*Original Article*

# A Randomized, Double-Blind, Placebo-Controlled Trial of Pre-emptive Pregabalin for Postoperative Pain after Laparoscopic Hysterectomy in Benign Gynecologic diseases

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***Objective:*** To investigate the efficacy of pre-operative pregabalin administration to relieve postoperative pain among patients undergoing laparoscopic hysterectomy.

***Materials and Methods:*** A randomized controlled trial study was conducted on 30 women with benign gynecologic diseases who underwent laparoscopic hysterectomy. The patients were randomly allocated into two groups: pregabalin group (n = 15) received 150-mg oral pregabalin capsule and placebo group (n = 15) received placebo of identical features. Either pregabalin or placebo was administered orally to each patient 2 hours before the commencement of laparoscopic hysterectomy. After the operation, all patients received patient-controlled analgesia with intravenous fentanyl. The outcome measures included postoperative pain assessed by visual analogue score (VAS) at 6, 12, and 24 hours after drug administration, fentanyl consumption within 24 hours after surgery, and side effects of pregabalin. The analysis was by per protocol.

***Results:*** Among 30 patients included, 27 patients were enrolled for analysis. There are 3 patients were excluded from the present study because 2 patients were converted operation to laparotomy and 1 patient did the operation more than 4 hours. The visual analogue scale (VAS) pain score at 6 and 12 hours was significantly decreased in the pregabalin group compared to the placebo group ($p$ = 0.001 and 0.001 respectively). The VAS scores at 24 hours of both groups were not significantly different ($p$ = 0.905). The fentanyl consumptions within 24 hours were 133.92±77.94 mcg in pregabalin vs. 337.63±178.47 mcg in placebo groups ($p$ = 0.001). Side effects of pregabalin including nausea, vomiting, and sedation were comparable between the two groups.

***Conclusion:*** The pre-emptive administration of 150-mg pregabalin significantly reduced postoperative pain for at least 12 hours after administration, without a significant increase in adverse effects, among patients undergoing laparoscopic hysterectomy.

***Keywords:*** Pregabalin, Pre-emptive, Postoperative pain, Laparoscopic hysterectomy

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Nowadays gynecologic laparoscopy has rapidly progressed with many new emerging technologies. Laparoscopic surgery has several benefits over laparotomy in terms of better evaluation of lesions than the naked eye, less postoperative pain, fewer infectious morbidities, and faster return to normal activity resulting in shorter hospital stay[1]. Although associated with less pain than laparotomy, previous studies had shown that the patients who undergo laparoscopic surgery experienced postoperative carbon dioxide inducing abdominal discomfort and shoulder pain aside from to incisional pain[2-4].

Many clinical trials have proven that pre-emptive analgesia effectively reduces postoperative pain by preventing the neural sensitization before surgery[5-11]. The reduction of postoperative pain requiring less analgesia also leads to a lesser risk of side effects of the opioids which is commonly used as postoperative analgesic drug.

Among analgesic drugs currently used as pre-emptive analgesia, pregabalin which is a GABA analog has been proposed. The mechanisms of action of pregabalin resemble it but has better affinity and bioavailability than gabapentin. Many researchers found that pre-emptive pregabalin significantly reduced postoperative pain[4]. Its analgesic effect has been observed to be positively correlated with its dosage. However, its side effects, including somnolence, dizziness, ataxia and nausea/vomiting were encountered more frequently with the increased dosage[3,4].

According to the study of Asgari et al[6], they compared the pre-emptive effects of 75 mg, 150 mg, 300 mg of oral pregabalin and placebo in laparoscopic hysterectomy. The results showed that pregabalin was more effective than

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placebo for postoperative pain control. Higher concentrations of pregabalin significantly better reduced postoperative pain. However, higher dosages of pregabalin were accompanied with more side effects. Hence, the authors from that study suggested 150 mg-dose of pregabalin as the suitable dosage to yield effective and safe postoperative pain management[6]. Another study that supported the benefit of pre-emptive pregabalin was the randomized, controlled trial of Kumari et al [7]. The result showed that pregabalin significantly reduced postoperative pain and intramuscular diclofenac consumption compared to placebo after abdominal hysterectomy. On the other hand, the prospective, randomized, controlled study of Nutthachote[12] who compared pregabalin to placebo for a relief of shoulder pain after laparoscopic gynecologic surgery. They found postoperative laparoscopic shoulder pain and amount of analgesic used were significantly decreased in pregabalin group. But there were no significant differences in VAS scores for surgical pain and adverse events between the two groups.

Various dosages of pre-emptive pregabalin were used in previous studies. These varied from 75 mg to 900 mg with difference in postoperative analgesic effects as well as degrees of side effects[13]. Taking into account the variations of dosages and their efficacy, more information is needed to determine which pregabalin dosage is optimal.

The aim of the present study was to compare postoperative pain after laparoscopic hysterectomy between patients who received pre-operative pregabalin administration and those receiving pre-operative placebo. A further aim was to compare postoperative side effects between the two groups.

## Materials and Methods

### *Study design and patient selection*

This randomized, double-blind, controlled trial was approved by the Vajira Institutional Review Board (COA 55/2561) and was registered to the Thai Clinical Trial (TCTR20180507002). The authors enrolled 30 patients who underwent laparoscopic hysterectomy due to benign disease at the Department of Obstetrics and Gynecology, Faculty of Medicine Vajira hospital, Navamindradhiraj University from May 2018 to September 2018. The inclusion criteria were aged 18 to 60 years, diagnosis of benign gynecologic disease, ASA class 1 or 2, BMI less than 35 kg/m$^2$, no emergency surgical conditions and good data communication. Patients with known allergy to pregabalin or gabapentin, underlying diabetes mellitus, hypertension or kidney diseases, chronic pain disease, anti-emetic or sedative drug use within 24 hours before surgery, operation time >4 hours, and operative complications (e.g. convert operation to abdominal hysterectomy, massive blood loss, injuries to adjacent organs, wound infection) were excluded from the study. Written informed consent was obtained from each patient.

Sample size was estimated by Repeated-measures ANOVA. The significance was set by $\alpha$ error = 0.05 and $\beta$ error = 0.2. Total of 30 patients or 15 in each group were required after adding 10% of the dropped-out.

### *Study intervention and randomization*

Pre-operative check-up was done as standard management for gynecologic surgery. The participants were randomly assigned into 2 groups with block randomization: 150-mg pregabalin (n = 15) and placebo (n = 15) groups. The 150-mg dosage was chosen in this research according to previous study of Asgar et al[6]. Data about pregabalin regarding its advantages and side effects as well as details of the research procedure were provided to all patients. All patients signed inform consent prior to entering into the study.

Capsules of either pregabalin or placebo which had identical colour and characteristic as pregabalin were given to the participants, by a nurse who was not involved in the study, 2 hours before the surgery. The nurse selected the capsule according to prior random number of the participants. The participants were instructed to report their pain score by visual analogue scale; score 0 to 10 (0 = no pain, 10 = worst possible pain).

All patients received peri-, intra-, and post-operative care according to the institution clinical guideline. General anesthesia and standard monitoring including continuous electrocardiography, pulse oximetry, non-invasive blood pressure, and capnography were performed. The operative time, estimated blood loss, and intra- and peri-operative complications were recorded. After extubation, the patients were observed in recovery room for 2 hours before transferred to the in-patient ward. All patients had received postoperative analgesic drug only via Patient-Controlled Analgesia (PCA). During 24 hours after operation, they received fentanyl 1 mg in NSS 100 ml (10 mcg/ml). PCA was identically set up; PCA dose only mode, Dose: 25 mcg, Lockout interval: 5 minutes, 4-hours limit: 300 mcg. 10-mg Plasil was administrated intravenously each 8 hours per day if patients needed. All patients were observed postoperative care for 2 days before discharged.

### *Data collection and outcome measures*

The participants, doctors, and data collectors were blinded regarding the treatment given to each participant. Data collected included demographic data including age, BMI, diagnosis, operation type, postoperative pain, total fentanyl consumption and side effects of pregabalin during 24 hours after surgery such as sedation score, nausea score, plasil consumption, blood pressure and pulse rate.

Postoperative pain was assessed by using visual analogue scale (VAS) at 6, 12, and 24 hours after taking capsule. Total fentanyl consumption was evaluated by PCA. Side effects of pregabalin included sedation score, nausea score, plasil consumption, blood pressure and pulse rate. Sedation score was used to assess pregabalin side effects; S = Sleep, easy to arouse, 1 = Awake and alert, 2 = slightly drowsy, easily aroused, 3 = frequently drowsy, arousable, drifts off to sleep during conversation, and 4 = Somnolent, minimal or no response to verbal or physical stimulation. If sedation score >2, intravenous fentanyl was ceased and the doctor in charge would evaluate and treated the condition

accordingly. About symptom of nausea and vomiting, it was evaluated by the nausea score; 0 = No clinical nausea/vomiting, 1 = Nausea without vomiting, no medication required, 2 = Nausea or vomiting, improved with medication, 3 = Nausea or vomiting, not improved with medication. The amount of fentanyl and plasil were estimated in milligram unit (mg).

### *Statistical analysis*

Statistical analysis was carried out using StataCorp. 2013 (Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). The *p*-value of <0.05 indicated a significant difference. Continuous variables are presented as median (range). The comparison of continuous data between the two groups was estimated with Mann-Whitney U test. Categorical variables are presented as number (percentage) and were compared using the Chi-square test. All data were analysed per protocol.

## Results

A total of 30 patients who met the inclusion criteria were enrolled to the study. The patients were randomly assigned into 2 groups; pregabalin (n = 15) and placebo (n = 15) groups. There were 3 patients were excluded from this study; 2 patients from the pregabalin group (one who was converted to laparotomy and the other one with operation longer than 4 hours). The numbers of patients included and excluded in the trial are shown in Figure 1. Total of 27 patients remained for the analysis.

Demographic data of the patients including age, body weight, height, operation type, and operative time were not significantly different between the two groups. Two characteristic features which were significantly different between both groups were BMI and diagnosis. Detail of patient characteristics are shown in Table 1.

For the primary outcome, patients who received pre-emptive pregabalin had a significant reduction of postoperative pain scores compared to patients who received placebo: VASs were 3 (range 0 to 5) vs. 6 (range 2 to 10) at 6 hours ($p = 0.001$) and 2 (range 1 to 4) vs. 4 (range 1 to 7) at 12 hours ($p = 0.001$) (Table 2). Figure 2 shows the relation of pain score and postoperative time. At 6 and 12 hours, the pain score of patients in the placebo group was higher than that in the pregabalin group. There was no significant difference in the rate of pain score change between the two groups. After 12 hours, pain score of patients in the pregabalin group gradually increased until its value was comparable to that of patients in the placebo group at twenty-four hours.

For the other outcomes, the amount of fentanyl use was significantly lower in the pregabalin group than that in the placebo group (133.9±77.94 mg vs. 337.6±178.47 mg, $p = 0.001$). There was no significant difference in plasil use within 24 hours between both groups (Table 3). Postoperative side effects of pregabalin were not significant different between the two groups. Of note, patients who

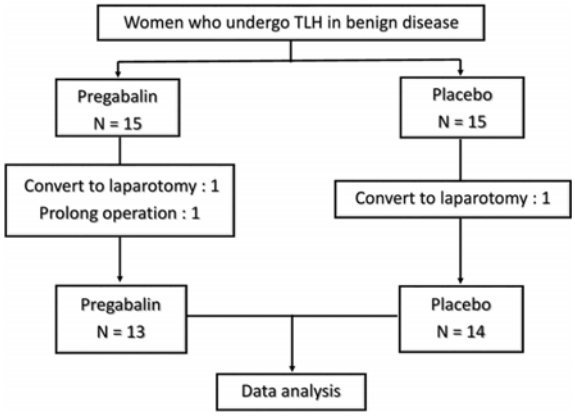


**Figure 1.** Consort diagram showing the patients included in the study.

**Table 1.** Patient's demographic data

| Characteristics | Pregabalin (n = 13) Mean ± SD | Placebo (n = 14) Mean ± SD |
|---|---|---|
| Age (years) | 43.38±4.54 | 45.71±5.50 |
| Weight (kg) | 60.81±11.38 | 67.06±11.43 |
| Height (cm) | 159.62±4.66 | 158.50±3.82 |
| BMI (kg/m$^2$) | 23.30±3.21 | 26.51±3.83 |
| Characteristics (n, %) | | |
| Diagnosis | | |
| Adenomyosis | 2 (15.4) | 6 (42.9) |
| Polyp | 1 (7.7) | 1 (7.1) |
| Anomaly | 10 (76.9) | 4 (28.6) |
| Myoma uteri | 0 (0.0) | 3 (21.4) |
| Operation | | |
| TLH | 8 (61.5) | 8 (57.1) |
| TLH with unilat SO | 1 (7.7) | 1 (7.1) |
| TLH with bilat SO | 4 (30.8) | 5 (35.7) |
| Operation time (mins) | 190.46 (165 to 218) | 200 (138 to 220) |

n = number; TLH = total laparoscopic hysterectomy; SO = salpingooophorectomy

**Table 2.** Postoperative pain

| Pain score (VAS) | Pregabalin (n = 13) median (range) | Placebo (n = 14) median (range) | *p*-value |
|---|---|---|---|
| 6 hours | 3 (0 to 5) | 6 (2 to 10) | 0.001* |
| 12 hours | 2 (1 to 4) | 4 (1 to 7) | 0.001* |
| 24 hours | 3 (0 to 7) | 3 (1 to 5) | 0.905* |

* Mann-Whitney U test
VAS = visual analogue scale

received pregabalin had significantly lower median of systolic blood pressure than those who received placebo (Table 4).

## Discussion

Gynecologic laparoscopy has been rapidly advanced in the past decades. Laparoscopic surgery provides many advantages compared with conventional laparotomy. These include a magnified view with better visualization of the operating field, less blood loss, less postoperative pain, shorter hospital stay, improved cosmetics outcomes due to small wound incisions[1].

However, patients who undergo laparoscopic surgery still have postoperative pain due to incisional wound and carbon dioxide inducing shoulder pain[2-4]. The management of postoperative pain has remained a challenge. Many clinical trials/studies have proven that pre-emptive analgesia effectively reduces postoperative pain[5-11] and also reduces a risk from side effects of opioids because patients require less postoperative analgesic treatment.

Pregabalin, which is a derivative of gabapentin, was tested in many studies. However, the optimal dosage remains to be answered. Previous study by Asgari et al[6] compared pre-emptive effects of orally pregabalin at different dosages of 75 mg, 150 mg, 300 mg and placebo given for a night before surgery, 30 minutes before surgery and 6 hours after surgery. The authors found that all dosages of pregabalin could reduce postoperative pain after laparoscopic hysterectomy, even from a 75-mg dosage. Higher dosages of pregabalin (150 mg and 300-mg) also significantly reduced

**Table 3.** Postoperative analgesic and antiemetic consumption

| Drug outcome | Pregabalin (n = 13) mean ± SD | Placebo (n = 14) mean ± SD | *p*-value |
|---|---|---|---|
| Fentanyl (mg) | 133.92±77.94 | 337.63±178.47 | 0.001* |
| Plasil (n, %) | | | 0.596* |
| Not received | 11 (84.6) | 3 (92.9) | |
| Received | 2 (15.4) | 1 (7.1) | |

* Student's t-test
SD = standard deviation; mg = milligram; n = number

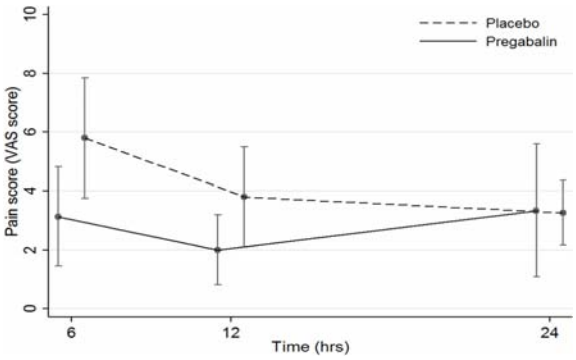


**Figure 2.** Postoperative VAS score in the first 24 hours postoperation.

**Table 4.** Pregabalin adverse effect

| Drug outcome | Pregabalin (n = 13) mean ± SD or median (range) | Placebo (n = 14) mean ± SD or median (range) | *p*-value |
|---|---|---|---|
| Sedation score | | | |
| 6 hours | 1 (0 to 2) | 1 (0 to 2) | 0.402* |
| 12 hours | 0 (0 to 1) | 0 (0 to 1) | 0.720* |
| 24 hours | 0 (0 to 1) | 0 (0 to 1) | 0.519* |
| Nausea score | | | |
| 6 hours | 0 (0 to 0) | 0 (0 to 0) | 1.000* |
| 12 hours | 0 (0 to 0) | 0 (0 to 0) | 1.000* |
| 24 hours | 0 (0 to 0) | 0 (0 to 0) | 1.000* |
| Systolic blood pressure | | | |
| 6 hours | 124 (90 to 135) | 131 (97 to 154) | 0.038* |
| 12 hours | 104 (91 to 136) | 121 (100 to 147) | 0.038* |
| 24 hours | 104 (90 to 125) | 116 (98 to 143) | 0.017* |
| Diastolic blood pressure | | | |
| 6 hours | 69 (52 to 84) | 76.5 (52 to 88) | 0.068* |
| 12 hours | 65 (54 to 78) | 69.5 (58 to 85) | 1.000* |
| 24 hours | 61 (51 to 74) | 72 (57 to 94) | 0.019* |
| Pulse rate | | | |
| 6 hours | 72 (50 to 95) | 70 (52 to 99) | 0.685* |
| 12 hours | 80 (50 to 94) | 71.5 (60 to 94) | 0.830* |
| 24 hours | 78 (46 to 100) | 73 (62 to 99) | 0.583* |

* Mann-Whitney U test

postoperative pain, however, at the disadvantage of more side effects. The authors in that study suggested 150 mg pregabalin which was shown to be effective and safe for postoperative pain management as the most suitable for clinical use. One randomized-controlled trial conducted by Nutthachote et al[12] divided the patients into two groups. The first group received 75-mg pregabalin 2 hours before operation and every 12 hours until 24 hours thereafter. Another group had only placebo. They found perioperative administration of pregabalin significantly reduced postoperative laparoscopic shoulder pain and amount of analgesic used after laparoscopic gynecologic surgery. However, there were no significant differences in postoperative surgical pain at 24 and 48 hours as well as adverse effects between patients who received pregabalin and placebo.

A recent systematic review by Yao et al[14], including 6 randomized trials with data on 452 patients undergoing gynecologic surgery, reported that pregabalin administration during the perioperative period had an analgesic and opioid-sparing effect. In addition, the adverse effects in acute postoperative pain management was not increased with pre-emptive pregabalin.

The present study found pain score significantly reduced at 6 and 12 hours after operation with 150-mg pregabalin. In line with several prior studies, pregabalin significantly reduced postoperative pain at least 12 hours after surgery. This result may be explained by its half-life of only 6.3 hours after oral administration. In clinical application, the authors suggest that 150-mg pregabalin may be considered an option for postoperative pain control in patients undergoing laparoscopic hysterectomy due to its ease of administration and low cost. However, an additional post-operative dose after 12 hours should be considered.

The fentanyl consumption in the pregabalin group was significantly lower than that in the placebo group. No significantly adverse effects between the two groups such as somnolence, dizziness, and nausea/vomiting. Although, systolic blood pressure in pregabalin was significantly lower than placebo, but the differences between the two groups did not reach significant level. These findings were in agreement with findings from the present study by Chotton et al[8] regarding the efficacy of pregabalin and its side effects. The authors in that study divided 90 patients who underwent elective abdominal hysterectomy to have 150-mg pregabalin or placebo 1 hour prior to induction of anesthesia. The results showed postoperative pain and analgesic consumption in pregabalin group was significantly lower than that in placebo group. There were no significant difference of sedation score between two groups. Moreover, the incidence and severity of postoperative nausea vomiting and postoperative anti-emetic consumption were not significantly different.

Recent ACOG committee opinion, released in September 2018 involving the concept of enhanced recovery after surgery (ERAS)[15], suggested gabapentin 600 mg orally as analgesic drug for the patients before entering into the operation room. One cohort study[13] found that gabapentin 900 mg/day was comparable to pregabalin 150 mg/day in neuropathic pain treatment. Many studies found that switching from gabapentin to pregabalin resulted in improved pain relief and also fewer adverse effects. Therefore, pregabalin may be used instead of gabapentin with better postoperative pain control and lower side effects. Future research is needed to compare analgesic effects as well as the cost utility between pregabalin and gabapentin in patients undergoing laparoscopic hysterectomy.

The strength of the present study was that it was a randomized, double-blind, controlled trial, so the selection bias was minimized. Only the patients who underwent laparoscopic hysterectomy were included in the trial to reduce the confounding factors from various gynecologic procedures which could affect operative time and consequent postoperative pain. In addition the dose of fentanyl was accurately assessed with the use of PCA machine. Nevertheless, this study was limited by a small number of participants. Moreover, our study was conducted in homogeneous Asian population. Hence, data from the other ethnic groups who have different demographic backgrounds and may have different pain receptor, or etc. should be explored.

## Conclusion

Pre-emptive 150-mg pregabalin was effective for reducing postoperative pain and had no significant adverse effects. Therefore, pregabalin can be used as alternative multimodal analgesics for postoperative pain among patients undergoing laparoscopic hysterectomy.

## What is already known on this topic?

Pre-emptive 150-mg pregabalin could significantly reduce postoperative pain after laparoscopic hysterectomy. Previous studies showed no significant differences postoperative analgesic consumption and adverse effects between patients who received pregabalin and placebo. However, previous studies gave 1 to 2 additional doses of pregabalin along with other analgesic drug post-operation.

## What this study adds?

Consistent with previous studies, pre-emptive 150-mg pregabalin can reduce postoperative pain after laparoscopic hysterectomy. This study additionally found that consumption of fentanyl were effective up to 12 hours post-operation. Hence, an additional doses of pregabalin especially after 12 hours post-operation should be considered.

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## Potential conflicts of interest

The authors declare no conflicts of interest.

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