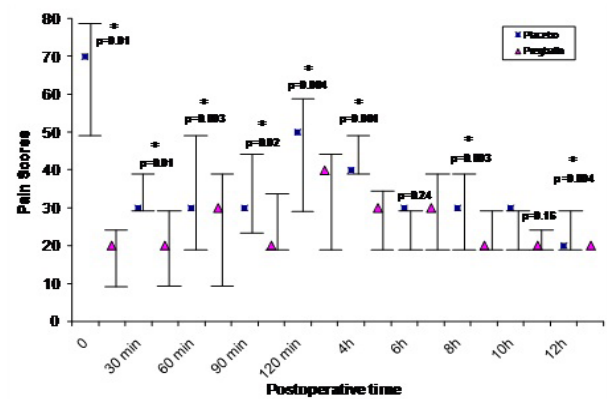
**Table 3:** Postoperative requirements of rescue analgesia.

The median postoperative pain scores at rest as well as on movement were higher in placebo group than pregabalin group at most of the measurement times (Figure 1 and 2).



**Figure 1:** Postoperative pain scores (median [IQR]) at rest by Mann-Whitney U-test.

(\* ) denotes P< 0.05 at that time.



**Figure 2:** Postoperative pain scores (median [IQR]) during movement by Mann-Whitney U-test. (\* ) denotes P< 0.05 at that time.

Incidence and severity of sedation were comparable between two groups. Incidence and severity of PONV, number of patients requiring anti-emetic, incidence of headache and respiratory depression were similar among the groups (P> 0.05) (Table 4).

Variables	Groups	
	Placebo (n=29)	Pregabalin (n=28)
Sedation score		
1	2	0
2	12	12
3	13	14
4	1	2
5	1	0
6	0	0
Median (IQR)	3 (1)	2 (1)

PONN		
No	13	12
Mild	2	-
Moderate	3	5
Severe	5	6
Patients requiring anti-emetic	5	6
Headache	8	10

**Table 4:** Incidence of side-effects; values are numbers and median (IQR). No significant differences between the groups by Fisher exact test ( $P > 0.05$ ).

## Discussion

Pregabalin has been shown to be effective for spontaneous and movement evoked pain. It is opioid sparing and accelerates physiological recovery after surgery. Preoperative dose as low as 75 mg provided limited analgesic benefit after laparoscopic cholecystectomy [9]. A recent dose-response study defined pregabalin 300 mg as the optimal preemptive dose for postoperative pain relief. Increasing the dose beyond 300 mg did not improve analgesia, but did increase the risk of side effects [2]. We thus empirically chose 150 mg of pregabalin as a reasonable compromise between efficacy and toxicity.

Pain scores at rest were significantly lower in pregabalin group during the first 4h, whereas pain scores during movement were significantly lower throughout the study period. The mechanism of action of pregabalin in the postoperative period is explained as prevention or reduction of development of central neuronal hyperexcitability induced by surgical procedure [4]. This hypothesis is supported by our findings that evoked pain during movement, that is during augmented afferent transmission to dorsal horn neurons, was significantly decreased, whereas pain at rest was affected to a lesser extent. Similarly, Peng and colleagues [9] had demonstrated that pain on movement during second to fifth postoperative day were lower in pregabalin group in patients undergoing laparoscopic cholecystectomy. They found no significant difference in pain scores at rest in pregabalin and placebo groups. Similar findings were also observed by Wichai and colleagues [10] in patients undergoing abdominal hysterectomy.

Although postoperative analgesic consumption is the primary outcome in many studies, time to first rescue analgesia is another useful outcome. We measured the time to first rescue analgesia which was longer in pregabalin group compared to placebo group. Also, in pregabalin group, only four out of 28 patients required morphine immediately after transfer to recovery room as compared to 20 out of 29 patients in the placebo group. Recently McQuay and colleagues [11] contended that trials that are able to achieve similar pain intensity scores with different intervention

groups should in theory constitute stronger evidence. However, they were not able to prove this hypothesis in their study. In the current study, pregabalin group consumed less morphine post-operatively and experienced less pain than the placebo group. A possible explanation could be that we administered intermittent boluses of I.V morphine for postoperative analgesia after assessing VAS for pain. Such analgesic protocol would lead to recording of higher pain scores as analgesic is administered according to pain score. On the contrary, a patient controlled analgesia system may ensure that pain scores are below 30 more consistently. The side effects of perioperative pregabalin include sedation, nausea, vomiting, and headache. In our study, we found that adverse events were comparable in the two groups. A reduction in pain score and morphine consumption would seem to predict a lower incidence of opioid-related side effects including sedation, respiratory depression, nausea, vomiting, and urinary retention. In a study by Methiesen and colleagues [12], a dose of pregabalin up to 300 mg was used and none of the patients experienced postoperative respiratory depression. The opioid sparing effect also appears to facilitate the recovery of bowel function and may allow patient to rapidly resume daily life activities.

Our study is limited by the facts that the study period was only 12h postoperatively, missing out a possible longer duration of effect of preoperative pregabalin and the trial evaluated only 150 mg of pregabalin. A dose-ranging study is warranted to determine the lowest dose with maximum efficacy for post-operative analgesia in mastectomy.

We conclude that oral pregabalin 150 mg administered 1h before mastectomy was effective in reducing postoperative pain and postoperative morphine requirement without significant side effects. These promising results should be validated in other surgical procedures, with multiple dosing and prolonged follow-up.

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