EFFECT OF PREOPERATIVE ORAL PREGABALIN ON POSTOPERATIVE PAIN AFTER MASTECTOMY

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Abstract

Background: This was a randomized, double-blinded clinical trial to study the effects of a single oral dose of pregabalin 150 mg in postoperative pain management after mastectomy.

Methods: Design: forty nine patients ASA I or II, aged between 20-60 years, scheduled for mastectomy with or without axillary lymph nodes dissection (ALND) were recruited into this study. They were randomized into two groups, placebo (n = 24) or pregabalin (n = 25) receiving either oral pregabalin 150 mg or placebo when called to operation theatre (OT). The assessment of pain score were performed at recovery, 2, 4, 6 and 24 hours postoperatively at rest and on movement, using the verbal numeral rating score (VNRS).

Results: VNRS scores for pain at rest were lower in the pregabalin group at 2 (p = 0.024), 4 (p = 0.006) and 6 (p = 0.003) hours postoperatively, and also at 4 (p = 0.005) and 6 (p = 0.016) hours postoperatively on movement compared to the placebo group. Incidences of dizziness were common, however, side effects such as nausea and vomiting, headache, somnolence and visual disturbance were low and comparable in both groups.

Conclusion: a single dose of 150 mg pregabalin given preoperatively compared to placebo significantly reduced postoperative pain scores after mastectomy.

Keywords: pregabalin, postoperative pain, mastectomy, opioid.

Introduction

Preventive analgesia is a treatment approach that aims to reduce the development of central sensitization in the postoperative period by reducing peripheral nociceptive input into the central nervous system, thus reducing postoperative pain and analgesics consumption. The concept of preventive analgesia includes multimodal antinociceptive techniques with analgesics that exceed the expected duration of action and also attenuate peripheral or central hypersensitivity. Effective methods include systemic NSAIDs, single dose epidural analgesia, systemic NMDA receptor antagonists, systemic opioids and local anaesthetic infiltration. Gabapentin and pregabalin have been proven to be effective medications in serving these purposes.

Pregabalin was originally developed as an antiepileptic drug with an improved pharmacological profile when compared to that of its predecessor gabapentin. Although gabapentin and pregabalin were first identified as useful in the treatment for neuropathic pain, recent reviews showed that they reduced postoperative acute pain and analgesic consumption as well. Gabapentin has been shown to be an effective analgesic for tonsillectomy, mastectomy and knee arthroplasty.
however pregabalin appears to be a better option when compared with gabapentin as it has better analgesic efficacy and an improved pharmacokinetic profile\(^9\). Pregabalin and gabapentin bind to the α\(_2\)δ sub-unit of pre-synaptic voltage-gated calcium channels in the spinal cord and brain\(^1,2,3,4,5\). By altering calcium currents, it reduces or modulates the release of several excitatory neurotransmitters including glutamate, norepinephrine, substance P and calcitonin gene-related peptide, producing inhibitory modulation of ‘over-excited’ neurons and returning them to a normal state.

One advantage of pregabalin in clinical use is that it has higher bioavailability when giving orally with linear pharmacokinetics property compared to gabapentin. It is rapidly and extensively absorbed after oral dosing in the fasting state with maximal plasma concentration occurring within 1 hour after single or multiple doses\(^9\). Absorption of gabapentin is limited by saturable, active and dose dependent transport in gastrointestinal tract but absorption of pregabalin is not saturable, resulting in a linear pharmacokinetic profile with bioavailability exceeding 90% and independent of dose\(^3,5\). In recent years, pregabalin has been introduced as an adjunct in multimodal management of postoperative analgesia in many studies because of its favourable pharmacokinetics\(^10-15\).

The aim of this study was to compare the effect of single-dose 150 mg oral pregabalin to placebo on postoperative pain after mastectomy for breast cancer.

**Methods**

This randomized, double-blinded clinical trial was done following approval of the Dissertation Committee of the Department of Anaesthesiology and Intensive Care, Universiti Kebangsaan Malaysia Medical Centre (UKMMC) and the Research Ethics Committee of UKMMC (Research No. FF–444–2012).

Forty nine, ASA I or II patients, aged 20 to 60 years who were scheduled for elective mastectomy with or without axillary lymph nodes dissection (ALND) were included in the study. Informed and written consent was obtained from all patients during preoperative anaesthetic assessment a day before surgery. Exclusion criteria included, known contraindication to medication use in the study, patients with chronic pain or on daily intake of analgesic and impaired kidney function (creatinine level >80 µmol/L). Patients were randomized using computer-generated randomized numbers to receive either pregabalin (Lyrica\(^a\)) or placebo (vitamin B complex). Information regarding the study and the verbal numerical rating scale (VNRS) range from 0 – 10 was explained to the patients. On the day of surgery, all patients were given premedication of oral midazolam 7.5 mg with either oral pregabalin 150 mg (in 2 tablets) or oral vitamin B complex (in 2 tablets) one hour before being sent to operating room. Patients were instructed to close their eyes before given the test drug to swallow.

In the operation theatre, basic monitoring included electrocardiogram (ECG), oxygen saturation (SpO\(_2\)) and non invasive blood pressure (NIBP). General anesthesia was induced with IV propofol 1.5 – 2.5 mg/kg and IV fentanyl. After the patient was adequately anaesthetized, a supraglottic airway device was inserted. Anaesthesia was maintained with sevoflurane in 50% O\(_2\) / 50% air mixture maintaining minimum alveolar concentration (MAC) of 0.8–1.0. Intraoperatively, patients were given IV morphine 0.1–0.2 mg/kg as an analgesic. Additional IV parecoxib 40 mg was given at the time of skin suturing. Adequate local anesthetic infiltration of levobupivacaine up to 2 mg/kg was given by the surgeon at the incision site.

Pain was assessed by independent observer in the recovery area, 2, 4, 6 and 24 hours postoperatively using the VNRS at rest and on movement. In the ward, all patients received oral etoricoxib 120 mg daily with oral paracetamol 1g every 6 hours as a standard analgesic. If the pain score was rated 5 or more, intravenous tramadol 50 mg was given as a rescue medication. Any incidence of side effects such as nausea, vomiting, headache, somnolence, dizziness and visual disturbance were documented.

Based on previous study\(^13\), with the power of 0.8, alpha value of 0.05 and dropout rate of 10%, the sample size calculated was 60. Statistical analysis and calculations was performed using SPSS for Windows Version 12.0. VNRS pain score and amount of intraoperative morphine used were analysed using Mann-Whitney U-test. Categorical variables such as number of patients needed rescue analgesic and
incidence of side effects were evaluated with X² test or Fischer’s exact test. A *p* value of <0.05 was considered statistically significant.

**Results**

Forty nine patients were recruited in this study in which 24 patients were in the placebo group and 25 patients were in the pregabalin group. There were no statistical differences with regards to age, weight, height, race, ASA and type of operation (Table 1).

Figure 1 showed VNRS at rest in pregabalin group compared to placebo. There were statistically significant differences at 2, 4 and 6 hours postoperatively.

Figure 2 showed VNRS on movement in

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**Table 1**

| Demographic data values are expressed as mean± SD or number(percentage) |
|--------------------------|------------|------------|
|                          | Placebo    | Pregabalin |
|                          | (n=24)     | (n=25)     |
| Age                      | 52.0 ± 8.4 | 51.5 ± 9.6 |
| Weight (kg)              | 62.4 ± 8.0 | 60.2 ± 5.0 |
| Height (cm)              | 156.9 ± 3.0| 156.2 ± 2.8|
| Race                     |            |            |
| Malay                    | 12 (50)    | 17 (68)    |
| Chinese                  | 8 (33.3)   | 5 (20)     |
| Indian                   | 4 (16.7)   | 3 (12)     |
| ASA                      |            |            |
| I                        | 12 (50)    | 15 (60)    |
| II                       | 12 (50)    | 10 (40)    |
| Type of operation        |            |            |
| Mastectomy               | 6 (25)     | 6 (24)     |
| Mastectomy with ALND     | 18 (75)    | 19 (76)    |

* *p* value = 0.024. ** *p* value = 0.006. ′ *p* value = 0.003.
pregabalin group compared to placebo. There were statistically significant differences at 4 and 6 hours postoperatively.

There was no statistically significant difference in the mean intraoperative morphine consumption in both placebo group and pregabalin group.

Six patients from the placebo group and three patients in the pregabalin group needed tramadol as a rescue drug postoperatively, however the difference was statistically not significant. There was no difference in postoperative oral analgesic consumption for both groups.

Adverse effects postoperatively in both groups, which was statistically not significant are presented in table 2.

<table>
<thead>
<tr>
<th>Incidence of side effects</th>
<th>Placebo n = 24</th>
<th>Pregabalin n = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9</td>
<td>16</td>
</tr>
</tbody>
</table>

Discussion

In this current study, we found that preoperative single dose of oral pregabalin 150 mg was effective in reducing both the resting and on movement postoperative pain in patients undergoing mastectomy with or without ALND. Spreng et al, showed a reduction of postoperative pain at rest and morphine consumption from 4 up to 24 hours postoperatively after lumbar discectomy with a single dose of oral pregabalin 150 mg10. In another study, Agarwal et al used a single dose of oral pregabalin 150 mg and effectively reduced postoperative pain and fentanyl consumption in patients undergoing laparoscopic cholecystectomy up to 24 hours11. Jokela et al used oral pregabalin 150 mg preoperative for day-case gynecological laparoscopic surgery and had better analgesia during the early recovery but not sustained up to 24 hours12. A study by Kim et al where mastectomy patients received oral pregabalin 75 mg twice a day showed that there was reduced postoperative pain and analgesic consumption respectively13. That study also showed the ability of divided doses of pregabalin to reduced pain after 48 hours up to 1 week after surgery.

Ititchaikulthol et al used a higher dose of oral pregabalin 300 mg preoperatively and showed reduction of pain scores and morphine consumption
for abdominal hysterectomy with or without salpingo-oophorectomy up to 24 hours post operatively. However, a study by Paech et al. using a lower dose of oral pregabalin 100 mg preoperatively was unable to reduce acute pain or improve recovery after minor gynecological surgery. Most of these studies also showed comparable rescue analgesic needed similar with the current study.

A meta-analysis on efficacy of pregabalin in acute postoperative pain by Zhang et al. concluded that postoperative opioid consumption and opioid related side effects were reduced but pain scores were not reduced. These conflicting results could possibly be due to differences in dosage, dosing regimen, type of surgery, the use of other analgesic regimes such as opioid or non-opioids, different anesthetic technique and surgical procedure.

Most studies showed pregabalin to be well tolerated and associated with dose dependent adverse effects that are mild to moderate and usually transient. Different doses of pregabalin have been used in the literature and doses ranging from 75 mg to 300 mg. It has been shown that higher doses are associated with increased frequencies of side effects. The common adverse effects of pregabalin are nausea and vomiting, visual disturbances, headache, dizziness and somnolence. Most of the studies showed no significant adverse effects when a lower dose of pregabalin was used. Nausea and vomiting were the common side effects in the current study followed by headache and dizziness. There were no documented side effects of somnolence or visual disturbances.

There are a few limitations in study. The pain score was assessed immediately in the postoperative period in the recovery area which makes it difficult to assess the effects of pregabalin at that point of time. Another confounding factor is the use of IV tramadol as a rescue drug which may affect the assessment of pain score postoperatively and incidence of side effects.

**Conclusion**

In conclusion, single dose of 150 mg pregabalin given preoperatively compared to placebo significantly reduced the postoperative pain scores after mastectomy.
References


The key to
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Postoperative Pain

**Step I: Initial bolus**
Inject 1 ampoule Tramal® 100 mg i.v. or i.m. slowly over 2-3 minutes.

**Step II: Ways of administration after initial bolus**
- **Infusion:** Inject 2 ampoules Tramal®, each 100 mg, in 500ml of infusion solution. Infusion rate 12-24 mg Tramal® (40-200 μg/min or 30-60 μg/min).
- **PCA:** Subsequent increments of 20 mg with a lock-out time of 5 minutes.
- **Injection:** Usual dose 50 mg or 100 mg 4-hourly up to a total daily dose of 480 mg except in special clinical circumstances which might necessitate daily doses up to 640 mg. Further treatment with Tramal® should be on demand.

**Step III: Follow-up**
- 50 mg 1-2 capsules every 4-6 hours
- 50 mg 20-40 drops every 4-6 hours
- 100 mg 1 suppository every 4-6 hours
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**Intra-Operative**
- **Loading Dose:** 2.5 - 3 mg/kg at wound closure
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- If intra-operative dose not given then:
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**Important safety information**
BRIDION is not recommended in patients with severe renal impairment. Studies in patients with hepatic impairment have not been conducted and, therefore, patients with severe hepatic impairment should be treated with great caution. Caution should be exercised when administering BRIDION to pregnant women as no clinical data on exposed pregnancies are available.

BRIDION has not been investigated in patients receiving rocuronium or vecuronium in the Intensive Care Unit (ICU) setting. If neuromuscular blockade is required within 24 hours of BRIDION administration, a nondepolarizing neuromuscular blocking agent should be used instead of rocuronium or vecuronium. The most commonly reported adverse reactions were dysgeusia (metal or bitter taste) and anesthetic complications (movement, coughing, grimacing, or sucking on the endotracheal tube). In patients treated with BRIDION, a few cases of awareness were reported. The relation to BRIDION was uncertain. In a few individuals, allergic-like reactions (ie, flushing, erythematous rash) following BRIDION were reported. Clinicians should be prepared for the possibility of allergic reactions and take the necessary precautions.

In a trial of patients with a history of pulmonary complications, bronchospasm was reported in 2 patients and a causal relationship could not be fully excluded. Volunteer studies have demonstrated a slight (17%-22%) and transient (<30 minutes) prolongation of the prothrombin time/activated partial thromboplastin time (PT/aPTT) with BRIDION; however, clinical studies have demonstrated no clinically relevant effect on peri- or postoperative bleeding complications with BRIDION alone or in combination with anticoagulants. As BRIDION has demonstrated an in vitro pharmacodynamic interaction with anticoagulants, caution should be exercised in patients on anticoagulation for a pre-existing or comorbid condition. This pharmacodynamic interaction is not clinically relevant for patients receiving routine postoperative prophylactic anticoagulation. Although formal interaction studies have not been conducted, no drug interactions were observed in clinical trials. Preclinical data suggest that clinically significant drug interactions are unlikely with the possible exceptions of toremifene, fusidic acid, and hormonal contraceptives.

*Train-of-four*
*Post tetanic counts*
*Second twitch*

**References**
1. BRIDION Summary of Product Characteristics (SPC)

Please see summary of product characteristics for full prescribing information.

**MSD Be Well**

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