

# Efficacy of Pregabalin as Premedication for Post-Operative Analgesia in Vaginal Hysterectomy

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Received 2015 November 11; Revised 2015 December 28; Accepted 2016 January 26.

## Abstract

**Background:** Pregabalin, a structural analogue of gamma amino butyric acid (GABA), is shown to be effective in treatment of several types of neuropathic pain, incisional injury, and inflammatory injury.

**Objectives:** The aim of the present study is to compare the efficacy of two doses (75 mg or 150 mg) of pregabalin with the administration of a placebo for post-operative analgesia in patients undergoing hysterectomy under spinal anesthesia.

**Patients and Methods:** A randomized, placebo-controlled trial was conducted on 135 patients undergoing vaginal hysterectomy under spinal anesthesia. The patients were divided in three groups of 45 patients each: group 0, placebo; group 1, 75 mg pregabalin; and group 2, 150 mg pregabalin; each treatment of which was administered one hour before surgery. The Ramsay sedation scale (RSS) was used for pre-operative assessment and the visual analog scale (VAS) was used to determine pain at rest and for cough on the first post-operative day. The time for the requirement of rescue analgesics on the first post-operative day was also assessed.

**Results:** The RSS scores were significantly higher in groups 1 and 2 as compared to the controls ( $P < 0.001$ ). Postoperative VAS scores for pain both at rest and on cough were significantly reduced in groups 1 and 2 ( $P < 0.001$ ). Rescue analgesic consumption decreased significantly in groups 1 and 2 ( $P < 0.001$ ). The time at which rescue analgesia was administered (first dose) was 4.45 hours in group 0, 10.86 hours in group 1, and 16.82 hours in group 2 ( $P < 0.001$ ).

**Conclusions:** Pregabalin administered as premedication provided significant postoperative pain relief and decreased the requirement of other parenteral analgesics. Pregabalin doses of 150 mg had a better analgesic profile, but the advantages of their use may be limited by side effects such as dizziness. Thus, it is concluded that pregabalin doses of 75 mg may be the optimal pre-emptive dose.

**Keywords:** Pregabalin, Post-Operative Analgesia, Hysterectomy

## 1. Background

Pain has been a major concern for all people at one time or another, and has been the object of many pervasive efforts to understand and control it. Postoperative pain is an acute form of pain which begins with surgical trauma and usually terminates with tissue healing. Even with the recent advances in the knowledge, skill, and sophisticated technology that characterize most modalities of treatment, patients continue to experience pain during the postoperative period.

Postoperative analgesia results in faster recovery and hence reduces medical costs. The current predominant approach of multimodal postoperative analgesia is mostly based on a combination of opioids, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, and perioperative administration of local anesthetics. Each of these approaches comes with its own set of complications (1). For instance, the use of opioids may be limited by adverse side

effects such as nausea, vomiting, excessive sedation, respiratory depression, pruritus, and urinary retention (1, 2). NSAIDs have adverse gastrointestinal effects such as gastritis and upper gastro intestinal ulceration (3). Furthermore, interventional techniques such as epidural analgesia require additional work and carry the potential risk of further complications such as hypotension and local anesthetic toxicity (2).

Pregabalin is a structural analogue of gamma amino butyric acid (GABA). It acts through presynaptic binding to the alpha-2-delta subunit of voltage gated calcium channels that are widely present in both the spinal cord and the brain. Therefore, it modulates the release of many excitatory neurotransmitters, such as glutamate, norepinephrine, substance-P, and calcitonin gene related peptide. It causes inhibitory modulation of overexcited neurons and restores them to a normal state. Centrally, pregabalin is able to decrease the hyper excitability of the dorsal

horn neurons that is caused by tissue damage (4, 5).

## 2. Objectives

Several studies have reported pregabalin as an effective post-operative analgesic with opioid sparing effects (5-8). However, there have been contrary reports of pregabalin having no significant post-operative analgesic effects (9). Against this background, it was hypothesized that preoperative use of pregabalin may reduce the requirement of post-operative analgesics. Hence, the primary objectives of the present study were to compare the efficacy of two doses (75 mg or 150 mg) of pregabalin against the administration of a placebo for post-operative analgesia in patients undergoing hysterectomy under spinal anesthesia, and to study the adverse effects (if any) due to pregabalin use.

## 3. Patients and Methods

After obtaining ethical committee clearance, a prospective randomized control study was conducted on 135 patients scheduled for vaginal hysterectomy under spinal anesthesia during the period of January 2013 to August 2014. Written informed consent was obtained from all of the patients. The visual analogue scoring (VAS) system was explained to the patients. Inclusion criteria for the study were as follows: 1) age 30 - 65 years old, 2) American society for anesthesiologists (ASA) physical status of 1 - 3, and 3) body mass index (BMI) of 18 - 35 kg/cm<sup>2</sup>. Exclusion criteria were the following: 1) refusal to participate in the study; 2) use of anti-anxiety drugs (or having anti-anxiety drugs given preoperatively); 3) history of drug/alcohol abuse; 4) history of headache, dizziness, or significant post-operative nausea or vomiting after any previous surgery; 5) history of chronic pain and daily intake of analgesic drugs; 6) history of epilepsy; 7) failed spinal anesthesia; and 8) any contraindication to spinal anesthesia.

The study subjects were allocated into 3 groups of 45 patients each using a computer generated random number table:

Group 0 (control): all patients belonging to this group were administered a placebo orally one hour before being shifted to the operation theatre.

Group 1 (75 mg pregabalin): all patients belonging to this group were administered a 75 mg capsule of pregabalin orally one hour before the patient was shifted to the operation theatre.

Group 2 (150 mg pregabalin): all patients belonging to this group were administered a 150 mg capsule of pregabalin orally one hour before the patient was shifted to the operation theatre.

The pre-operative baseline blood pressure and heart rate (before premedication, at 30 minutes after premedication, and at 1 hour after premedication) were recorded. The Ramsay sedation score (1 to 6) was assessed 1 hour after administering the drug. A score of 3 or more was taken as implying that adequate sedation had been obtained.

All of the patients were administered spinal anesthesia in the sitting position, between the 2<sup>nd</sup> and 3<sup>rd</sup> lumbar intervertebral space with a 25-gauge Whitacre needle (0.5% hyperbaric bupivacaine at 0.3 mg/kg intrathecally). For post-operative pain analgesia, intravenous paracetamol of 1 g 8<sup>th</sup> hourly was given to all patients. Rescue analgesics were administered if VAS > 4. The first rescue analgesic was intravenous tramadol of 50 mg, and intravenous diclofenac of 75 mg was given if VAS > 4 persisted for 30 minutes after the first rescue analgesic.

The following parameters were assessed: 1) VAS was assessed for pain at rest and on cough at 30 minutes, 1 hour, 2 hours, 6 hours, 12 hours, and 24 hours post-operatively. The number of doses of rescue analgesics required and the time to first or second rescue analgesic was noted on post-operative day one; 2) post-operative sleep quality was assessed on a grade of 1 to 5, where grade 1 meant "could not sleep at all," grade 2 meant "difficulty in falling asleep," grade 3 meant "woke up two or more times during the night," grade 4 meant "woke up once during the night," and grade 5 meant "did not wake up even once during the night. A grade of 4 or 5 was considered as adequate post-operative sleep; 3) Other adverse effects such as dizziness, nausea, and vomiting were also noted.

A study carried out by Kohli and colleagues (7) on the "optimization of subarachnoid block by oral pregabalin for hysterectomy" with 3 groups, group 1 was the control group, group 2 was administered 150 mg pregabalin, and group 3 was administered 300 mg pregabalin, all of which was given orally one hour before surgery. It was observed that the time required for the first rescue analgesia with pregabalin 150 mg as premedication was 178.38 ± 4.80 minutes post-surgery, and with the placebo group, it was 131.38 ± 5.15 minutes post-surgery. The study had a power of 80% and a confidence interval of 95%. For the present study, in order to obtain the same power of 80% and confidence interval of 95%, 43 patients needed to be included in each group. Thus it was proposed to include a total of 135 patients with 45 patients in each group.

Descriptive and inferential statistical analysis was carried out. The results of the continuous measurements are presented as mean ± SD (minimum - maximum), and the results of the categorical measurements are presented as numbers (%). The significance level was assessed at 5%. The following assumptions about the data were made: 1) dependent variables should be normally distributed; and 2)

samples drawn from the population should be random.

Analysis of variance (ANOVA) was used to determine the significance of study parameters between three or more groups of patients. A post-hoc Tukey's test was used to find the group significance for the pairs. Chi-square and Fisher's exact tests were used to determine the significance of the study parameters on a categorical scale between two or more groups. Statistical software, namely SAS 9.2 and R environment ver. 2.11.1 were used for the analysis of the data. A P value of  $< 0.05$  was taken as significant.

#### 4. Results

In terms of the demographic profile, the groups were comparable with respect to age and BMI (Table 1).

**Table 1.** Comparison of Age and BMI Distribution<sup>a</sup>

Demographic Profile	Group 1	Group 2	Group 0
Average Age, y	46.73 $\pm$ 9.85	46.42 $\pm$ 10.57	47.69 $\pm$ 9.12
Average BMI	24.48 $\pm$ 3.88	25.09 $\pm$ 2.6	25.88 $\pm$ 3.89

<sup>a</sup>Values are expressed as mean  $\pm$  SD.

After comparing the preoperative Ramsay sedation score (RSS) between the groups one hour after receiving premedication, it was found that a majority of patients (i.e. 44 or 97.8%) had an RSS score of 1 or 2. However, in groups 1 and 2, 66% and 24.4% of patients had the same scores, respectively. A majority of the patients (i.e. 34 or 75.6%) in group 2 had an RSS score of  $\geq 3$ . In group 1, 11 patients (24.4%) and in group 0, 1 patient (2.2%) had an RSS score of  $\geq 3$ . With respect to the inter-group comparison for patients with RSS  $\geq 3$ , in group 1 versus group 0, the p value was 0.002, and thus group 1 had significantly more patients with RSS scores of 3 and 4. When comparing group 2 and group 0, the P value was  $< 0.001$ , showing that group 2 had significantly more patients with RSS scores of 3 and 4. When looking at group 1 and group 2, the P value was  $< 0.001$ , showing that group 2 had significantly more patients with RSS scores of 3 and 4.

With respect to the VAS scores, as shown in Table 2, the pain scores were lower for group 1 and group 2 as compared to group 0 at all times. When comparing group 1 with group 0, it was seen that the pain scores were significantly low ( $P < 0.05$ ) for group 1 at all times except at 6 hours, 12 hours and 24 hours. In group 2 as compared to group 0, it was observed that pain scores were significantly low in group 2 ( $P < 0.05$ ) at all times except at 12 and 24 hours. When comparing group 1 with group 2, it was seen that pain scores were significantly lower in group 2 ( $P < 0.05$ ) at all times except at 24 hours.

Table 3 shows the VAS results for pain on coughing. Pain scores were lower in group 1 and group 2 as compared to group 0 for most observations. Upon inter-group comparison between group 1 and group 0, group 1 had significantly lower pain scores ( $P < 0.05$ ) at all times except at 6 hours, 12 hours, and 24 hours post-op. In group 2 compared to group 0, it was shown that the pain scores were significantly lower in group 2 ( $P < 0.05$ ) at all times except at 12 and 24 hours. When comparing group 1 with group 2, it was shown that pain scores were significantly lower in group 2 ( $P < 0.05$ ) at all times except at 24 hours. Ultimately, these values revealed that pregabalin 75 or 150 mg reduced post-operative pain at rest as well as on coughing.

Table 4 shows the values for the rescue analgesics. An inter-group comparison between group 1, group 2, and group 0 showed that there were significantly lower ( $P < 0.001$ ) requirements for rescue analgesics as compared to those required for group 0. Also group 2 had significantly less analgesic requirements ( $P < 0.001$ ) than group 1.

Table 5 shows the average times for the first rescue analgesic, which were 4.45 hours for group 0, 10.86 hours for group 1, and a maximum of 16.8 hours in group 2. Inter-group comparison revealed a significant difference in time for the first rescue analgesic consumption with a P value of  $< 0.001$  for each comparison.

Concerning post-operative sleep, in the placebo group, a majority of patients had grade 3 (42.2%) or grade 4 (35.6%) sleep character; 8 (17.8%) of the patients had grade 2, and there was 1 (2.2%) patient each in the grade 1 and grade 5 groups. In group 1, a majority of the patients had grade 4 sleep character (53.3%); 10 (22.2) patients had grade 5 sleep, 8 (17.8%) patients had grade 3, and 3 (6.7%) patients had grade 2 sleep character. In group 2, a majority of the patients (i.e. 28 or 62.2%) had grade 5 sleep character, 16 patients (35.6%) had grade 4, and 1 patient (2.2) had grade 3. With respect to inter-group comparison, significant differences were seen between the groups ( $P < 0.05$ ) which revealed that patients in group 1 and group 2 had better sleep than those in group 0. Also, patients in group 2 had better sleep than those in group 1. With respect to other adverse effects, the incidence of nausea was 84.4% (38 patients), 88.9% (40 patients), and 84.4% (43 patients) in groups 0, 1, and 2, respectively. The incidence of vomiting was 35.6% (16 patients), 31.1% (14 patients), and 48.9% (22 patients) in each of the respective groups. Nausea and vomiting were comparable between the groups with  $P > 0.05$ . The incidence of dizziness was significantly higher ( $P < 0.001$ ) in both group 1 (28 patients or 62.2%) and group 2 (42 patients or 93.3%), whereas in group 0, only 2 patients (4.4%) had dizziness. Inter-group comparison between group 1 and group 2 showed that the incidence of dizziness more significant in group 2 ( $P < 0.001$ ).

**Table 2.** Comparison of VAS Scores at Rest in the 3 Groups Studied

VAS-rest	Results <sup>a</sup>				Significance (P Value) <sup>b</sup>		
	Group I	Group II	Group 0	Total	G1-GII	G1-G0	GII-G0
30 min	1.53 ± 0.76	1.04 ± 0.21	2.49 ± 0.94	1.69 ± 0.93	0.004	< 0.001	<0.001
1 h	1.73 ± 0.65	1.13 ± 0.34	3.00 ± 0.71	1.96 ± 0.98	< 0.001	< 0.001	< 0.001
2 h	2.42 ± 0.75	1.78 ± 0.42	3.33 ± 0.83	2.51 ± 0.94	< 0.001	< 0.001	< 0.001
6 h	2.60 ± 0.69	2.07 ± 0.25	2.80 ± 1.10	2.49 ± 0.82	0.003	0.430	< 0.001
12 h	3.27 ± 1.01	2.78 ± 0.70	2.96 ± 0.93	3.00 ± 0.91	0.027	0.225	0.611
24 h	3.33 ± 0.80	3.13 ± 0.59	3.44 ± 0.72	3.30 ± 0.72	0.377	0.738	0.097

<sup>a</sup>Values are expressed as mean ± SD.<sup>b</sup>ANOVA test; post-hoc Tukey's test.**Table 3.** Comparison of VAS Scores on Cough in the 3 Groups Studied

VAS-Cough	Results <sup>a</sup>				Significance (P Value) <sup>b</sup>		
	Group 1	Group 2	Group 0	Total	G1-G2	G1-G0	G2-G0
30 min	2.47 ± 0.76	2.00 ± 0.00	3.13 ± 0.99	2.53 ± 0.85	0.007	< 0.001	< 0.001
1 h	2.64 ± 0.68	2.02 ± 0.15	3.62 ± 0.89	2.76 ± 0.92	< 0.001	< 0.001	< 0.001
2 h	3.27 ± 0.84	2.58 ± 0.50	4.42 ± 1.08	3.42 ± 1.13	< 0.001	< 0.001	< 0.001
6 h	3.58 ± 0.75	3.00 ± 0.21	3.80 ± 1.24	3.46 ± 0.90	0.004	0.427	< 0.001
12 h	4.36 ± 1.21	3.58 ± 0.78	3.87 ± 1.04	3.93 ± 1.07	0.001	0.065+	0.377
24 h	4.36 ± 0.91	4.07 ± 0.65	4.42 ± 0.92	4.28 ± 0.84	0.232	0.924	0.112

<sup>a</sup>Values are expressed as mean ± SD.<sup>b</sup>ANOVA test; post-hoc Tukey's test.**Table 4.** Rescue Analgesics<sup>a,b</sup>

Rescue Analgesics	Group 1	Group 2	Group 0	Total
0 dose	20 (44.4)	34 (75.6)	4 (8.9)	58 (43)
1 dose	16 (35.6)	11 (24.4)	18 (40)	45 (33.3)
2 doses	9 (20)	0	23 (51.1)	32 (23.7)
Total	45 (100)	45 (100)	45 (100)	135 (100)

<sup>a</sup>Values are expressed as No. (%).<sup>b</sup>Group 1-group 2: P < 0.001; Group 1-group 0: P < 0.001; Group 2-group 0: P < 0.001.**Table 5.** Time to Rescue Analgesic: A Comparison of the 3 Groups Studied

Time; Rescue Analgesic	Results				Significance (P Value)		
	Group 1	Group 2	Group 0	Total	G1-G2	G1-G0	G2-G0
First dose, h	10.86 ± 5.38	16.82 ± 3.06	4.45 ± 3.05	8.33 ± 5.99	< 0.001	< 0.001	< 0.001
Second dose, h	19.67 ± 4.06	-	17.78 ± 4.17	18.31 ± 4.16	-	0.256	-

## 5. Discussion

Surgery produces tissue injury with consequent release of histamine and other inflammatory mediators and

neurotransmitters which activate peripheral nociceptors causing pain (10). Continuous release of inflammatory me-

diators in the periphery sensitizes functional nociceptors and activates dormant ones. The intensity of acute postoperative pain is a significant predictor of chronic postoperative pain (11). Thus, control of perioperative pain and the fashion in which it is implemented is important in facilitating short and long term convalescence after surgery. A number of drugs like NSAIDs, opioids, ketamine, gabapentinoids, and a variety of regional anesthesia techniques have been used in multimodal approaches to achieve postoperative analgesia (12-14).

Pregabalin (S-[+]-3-isobutylgaba) was designed as a lipophilic GABA ( $\gamma$ -aminobutyric acid) analog. Pregabalin, like gabapentin, has been shown to be effective in several models of neuropathic pain, incisional injury, and inflammatory injury. It is also effective in the treatment of anxiety and as a sleep-modulating drug. Pregabalin has been shown to increase slow-wave sleep in healthy volunteers. Slow-wave sleep has been correlated with the restorative aspects of sleep, and is therefore important for the postoperative healing process (5, 15, 16).

Vaginal hysterectomies constitute a major part of gynecological surgeries. This study compared the effects of two doses of pregabalin (75 mg and 150 mg) with a placebo as pre-operative medication on post-operative pain relief in patients undergoing vaginal hysterectomy. In our study, VAS scores were significantly lower ( $P < 0.05$ ) in the pregabalin groups with respect to placebo at 30 minutes, 1 hour, and 2 hours post-operatively. When comparing group 1 and group 2, it was observed that the pain scores were significantly lower ( $P < 0.05$ ) in group 2. These differences may be attributed to higher doses of pregabalin (150 mg) in group 2, which produced a prolonged effect. The pain scores were comparable at 6 hours, 12 hours, and 24 hours post-operatively both at rest and on coughing. This is in accordance with the pharmacokinetic profile of pregabalin, which has an elimination half-life of 4.6 to 6.8 hours after a single dose, which could be the reason for the comparable VAS score at 6 hours. Similar results of lower VAS at rest and upon movement were reported by Jokela and colleagues (9) and Agarwal et al. (17) with the administration pre-operative single doses of pregabalin. Similarly, a lower pain intensity was reported by Alimian et al. in their study of laparoscopic gastric bypass patients receiving pregabalin premedication (18). However, Paech et al. (19) found no such reduction in VAS in their study.

The results of this study have revealed that the time for first rescue analgesic was significantly increased ( $P < 0.001$ ) in the pregabalin group. Post-operative rescue analgesic requirements were also significantly lower in the pregabalin groups (group 2 < group 1 < group 0). Similar studies have been reported by others (7, 8, 18, 20). These results signify that pregabalin premedication provides significant

postoperative analgesia. Furthermore, sedation has been described as a significant effect in the pharmacology of pregabalin (4). We found that pregabalin patients were adequately sedated (RSS > 3) one hour after administration. They also had better sleep profiles postoperatively. Dizziness has been described as the most common adverse effect after a single dose (21). However, despite these advantages, dizziness was found to be significantly high in the study group (group 2 > group 1 > group 0) which was observed in other similar studies (7, 17, 18). Agarwal et al. (17) also reported significant nausea and vomiting in the pregabalin group, but none of the patients in our study had such occurrences. Therefore, it can be said that the advantages clearly outweigh the potentially adverse side effects.

One of the limitations of this study is that the total duration of surgery was not variable in the final results. Longer surgery would have involved more tissue handling and subsequently more post-operative pain. To keep the surgical time comparable, only those cases which could be completed within the duration of spinal anesthesia with bupivacaine were included. We excluded those cases where the surgical time exceeded the duration of spinal anesthesia and required additional intravenous opioids/local infiltration at the surgical site or those converted to general anesthesia.

The present study clearly reveals the analgesic and sedative efficacy of pregabalin given administered premedication in patients undergoing vaginal hysterectomy under spinal anesthesia. This was shown through the lower post-operative VAS scores, the decreased need of rescue analgesics, and the greater time before the first rescue analgesic. Pregabalin 150 mg had a better analgesic profile but its use may be limited by the increased incidence of dizziness. Thus, pregabalin 75 mg may be the optimal pre-emptive dose for vaginal hysterectomies under spinal anesthesia.

## Footnote

**Authors' Contribution:** All authors have contributed as follow: 1- study concept and design; 2- acquisition of data; 3- analysis and interpretation of data; 4- drafting of the manuscript; 5- critical revision of the manuscript for important intellectual content; 6- statistical analysis; 7- administrative, technical, and material support; 8- study supervision.

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