Effects of Pregabalin on Post operative Morphine Consumption and Pain after Abdominal Hysterectomy with/without Salphingo-oophorectomy: A Randomized, Double-Blind Trial

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Background: *Achieving post operative pain management is difficult with the use of only opioids analgesia. Multimodal pain management is a method to improve post operative analgesia with minimal side effects. Pregabalin has an analgesic and opioids sparing effects in post operative analgesia.*
Objective: *The objective of the present study was to evaluate the effect of premedication with pregabalin 300 mg compared with lorazepam 0.5 mg. on post operative morphine consumption in women undergoing abdominal hysterectomy with/without salphingo-oophorectomy.*
Material and Method: *Eighty ASA I-III, aged 18-65 year, patients undergoing elective abdominal hysterectomy with/without salphingo-oophorectomy were randomized to receive either lorazepam 0.5 mg or pregabalin 300 mg 1 hr before surgery. Anesthesia was induced with thiopental (3-5 mg/kg) and atracurium (0.6 mg/kg) and maintained with sevoflurane with a fresh gas flow of 2 L/min (50% N_2O in O_2) and morphine 0.1-0.2 mg/kg. All patients received patient-controlled analgesia with morphine with a 1 mg incremental dose, 5-min lockout interval, and 4-hr limit of 40 mg post operative. Patients were studied at 0, 1, 4, 12 and 24 hours post operatively for verbal numerical rating scale (VNRS), morphine consumption, satisfaction score and side effects.*
Results: *The VNRS scores of the pregabalin group were significantly lower than the control group at 1, 4, 12 and 24 hours after surgery. The total morphine consumption at 24 hours post operatively of pregabalin group (7.11 ± 5.57) was significantly lower than the control group (21.18 ± 7.12) ($p < 0.01$). There were no differences between groups in somnolence and dizziness ($p = 0.93$) and nausea-vomiting ($p = 0.11$). The satisfaction score was higher in the pregabalin group.*
Conclusion: *A 300 mg pregabalin administered 1 hr preoperatively before abdominal hysterectomy with/without salphingo-oophorectomy significantly reduced morphine consumption, VNRS pain score and improved satisfaction score at 24 hr post operatively without any significant differences in side effects. Pregabalin is an alternative combination to opioids as multimodal analgesia.*

Keywords: *Pregabalin, Postoperative pain, Morphine*

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Post operative pain may result from diverse etiology and mechanism. Therefore, management of post operative pain is difficult to achieve with the use of just only one drug. It makes sense to use multimodal analgesia regimen, with a combination of opioid and non-opioid analgesia for improving post surgical pain treatment. The use of opioids by patients controlled analgesia (PCA) is popular but limited by side effects and by the fact that certain types of pain respond poorly to opioids. The combination of opioid and non-opioid analgesia drug is often used to enhance analgesic

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efficacy and reduce opiod requirements and side effects.

Pregabalin (S-[+]-3-isobutylgaba) was designed as a lipophilic GABA (γ-aminobutyric acid) analog substituted at the 3'-position to facilitate diffusion across the blood-brain barrier[1]. Pregabalin, like gabapentin, showed to be affective in several models of neuropathic pain[2], incisional injury, and inflammatory injury[3,4]. It is also effective in the treatment of anxiety, and is also a sleep-modulating drug[5].

The objective of the present study was to investigate the opioid-sparing effect of pregabalin premedication for patients undergoing abdominal hysterectomy with or without salphingo-oophorectomy.

Material and Method

After obtaining the approval from the Institutional Ethics Committee and written informed consent from the 80 patients, aged 18-65 years, ASA physical status I–III, scheduled for elective total or subtotal abdominal hysterectomy with or without salpingo-oophorectomy under general anesthesia, patients were eligible for participation and could operate a PCA device. Exclusion criteria were known allergy to opioids or pregabalin, history of drug or alcohol abuse, history of chronic pain and daily intake of analgesic drugs, renal insufficiency (creatinine clearance < 40 ml/min), and refusal of study participation. During the pre-operative visit, the PCA technique and the verbal numerical rating scale (VNRS, 0 = no pain, 10 = worst pain imaginable) were explained to the patients.

The patients were divided into 2 groups with 40 patients in each by randomly and double-blind to the patients and anesthesiologists. Patients in the control group received oral premedication with lorazepam 0.5 mg and those in the pregabalin group received 300 mg pregabalin (Lyrica1 50-mg capsule) 1 hour before surgery.

In the operating room, a crystalloid infusion was started through an IV cannula inserted in a vein at dorsum of the hand, and the mean arterial blood pressure(MAP), heart rate (HR), and peripheral oxygen saturation (SpO_2) were monitored. Anesthesia was induced with thiopental (3-5 mg/kg) and atracurium (0.6 mg/kg) and maintained with sevoflurane with a fresh gas flow of 2 L/min (50% N_2O in O_2), morphine (0.1 mg/kg) and atracurium 0.2 mg/kg as clinical needed. Surgery was performed via a Pfannenstiel incision. At the end of surgery, neuromuscular block was antagonized with neostigmine 2.5 mg and atropine 1.2 mg.

All patients were transferred to the post operative care unit. Pain score was evaluated by a nurse observer who was blind to the present study. If the VNRS was more than 4, additional 3 mg of morphine intravenously was administered prn every 10 minutes. Ondansetron 4 mg intravenously was administered on patient request. No other medications were administered during the 24 hour observation.

Patients were connected to an intravenous PCA pump (IVAC®, PCAM®) on arrival at the ward. Initial settings were as follows: incremental dose: morphine 1 mg; lockout interval: 5 minutes; and 4-hour limit: 40 mg.

Total morphine consumption was recorded from 0 to 24 hours post operatively. Pain scores (VNRS) at rest were assessed by the patients at 0, 1, 4, 12 and 24 hour after surgery.

Patient satisfaction was measured at 24 hours post operatively on a numerical score of 1-4. (1 = poor, 2 = fair, 3 = good, 4 = very good).

The occurrence of side effects, such as nausea/vomiting, constipation, dizziness, somnolence, and peripheral edema were recorded. Sedation scores were measured at 4 hours post-operatively on a numerical score of 1-4 (1, completely awake; 2, sometimes drowsy, easily roused; 3, often drowsy, easily roused; 4, often drowsy, difficult to rouse.)

A sample size of 40 patients by group was calculated to detect a significant difference of 2. VNRS at rest pain at the 12 hours post operative period with a power of 80% and a significant level of 5%. Descriptive statistics are expressed as mean $\pm$ SD unless otherwise stated. Student's t-test was used for comparison of the means of continuous variables and normally distributed data. The Mann-Whitney U-test was used otherwise. P-value < 0.05 was considered statistically significant.

Results

Patients

Eighty consecutive patients who fulfilled the inclusion criterions were included in the present study. 2 patients from the pregabalin group were excluded from the present study. One patient had been given morphine by mistake more than the recommended dose and the other had a surgical complication. Data from 78 patients were therefore analyzed. The groups were comparable with respect to age, body weight, height, ASA physical status, intra-operative blood loss, and duration of surgery (Table 1).

Table 1. Dermographic data

Variable	Control (n = 40)	Pregabalin (n = 38)	p-value
Age (year)	43.3 ± 7.1	43.9 ± 7.6	0.69
Weight (kg)	60.9 ± 10.4	60.3 ± 11.1	0.81
Height (cm)	157.5 ± 7.5	155.7 ± 4.8	0.18
ASA physical status (I/II/III)	19/19/2	14/20/4	0.27
Intraoperative blood loss (ml)	486.5 ± 424	340.7 ± 322.5	0.12
Duration of anesthesia (hour)	2.3 ± 0.8	2.0 ± 0.7	0.10

Pain scores

Fig. 1 displayed post operative pain scores in 24 hours post operatively. Pain scores were significantly lower in the pregabalin group compared with the control group at all the measured times (p-value < 0.01).

Morphine consumption

Fig. 2 shows the average PCA-administered morphine consumption at each of the post operative time intervals up to 24 hours. Morphine consumption at 0, 1, 4, 12, and 24 hours-post operative were significantly-less in the pregabalin group compared with the control group (p-value < 0.01).

Patients satisfaction

The percentage of satisfaction level 4 of the pregabalin group (55.26%) was significantly higher than the control group (30%) (p-value < 0.01).

Side effects

The most common side effects were N/V and dizziness. N/V classified by severity (no, mild, moderate, severe). The control group had not significantly higher percentage of moderate to severe N/V (moderate 20%, severe 2.53%) than pregabalin group (moderate 2.63%, severe 0%) (p-value 0.11). There was no difference in incidence of dizziness in both the control (32.5%) and pregabalin (34.2%) group (p-value 0.874). The level of sedation score was not significantly different in both control (sedation score 1; 0%, score 2; 67.5%, score 3; 32.5%, score 4; 0%) and pregabalin (sedation score 1; 7.89%, score 2; 55.26%, score 3; 36.84%, score 4; 0%) groups (p-value 0.93).

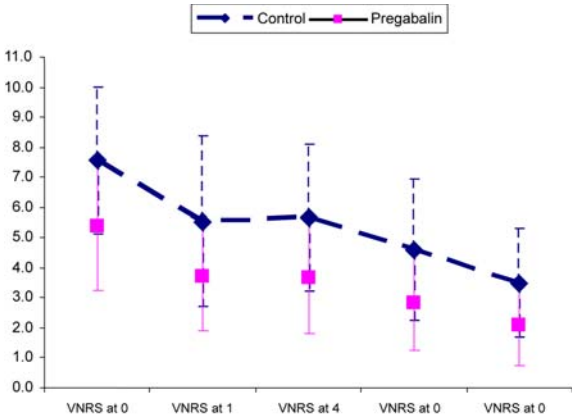

Fig. 1 Verbal numerical rating scale (VNRS) pain at rest over the 24 hour postoperative period. The pregabalin group had a lower pain score than the control group. Data are shown as mean ± SD

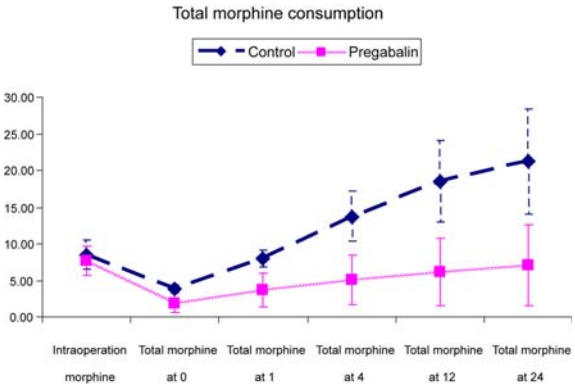

Fig. 2 Morphine delivered by patient-controlled analgesia (PCA). The group receiving preoperative pregabalin consumed less amount of morphine over the 24-h postoperative period. Data are shown as mean ± SD

Discussion

In the present study, the authors found that premedication with pregabalin 300 mg 1 hour before elective total or subtotal abdominal hysterectomy with

or without salpingooophorectomy can reduce post operative pain score and total morphine requirement during the first 24 hours and had a high percentage of patient satisfaction. There were no significant differences in side effect between the two groups in somnolence and dizziness. Percentage of moderate to severe N/V was significantly higher in the control group.

Experimental models of neuropathic pain and inflammatory hyperalgesia have shown that γ-aminobutyric acid analogs, such as gabapentin and pregabalin, have antinociceptive and antihyperalgesic properties. It has been suggested that central neuronal sensitization may result in an amplification of post operative pain[6-10], and that pre-operative administration of pregabalin, before inflammatory trauma or surgical stimulation, may reduce the degree of central sensitization[7].

Hill et al[11] compared pregabalin (50 and 300 mg) to placebo and 400 mg of ibuprofen in 198 patients who had undergone elective surgery to remove one or two third molars in terms of pain relief and pain intensity. Pain relief and pain intensity were significantly better in the 300 mg pregabalin group. The 300 mg pregabalin group also had the higher score on patient global impression than the ibuprofen group.

Ritva et al[12] studied premedication orally 1 hour before surgery with 150 mg or 300 mg and second dose of study medication was given 12 hours after the premedication. They found that 300 mg of pregabalin was more effective than pregabalin 150 mg in terms of oxycodone consumption (43%). The incidence of dizziness, headache and blurred vision were higher in the 300 mg pregabalin group.

These studies suggest that pregabalin also has a significant analgesic effect on acute post operative pain.

Michael et al[13] studied 90 patients undergoing minor gynecological surgery involving the uterus who were randomized to receive either oral pregabalin 100 mg or placebo 1 hour before surgery. There were no significant differences in pain score and fentanyl requirement in the recovery room and thereafter. Patients receiving pregabalin were more likely to experience post discharge side effects such as feeling light-headache or drowsiness. The present study was different from other studies in analgesic effect of pregabalin. The authors' explanations were pain scores in the placebo group which were substantially low and the dose of pregabalin in the present study was subtherapeutic. Therefore the present study used 300 mg of pregabalin.

Methiesen et al[14] used 300 mg pregabalin and 8 mg dexamethasone in combination with 1000 mg paracetamol orally 1 hour before anesthesia for post-operative pain control after abdominal hysterectomy. They found that the combination of paracetamol + pregabalin or paracetamol + pregabalin + dexamethasone did not reduce morphine consumption and pain score compared with paracetamol alone. They concluded that the use of pregabalin in treatment of acute pain with a major visceral component is questionable. The different study design might be the cause of different results from the present study.

Garaj[1] reviewed the phamacology of pregabalin and found that somnolence (29.2%) and dizziness (22.2%) were the most common side effects which were similar to the present study (dizziness/ somnolence 34.21%).

In conclusion, a single pre-operative dose of pregabalin 300 mg in patients undergoing elective total or subtotal abdominal hysterectomy with or without salpingo-oophorectomy resulted in significant reduction in pain score, morphine requirement and patient satisfaction score in 24 hours post operatively without significant difference in side effects. The satisfaction scores were higher in the pregabalin group. The authors recommend 300 mg of pregabalin oral pre-operatively as an alternative for multimodal analgesia in post surgical pain.

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การศึกษาผลของ pregabalin ต่อการใช้ยาแก้ปวดมอร์ฟีนในผู้ป่วยหลังผ่าตัดมดลูกและ/หรือรังไข่

วิชัย อิทธิชัยกุลฑล, ธนิต วีรังคบุตร, มุทิตา กันโอภาส, วชิรพล เข็มหอม, พิพัฒน์ ภัทรวุฒิชัย, รุ้งเพ็ชร สุยะเวช

ภูมิหลัง: *เทคนิคการใช้ยาระงับปวดที่ไม่ใช่ opioids ร่วมกับ opioids เพื่อบำบัดความปวดหลังผ่าตัด (Multimodal pain management) เป็นที่ยอมรับว่าได้ผลดี ทำให้มีอาการข้างเคียงของยาลดลง และสามารถระงับปวดได้ดีขึ้น*

วัตถุประสงค์: *เพื่อศึกษาการให้ pregabalin ขนาด 300 มก. 1 ชั่วโมง ก่อนผ่าตัดเปรียบเทียบกับยาหลอกในผู้ป่วยผ่าตัดมดลูก และ/หรือรังไข่ในด้านของปริมาณการใช้มอร์ฟีน และระดับความปวดหลังผ่าตัด*

วัสดุและวิธีการ: *ทำการศึกษาในผู้ป่วย 80 รายอายุ 18-65 ปี ASA I-III ที่มารับการผ่าตัดมดลูกและ/หรือรังไข่ แบ่งผู้ป่วยเป็น 2 กลุ่ม กลุ่มควบคุมจะได้รับ lorazepam 0.5 มก. และกลุ่มศึกษาได้รับ pregabalin 300 มก. 1 ชั่วโมงก่อนผ่าตัด ในระหว่างให้ยาระงับความรู้สึกนำสลบด้วย thiopental 3-5 มก./กก. และ atracurium 0.6 มก./กก. 50% N_2O, O_2, Sevoflurane และมอร์ฟีน 0.1-0.2 มก./กก. หลังผ่าตัดผู้ป่วยจะได้รับการระงับปวดด้วยมอร์ฟีนในเครื่อง PCA วัดระดับความปวดด้วย verbal numerical rating scale (VNRS) จำนวนมอร์ฟีน และภาวะแทรกซ้อนที่เวลา 0,1,4,12 และ 24 ชั่วโมงหลังผ่าตัด*

ผลการศึกษา: *พบว่า VNRS ในผู้ป่วยทั้ง 2 กลุ่มมีค่าไม่แตกต่างกันที่ 0 ชั่วโมง หลังผ่าตัดแต่จะแตกต่างกันอย่างมีนัยสำคัญที่เวลา 1,4,12 และ 24 ชั่วโมง ($p < 0.01$) มอร์ฟีนที่ใช้ใน 24 ชั่วโมง หลังผ่าตัดของกลุ่ม pregabalin เท่ากับ 7.11 ± 5.57 มก. ซึ่งมีค่าน้อยกว่ากลุ่มควบคุม (21.18 ± 7.12 มก.) อย่างมีนัยสำคัญ ($p < 0.01$) อาการง่วงซึมและคลื่นไส้ อาเจียน มีค่าไม่แตกต่างกัน ($p = 0.93$) และ ($p = 0.11$) ตามลำดับ คะแนนความพึงพอใจของการระงับปวดในผู้ป่วยกลุ่ม pregabalin มีค่าสูงกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ*

สรุป: *การให้ pregabalin 300 มก. 1 ชั่วโมงก่อนผ่าตัดในผู้ป่วยที่มารับการผ่าตัดมดลูกและ/หรือรังไข่ สามารถลดอัตราการใช้มอร์ฟีน, และความรุนแรงของความปวดใน 24 ชั่วโมง หลังผ่าตัดโดยอาการข้างเคียงของยาไม่มีความแตกต่างกัน ผู้ป่วยในกลุ่ม pregabalin มีความพึงพอใจในการระงับปวดมากกว่ากลุ่มควบคุม pregabalin จึงเป็นอีกทางเลือกหนึ่งของการใช้ multimodal analgesia*