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Original Contribution

Dose ranging effects of pregabalin on pain in patients undergoing laparoscopic hysterectomy: A randomized, double blinded, placebo controlled, clinical trial

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ABSTRACT

Objective: The study aimed to investigate the preemptive analgesia efficacy of different concentrations (75, 150 and 300 mg) of preemptive pregabalin for the postoperative pain management after laparoscopic hysterectomy.
Design: Prospective, randomized, placebo-controlled, double-blind study.
Setting: The Gynecology and Obstetrics Center of Arash Hospital, Tehran, Iran, from October 2013 to November 2014.
Patients: A total of 96 women with American Association of Anesthesiologist (ASA) physical status I and II underwent elective laparoscopic hysterectomy surgery. Patients were then randomly assigned to four groups, of which groups 1–3 (treatment groups; n = 20) received orally pregabalin concentrations of 75 mg, 150 mg, and 300 mg, respectively, for a night before surgery, 30 min before surgery and 6 h after surgery, whereas group 4 (control group; n = 22) received a matching dosage of placebo at the same scheme.
Measurements: Visual Analog Scale (VAS) scores for postoperative pain at rest and on movement at first 24 h after surgery were evaluated as primary outcome. Drug-related side effects were also evaluated as a secondary outcome. Somnolence was evaluated using Ramsay Sedation Scale, while nausea and vomiting were assessed using numeric scores. The data were analyzed using SPSS.
Main results: Preemptive pregabalin in different concentrations provided better pain relief as compared with placebo. Post-hoc test indicated that there was a significant difference among four groups, indicating where the concentration was increased, the pain score decreased as an independent variable of time. The highest concentration of pregabalin (300 mg) revealed higher sedation scores as compared with other groups.
Conclusion: Our data demonstrated preemptive administration of 75, 150, and 300 mg pregabalin play an important role in reducing postoperative pain after laparoscopic hysterectomy. Comparison of different concentrations and side effects indicates oral administration of 150 mg pregabalin is an effective and safe method for postoperative pain management after laparoscopic hysterectomy.

1. Introduction

Pain relief after surgical procedures is an important medical challenge [1]. Preemptive analgesia prevents central hypersensitization by applying analgesic methods before the onset of nociceptive stimuli that consequently decreases postoperative pain and contributes to a more comfortable recovery period [2,3]. This pain control technique that includes non-steroidal anti-inflammatory drugs (NSAIDS), opiates and antiepileptic drugs has been shown to be more effective than preventive analgesia [3].

Opioids have side effects, including nausea, vomiting, ileus, pruritus, respiratory depression, urinary retention, sedation and constipation, diminish the benefits of laparoscopic procedures [4]. Therefore, the use of opioid should be minimized, while the pain should be to a level at which narcotic analgesics is no longer required.

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Pregabalin is an anticonvulsant drug that reduces calcium entry to the nerve terminals of the central nervous and also decreases the levels of substance P, glutamate and noradrenalin that all play major roles in creating a sense of pain [5–8]. Several reports have also shown that administration of pregabalin may improve the treatment of postoperative pain, so reduces the use of opioid and its related side effects [9–12]. However, some studies pointed out that pregabalin failed to reduce pain in major operations and its analgesic effect is limited to some minor operations [8,9]. Yet, further studies are needed to determine the long-term benefits, optimal dose, and duration of treatment.

Therefore, the aim of this study was to evaluate preemptive analgesia efficacy of different concentrations (75, 150 and 300 mg) of pregabalin in patients undergoing laparoscopic hysterectomy in the following selected time intervals: the night before surgery, 30 min before surgery and 6 h after surgery. We also intended to find out the optimal and effective concentration of pregabalin to reduce postoperative acute pain in these patients.

2. Materials and methods

2.1. Ethical statement

This prospective, randomized, placebo-controlled, double-blind study was conducted at the Gynecology and Obstetrics Center of Arash Hospital, Tehran, Iran, from October 2013 to November 2014. This study was approved by the Research Ethics Committee of Tehran University of Medical Sciences and registered in the Iranian Registry for Clinical Trials (201412028897N3). A written informed consent was obtained from all participants.

2.2. Study design and population

A total of 130 patients were assessed for eligibility, of whom 34 patients were excluded due to non-fulfillment of the inclusion criteria. Therefore, a total of ninety six patients with the following criteria were included in the study: classified as American Society of Anesthesiologists (ASA) physical status I and II, aged 35–65 years, and undergoing elective laparoscopic hysterectomy. The patients with psychiatric problems, use of analgesics regularly, history of chronic pain, allergic to pregabalin, history of drug abuse, inability to understand the questions of Visual Analog Scale (VAS), serious organ disease, physical dysfunction, and duration of surgery > 3 h were excluded from study.

2.3. Study intervention and randomization

Patients were instructed to report their pain using the numeric visual scale on a scale of 0–10, indicating 0 for no pain and 10 for worst imaginable pain. The placebo and pregabalin (triple package) were prepared in capsules of identical color and appearance and were packaged by the hospital pharmacy according to a computer generated randomization list. Then, the study drugs were administrated by a nurse who was not involved in any part of the study. Patients were randomly allocated into four groups using computer-generated random numbers in a sealed opaque envelope. Groups1, 2, and 3 (treatment group; n = 20/each) received pregabalin capsule (Sobhan Co., Iran) in concentrations of 75 mg, 150 mg, and 300 mg, respectively, whereas group 4 (control group; n = 22) received a matching dosage of placebo at the same scheme. The elimination half-life of pregabalin (in different concentrations) ranges between 5.5 and 6.7 h [10,11]. Due to these specific properties, we administered preoperative single dosage at the night before surgery and 30 min before surgery that was followed by a single dosage at 6 h after surgery, for all of patients, meaning that the total concentrations of pregabalin used were 75 × 3 mg, 150 × 3 mg, and 300 × 3 mg. In the operating room, all of vital sign and sedation score were checked. After establishing an intravenous line and monitoring, Ringer's solution 3 ml/kg, midazolam 2 mg (Tehran Chemie Pharmaceutical, Co., Iran) and fentanyl 1 μg/kg (Darou Pakhsh Co., Iran) were used as a premedication. The patients then received sodium thiopental 5 mg/kg (Trettau Co., Germany) and atracurium 0.5 mg/kg (Caspian Tamin, Iran) for induction before being intubated. For maintenance of anesthesia, propofol 100–150 μg/kg (Melsungen, Germany) was administered. During the operation, atracurium 10 mg and fentanyl 50 μg were given every 30 min [12].

If the patient's blood pressure exceeded 160/100 mm Hg during the operation, incremental dosage of trinitroglycerin (TNG) 5 μg/min were administered to lower the blood pressure to below 140/90 mm Hg.

Pneumoperitoneum was established using the Veress needle with CO2 to maintain intraabdominal pressure of 14 mm Hg, and four trocars (two 10 mm and two 5 mm) were used in standard positions. The anesthesiologist, patients and surgeons were blinded to group allocation. Total or subtotal laparoscopic hysterectomy was performed by a team of expert surgeons, using the same technique for all groups. Time of surgery, average blood loss (based on suction fluid), uterine size, uterine weight and closed drain insertion after surgery were recorded. Duration of anesthesia and surgery were also recorded. Patients were informed before surgery that they could request an analgesic if needed. After being extubated, patients were transferred to the recovery care unit and received diclofenac 100 mg (Aburaihan Pharmaceutical Co., Iran). After awakening completely, the patients were transferred to the ward that was followed by assessment of the pain intensity using VAS scores at rest at the following time intervals: 0, 2, 4, 6, 12, and 24 h postoperatively and on active movement at 12 and 24 h postoperatively. All patients were given diclofenac sodium 100 mg (maximum dose of 300 mg per day) only if requested. If the patients requested a better analgesia or had VAS scale > 5, a 50 mg dosage of pethidine was given intramuscularly, with maximum dosage of 200 mg (q6 hour) per day.

2.4. Data collection and outcome

The total concentrations of pethidine and diclofenac sodium used within 24 h were recorded. If a patient requested more analgesia than the maximum recommended dosage, that patient was excluded from the study. A nurse from a different surgical department who was blinded to the study recorded an assessment of pain. Furthermore, postoperative side effects related to pregabalin, such as nausea and vomiting, dizziness, headache, sedation, visual disturbance and itching, were all recorded. The frequency of postoperative nausea and vomiting was recorded in first 24 h following surgery for each patient using a 3-point scale (0 = no nausea, 1 = mild nausea, 2 = moderate nausea and 3 = vomiting). Moderate to severe nausea and vomiting was treated by an intravenous injection of metoclopramide 8 mg. The conscious level of the patient was observed and graded according to Ramsay Scale as follows: 1 = anxious, agitated and restless, 2 = calm and cooperative, 3 = responsive on commands only, 4 = exhibiting brisk response to loud auditory stimulus, 5 = exhibiting sluggish response to loud auditory stimulus and 6 = unresponsive to verbal order [7]. Patients with Ramsay Scale ≥ 4 were considered as sedated. The primary outcomes were the VAS scores at rest and on movement, while the secondary outcomes were surgical time, average blood loss, sedation scale, incidence of adverse effects and postoperative nausea and vomiting (PONV) within the first 24 h after procedure.

2.5. Sample size

Sample sizes were determined to provide 80% power to detect a clinical difference of 1 point on the VAS score on rest with two-tailed pairwise comparisons between treatment and control groups at an alpha level of 0.05 in the intent to-treat population.

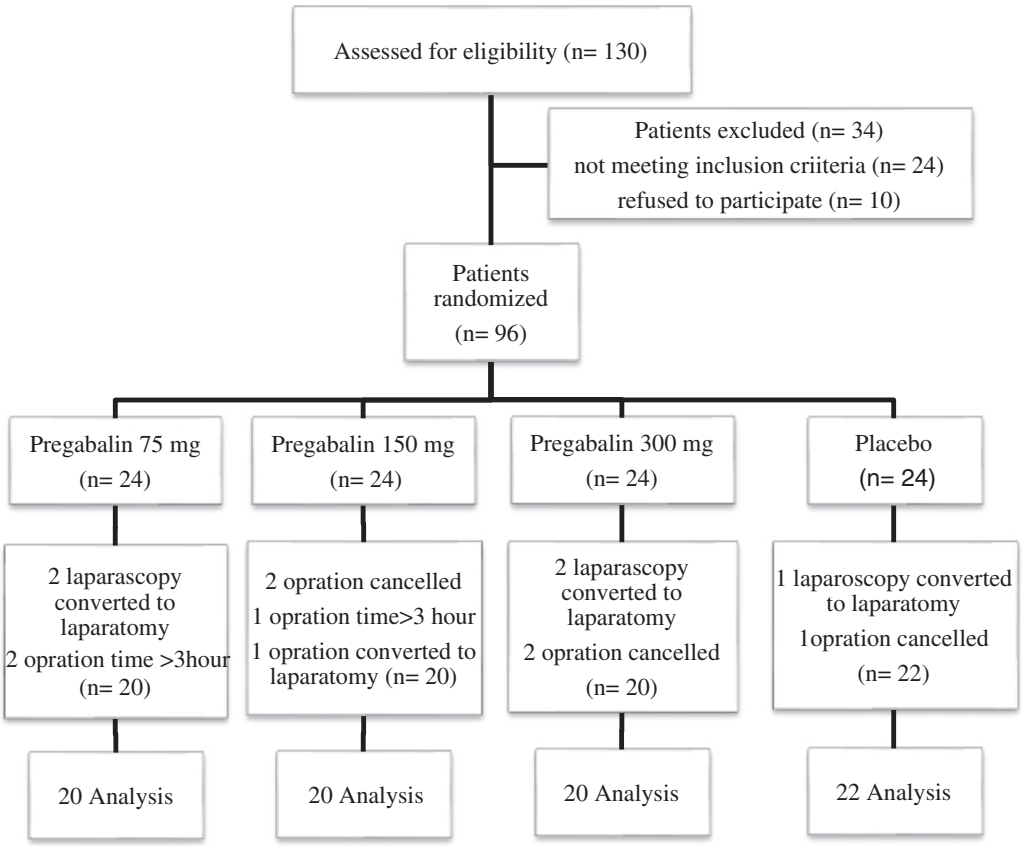

Fig. 1. Flowchart showing participant recruitment.

2.6. Statistical analysis

Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS; SPSS Inc., USA) version 18. One way analysis of variance (ANOVA) and chi-square test were applied to compare baseline characteristics, secondary outcomes and side effects among groups. The primary outcomes (mean values of VAS scores at rest and on movement) were analyzed using repeated measures ANOVA. The model included treatment as fixed factor as well as age, weight and pethidine and diclofenac concentrations as covariates. Bonferroni post hoc test was also used to detect difference among groups at a particular time point. A P value of <0.05 indicated a significant difference.

3. Results

Of 130 patients screened for the study, 96 individuals were eligible and recruited in this trial. Subsequently, 60 were randomly assigned to three treatment groups and 22 to placebo group (Fig. 1). For analyzing data, intention-to-treat approach was adopted. Patients' demographic characteristics are shown in Table 1. The study groups were well matched with respect to demographics and disease characteristics.

A significant main effect of treatment was found for patients who received the pain relief at rest [$F(3, 74) = 17.38$; $P < 0.001$]. The model indicated that effect size for the treatment accounted for approximately 41.3% of the variations of pain relief at rest. Bonferroni post hoc test indicated a statistically significant difference regarding VAS score among four groups. Although the mean values of pain decreased for all groups during the study, repeated measures ANOVA revealed that there was no significant difference in this regard, indicating no significant changes over time occurred in four groups [$F(5, 375) = 1.59$; $P = 0.16$]. Also there was no interaction effect between the concentration used and particular time point, indicating that the difference in pain relief scores were identical in the different time intervals based on the concentration of pregabalin used [$F(15, 370) = 0.995$; $P = 0.46$].

For other primary outcome (pain relief on movement), there was a statistically significant difference regarding the position of patient [$F(1, 74) = 5.56$; $P = 0.021$], indicating treatment was effective [$F(3, 74) = 5.62$; $P = 0.002$] and only accounted for approximately 18.6%

Table 1
Baseline demographics and disease characteristics of all participants.

	Group 1 (n = 20)	Group 2 (n = 20)	Group 3 (n = 20)	Placebo (n = 22)	P-value
Age (years)	46.75 ± 5.82	47.2 ± 4.71	45.2 ± 7.43	44.45 ± 6.52	0.446
Weight (kg)	75.05 ± 7.33	74.95 ± 9.01	76.15 ± 6.79	72.95 ± 11.36	0.7
Height (cm)	161.3 ± 7.01	161.1 ± 4.1	161.5 ± 3.92	160.22 ± 4.57	0.852
Parity	3.4 ± 0.68	3.35 ± 0.74	3.35 ± 0.58	3.27 ± 0.76	0.949
Type of hysterectomy (n %)					
TLH	13 (65)	18 (90)	16 (80)	16 (72.7)	0.296
SLH	7 (35)	2 (10)	4 (20)	6 (27.3)	

TLH = total laparoscopic hysterectomy, SLH = supracervical laparoscopic hysterectomy. Values are given as mean ± SD or number (percentage) unless otherwise indicated.

of the variations of pain relief on movement (Fig. 2). All groups were different based on post hoc analysis. Similar to primary outcomes, the effect of treatment was homogenous during all three time intervals and there was no interaction effect between treatment types and time intervals [$F(3, 74) = 1.28$; $P = 0.28$]. Tables 2 and 3 show scores [means and standard deviation (SD)] of pain at rest and on movement in six time-interval measurements for all groups.

3.1. Secondary outcomes and side effects

Frequency of side effects, such as nausea and vomiting, were similar among all groups, suggesting there were no significant differences in this regard ($P = 0.098$). The side effects and secondary outcomes of the four groups are given in Table 4. A significant difference was observed for sedation scores among the groups ($P < 0.001$). Post hoc tests analysis showed in group 3, the mean values of sedation scores were significantly higher than other groups, but there was no significant difference among four groups. There were also no significant differences among the groups regarding duration of surgery ($P = 0.052$) and average blood loss ($P = 0.56$). There was no statistically significant difference regarding insertion of closed drain (as a factor affecting pain score) after surgery among four groups ($P = 0.89$). Frequency of other side effects, such as dizziness, headache, visual disturbance and itching, was negligible in all groups.

4. Discussion

Minimally invasive technique was introduced for patients to feel comfortable with less postoperative pain than open procedure [1]. But tissue trauma or injury is excruciatingly painful in the postoperative period [13]. Opioids have been used exclusively; however, its side effects that diminish the benefits of laparoscopic procedures [4]. Pregabalin may play a significant role in postoperative pain management by reducing the hyperexcitability of dorsal horn neurons induced by tissue damage. The time required to reach peak plasma concentration of pregabalin is 1 h, while steady state is achieved within 24–48 h [14]. The effect of pregabalin in acute postoperative pain management has been evaluated in several studies, but pregabalin concentrations and types of surgeries are controversial [8,15–18].

The major finding of the current study is that preemptive pregabalin for laparoscopic hysterectomy was associated with better pain relief regardless of its concentrations. These observations are in accordance with a number of studies [16,17]. Our result showed use of low concentration of pregabalin (75 mg) was significantly more effective than control group in postoperative pain management. Two other studies revealed that low concentration of pregabalin did fail to decline postoperative pain that may be due to single low-concentration of pregabalin administrated or the heterogeneous characteristic of cases [9,19].

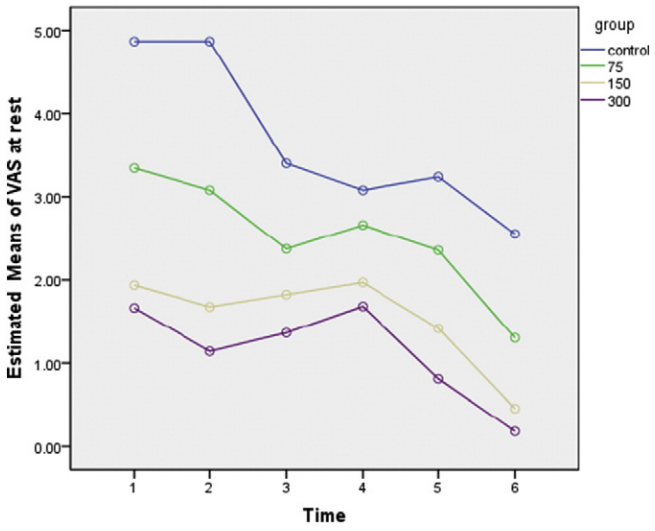

Fig. 2. Pain scores in patients who underwent laparoscopic hysterectomy.

Table 2
Comparison of the results of pain scores (VAS at rest).

Parameters	Group 1 (n = 20)	Group 2 (n = 20)	Group 3 (n = 20)	Placebo (n = 22)
Time0	3.35 ± 0.74	1.95 ± 0.6	1.65 ± 0.58	4.86 ± 0.71
Time2	3.1 ± 0.44	1.7 ± 0.8	1.15 ± 0.81	4.81 ± 0.79
Time4	2.4 ± 0.59	1.8 ± 0.74	1.4 ± 0.68	3.31 ± 0.94
Time6	2.65 ± 0.81	1.95 ± 0.51	1.7 ± 1.03	3.09 ± 0.97
Time12	2.35 ± 0.67	1.4 ± 0.5	0.85 ± 0.67	3.22 ± 0.92
Time24	1.3 ± 0.47	0.45 ± 0.6	0.2 ± 0.41	2.54 ± 0.67

We demonstrated that the higher concentrations of pregabalin (150 mg and 300 mg) improved VAS score significantly. Similar results were observed in the studies including patients with laparoscopic cholecystectomy and abdominal hysterectomy [16–18,20,21]. However, in some other studies, higher concentration of pregabalin was associated with an increased risk of adverse effects [21].

On the contrary, Jokela et al. concluded that preoperative concentrations of 150 and 300 mg of pregabalin not only failed to decrease postoperative pain score after laparoscopic hysterectomy, but also was associated with an increased incidence of adverse effects (dizziness, blurred vision and headache) [22]. The differences between our findings and those of Jokela et al. may be attributed to the fact that our patients received preemptive analgesia in two concentrations before surgery, and third concentration was giving 6 h after surgery to produce a better control of analgesia. Furthermore, Jokela et al. used the simple statistical analysis such as *t*-test or ANOVA test leading to less accurate results as compared to repeated measures ANOVA we used to control the confounder factors [8,9,16,17,19,21,22].

However, randomization in clinical trial can control confounder variable, but there is some unknown relation between several variable that cause some interactions between pregabalin and NSAIDs [23]. For instance, if pain score and analgesic consumption are evaluated as two separate outcomes, pure effect of pregabalin or influence of analgesic consumption on pain score will not be considered. We used the analgesic drugs (pethidine and diclofenac) as cofounder variables in repeated ANOVA. Pain scores at rest and on movement were less in pregabalin groups than control group, and 300 mg of pregabalin was the most effective concentration.

In a recent meta-analysis, Mishriky et al. concluded that pregabalin was associated with a significant reduction in pain scores at rest and on movement in opioid-consumption group as compared with placebo; however, they did not suggest the proper concentrations of pregabalin for acute pain management [24]. In our study, incidence of side effects was not significant, although sedation score was significantly greater in 300 mg of pregabalin.

Moreover, studies administering higher concentration of pregabalin (600 mg) were accompanied with a higher incidence of side effects such as dizziness and sedation [21,22,25]. Hence, we suggest the use of 150 mg of pregabalin for better pain control and lower side effect. The number of patients who complained of postoperative nausea and vomiting was the same in four groups, indicating a safe medication as compared to the control group.

Table 3
Comparison of the results of pain scores (VAS on movement).

Parameters	Group 1 (n = 20)	Group 2 (n = 20)	Group 3 (n = 20)	Placebo (n = 22)
Time12	2.9 ± 0.71	2.05 ± 0.51	1.15 ± 0.58	3.86 ± 0.83
Time24	1.9 ± 0.44	1.25 ± 2.12	0.25 ± 0.44	3.04 ± 0.65

Values are given as mean ± SD.

Table 4
Comparison of the results of secondary outcomes and side effects.

	Group 1 (n = 20)	Group 2 (n = 20)	Group 3 (n = 20)	Placebo (n = 22)	P-value
Surgery time (min)	147.5 ± 21.49	138.75 ± 22.93	135.5 ± 22.35	122.63 ± 34.15	0.052
Average blood loss (ml)	74.5 ± 14.39	58.5 ± 7.98	58 ± 7.73	75 ± 13.68	0.56
Sedation score	1 ± 0.28	1.25 ± 0.55	4.75 ± 0.71	0.95 ± 0.21	<0.001
Pethidine dosage					
0	0 (0)	1 (5)	20 (100)	20 (100)	<0.001
50 (one dose)	4 (18.2)	19 (95)	0 (0)	0 (0)	
100 (two dose)	18 (81.8)	0 (0)	0 (0)	0 (0)	
Drain after surgery					
Yes	8 (40)	9 (45)	7 (35)	10 (45.5)	0.89
No	12 (60)	11 (55)	13 (65)	12 (54.5)	
Side effect					
Without nausea	12 (60)	10 (50)	10 (50)	10 (45.5)	0.98
Mild nausea	5 (25)	7 (35)	5 (25)	6 (27.3)	
Moderate nausea	2 (10)	2 (10)	3 (15)	3 (13.6)	
Nausea with vomiting	1 (5)	1 (5)	2 (10)	3 (13.6)	

Values are given as mean ± SD or number (percentage) unless otherwise indicated.

Our study has some advantages. It is a prospective randomized clinical trial survey with different concentrations of pregabalin, same type of surgery with only a surgical team, as well as use of more accurate statistical analysis. Limitations of the present study were small sample size. Efficacy should, therefore, be tested in larger samples.

5. Conclusion

Our data demonstrated preemptive administration of 75, 150, and 300 mg pregabalin play an important role in reducing postoperative pain after laparoscopic hysterectomy. Comparison of different concentrations and side effects indicates oral administration of 150 mg pregabalin is an effective and safe method for postoperative pain management after laparoscopic hysterectomy.

Acknowledgments

The authors have no conflicts of interest.

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