

A randomized controlled trial to compare pregabalin with gabapentin for postoperative pain in abdominal hysterectomy

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ABSTRACT

Background: Pregabalin is a potent ligand for alpha-2-delta subunit of voltage-gated calcium channels in the central nervous system, which exhibits potent anticonvulsant, analgesic and anxiolytic activity. The pharmacological activity of pregabalin is similar to that of gabapentin and shows possible advantages. Although it shows analgesic efficacy against neuropathic pain, very limited evidence supports its postoperative analgesic efficacy. We investigated its analgesic efficacy in patients experiencing acute pain after abdominal hysterectomy and compared it with gabapentin and placebo. **Methods:** A randomized, double-blind, placebo-controlled study was conducted in 90 women undergoing abdominal hysterectomy who were anaesthetized in a standardized fashion. Patients received 300 mg pregabalin, 900 mg gabapentin or placebo, 1–2 hours prior to surgery. Postoperative analgesia was administered at visual analogue scale (VAS) ≥ 3 . The primary outcome was analgesic consumption over 24 hours and patients were followed for pain scores, time to rescue analgesia and side effects as secondary outcomes. **Results:** The diclofenac consumption was statistically significant between pregabalin and control groups, and gabapentin and control groups; however, pregabalin and gabapentin groups were comparable. Moreover, the consumption of tramadol was statistically significant among all the groups. Patients in pregabalin and gabapentin groups had lower pain scores in the initial hour of recovery. However, pain scores were subsequently similar in all the groups. Time to first request for analgesia was longer in pregabalin group followed by gabapentin and control groups. **Conclusion:** A single dose of 300 mg pregabalin given 1–2 hours prior to surgery is superior to 900 mg gabapentin and placebo after abdominal hysterectomy. Both the drugs are better than placebo.

Key words: Abdominal hysterectomy, gabapentin, postoperative pain, pregabalin

INTRODUCTION

High-quality pain control after surgery is still a major challenge. Although opioids have been the mainstay of postoperative pain management, they are not free from side effects. A multimodal approach has been suggested to improve postoperative analgesia and to reduce opioid related side effects. Surgical stimulation is associated with central and peripheral sensitization. Antihyperalgesic drugs

improve postoperative pain by preventing the development of central sensitization.^[1]

Gabapentin is a structural analogue of gamma-aminobutyric acid (GABA) which was initially introduced as an antiepileptic drug. It binds to $\alpha 2$ - δ protein subunit of voltage-gated calcium channels widely distributed in the central and peripheral system. This inhibits calcium influx and reduces excitatory neurotransmitter release in pain pathways.^[2] Pregabalin has an amino acid substitution at third position, which allows increased lipid solubility and diffusion across blood brain barrier, better pharmacokinetic profile and fewer drug interactions due to the absence of hepatic metabolism.^[3] It is a potent and more effective analogue of gabapentin and acts as a better ligand for $\alpha 2$ - δ protein subunit than gabapentin.^[4] It has shown superior analgesic potency than gabapentin in rodent models of neuropathic pain.^[5] Pregabalin has been found to be equally

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Quick Response Code:	Website: www.saudija.org
	DOI: 10.4103/1658-354X.84097

effective to gabapentin, however, at much lower doses. It is due to much higher bioavailability (90% vs. 33–66%) with low intersubject variability.^[6] Pregabalin does not undergo hepatic metabolism and is not bound to plasma proteins.^[7,8] It does not induce or inhibit liver enzymes such as the cytochrome P450 system. Therefore, pregabalin is unlikely to cause, or be subject to, pharmacokinetic drug–drug interactions studies. It is excreted virtually unchanged (<2% metabolism) by the kidneys and the elimination half-life ranges from 5.5 to 6.7 hours. This is not true with gabapentin as plasma concentrations have been found to have a non-linear relationship to increasing doses. The elimination half-life is 5–9 hours.^[9]

The analgesic effects of gabapentin have been investigated widely in surgical settings during the past few years. The findings of these trials suggest that gabapentin has analgesic effects in postoperative pain management.^[10-17] So far, evidence of the analgesic properties of pregabalin in postoperative pain is limited to controlled randomized trials conducted in patients of dental pain, minor and day-case gynecological surgery, laparoscopic hysterectomy and hip arthroplasty.^[18-22] The pharmacological and pharmacokinetic profiles of pregabalin provide a predictable basis for its use in clinical practice. To the best of our knowledge, there are no trials comparing pregabalin with gabapentin in postoperative pain in the available literature. With this background in mind, we designed this study to test the hypothesis that the preoperative use of pregabalin will reduce the consumption of analgesics after abdominal hysterectomy and to compare its efficacy and side effects with that of gabapentin and placebo. Another objective was to determine their effects on postoperative pain scores and side effects.

METHODS

The study was registered in a public database. The Ethical Committee of University of Health Sciences Chairman Prof. SS Sangwan approved the study in June 2007. After getting written informed consent from each participant, 90 women in the age group of 35–65 years, undergoing abdominal hysterectomy, were enrolled at Postgraduate Institute of Medical Sciences, Rohtak, Haryana. The inclusion criteria were ASA physical status I and II, not having any contraindications to the use of any of the study drugs or current use of gabapentinoids. Patients of age more than 65 years; having history of central nervous system disorders, chronic pain; using regular analgesics, sedatives and anticonvulsants; having known hypersensitivity to the study drug; impaired renal functions; and 20% more than the ideal body weight were excluded.

Study design

The study was randomized, double blind and placebo controlled. The computer-generated block randomization schedule was prepared using random number generator to create a list of random numbers by a statistician and was handed over to the hospital pharmacist. To ensure an equal number of patients in each group, block randomization was done. Stat Trek program was used to derive the randomization list. They also masked the study medication by packing these drugs in identical looking gelatine capsules containing either 900 mg gabapentin, 300 mg pregabalin or placebo. These were further packed and sealed in opaque envelopes labeled with name of the project, the investigator's name, and randomization number. Each patient received an appropriate randomization number. Participants were assigned to their group according to their number. The allocation sequence and enrollment of the patients was done by the same anesthetists who were involved in intraoperative and postoperative data collection. A total of four anesthetists were involved in the study (screening, enrollment of the patients, intraoperative and postoperative data collection). No person was aware of group assignment until all the 90 patients were included and the assessments were completed. Ultimately, there were 90 sequentially numbered opaque envelopes containing the masked study drug. Four anesthetists enrolled patients in the study.

Ninety women were allocated by means of sealed opaque envelopes bearing a code to three groups to receive pregabalin 300 mg (Group P), gabapentin 900 mg (Group G) or a matching placebo (Group C) ($n=30$ each) prepared by pharmacy. The study drug was administered orally 1–2 hours prior to surgery and no other sedative premedication given. Patients were familiarized with the use of a 10-cm linear visual analogue scale (VAS) for pain, where 0 denotes “no pain” and 10 denotes “worst imaginable pain”, the evening before surgery. Though they were explained about pain scale, no scores were recorded in this visit as the patients were not in pain preoperatively. In the operating room, electrocardiogram (ECG), noninvasive blood pressure (NIBP), heart rate (HR), and peripheral oxygen saturation (SpO_2) were monitored (Philips intellivue MP70). Anesthetic technique was standardized using propofol (2 mg/kg), fentanyl (2 μ g/kg), and vecuronium bromide (800 μ g/kg) and maintained using N_2O in oxygen and sevoflurane. Patients were extubated when fully awake. All the patients were transferred to post anesthesia care unit (PACU). An anesthesiologist, not a part of anesthesia team, assessed various parameters like VAS for pain scores at rest and on cough, during the first 2 hours at hourly intervals, then at 4, 6, 8, 12, 18 and 24 hours.

Outcome

Rescue analgesia was administered at VAS \geq 3 with intramuscular diclofenac sodium 1 mg/kg. Though abdominal hysterectomy is a highly painful surgery and usually requires good postoperative analgesia in the form of PCA morphine, we did not use it as an option due to non-availability of PCA in our institute. Secondly, while conducting pilot cases with 600 mg pregabalin, we found that patients even did not require any rescue analgesia in any form, while with 300 mg, either one or maximum two injections were required. Both the dosages were associated with good sedation and use of morphine could be further associated with added sedation; so, a milder form of analgesia was chosen. If the score did not decrease to the desired level, analgesia was supplemented with titrating tramadol 10 mg intravenously every 5 minutes till the score decreased to the desired level. Total analgesic consumption over 24 hours was noted in all the three groups and was considered as primary outcome. Pain scores and the time interval between end of surgery and patient's first request for analgesic (rescue interval) were considered as secondary outcomes. Sedation was assessed and scored as 0 = alert and conversant, 1 = awake but drowsy, 2 = asleep but arousable, 3 = asleep and not arousable. Side effects like nausea, vomiting, skin rash, somnolence, headache, dizziness, drowsiness, visual disturbances, peripheral edema and respiratory depression (sedation score > 2 and respiratory rate < 10 breaths/minute) were noted. Injection ondansetron 0.1 mg/kg was given when required. At the end of study, the data were unblinded and analyzed using SPSS 14.0.

Statistical analysis

Sample size was decided in consultation with a statistician. Sample size was calculated using a power of 90% and an α value of 0.05. Based on preliminary results from our department, the anticipated consumption of diclofenac sodium was 175 mg (standard deviation = 40 mg) in gabapentin group and a reduction in pregabalin group by 20% was considered significant. Based on these assumptions, a sample size of 28 per group was required. The sample size required for comparison between pregabalin and gabapentin came out to be 23 with tramadol using a power of 90% and an α value of 0.05. It seemed appropriate to adhere to 30 patients in each group, taking the sample size of previous trials also into consideration. No adjustment to the Type 1 error rate was made to accommodate the multiple analyses associated with the secondary outcome measures. One-way analysis of variance (ANOVA) was used for comparison of total analgesic consumption over 24 hours and the time intervals to first analgesic, whereas Tukey's Honestly Significant Difference (HSD) was used for multiple comparisons. Non-parametric Kruskal–Wallis test was used to compare the sedation

scores over 24 hours. The Chi-square test was applied to test the association between side effects and the study drug. Descriptive statistics are expressed as mean (SD).

RESULTS

This randomized, double-blind, placebo-controlled trial was conducted at PGIMS, University of Health Sciences, Rohtak, Haryana. A total of 100 patients were screened for the study, out of whom 90 were enrolled and randomized as the rest did not meet the inclusion criteria. None of the cases were dropped out as all were able to complete the study. The groups were comparable with respect to age, body weight and duration of surgery [Table 1]. Table 2 shows difference for consumption of diclofenac sodium ($P<0.001$), tramadol ($P<0.001$) by applying ANOVA on all three groups and time to first analgesia. The difference in the diclofenac consumption was statistically significant between pregabalin and control groups, and gabapentin and control groups; however, pregabalin and gabapentin groups were comparable. The difference in the consumption of tramadol was statistically significant between pregabalin and control groups, gabapentin and control groups, pregabalin and gabapentin groups. Time to first request for analgesia was 31 (32) minutes in pregabalin group, followed by 16 (18) minutes in gabapentin and 7 (2) minutes in control group. Though ANOVA has been used to compare time to first analgesic requirement despite the wide variations between groups, studies have shown that the significance level of hypothesis and confidence intervals remained close to the stated values if the sample sizes were equal. Analysis of sedation scores revealed significance in all the groups ($P<0.001$) at all measured times except at 24th hour. Sedation scores are shown in Table 3. The common side effects in the study were somnolence, dizziness, nausea

Table 1: Demographic and intraoperative characteristics

Group	Age (years)	Weight (kg)	Duration of surgery (minutes)
Pregabalin (n=30)	45 (7)	54 (11)	106 (33)
Gabapentin (n=30)	46 (6)	55 (10)	105 (29)
Control (n=30)	43 (6)	55 (7)	112 (30)

Data are expressed as mean (SD)

Table 2: Time to first analgesic and requirement of rescue analgesic (mean \pm SD)

Group	Time interval (minutes)	Diclofenac sodium (mg)	Tramadol (mg)
P	31.33 \pm 32.46	152.50 \pm 46.12	42.78 \pm 18.73£
G	16.23 \pm 17.50*	170.00 \pm 39.06	54.40 \pm 15.57
C	7.00 \pm 2.49**	250.00 \pm 35.9£	105 \pm 23.6££

*I versus II (P value < 0.05), £III versus II, I (P value < 0.001), **I versus III (P value < 0.001), £I versus II (P value < 0.05), ££III versus II, I (P value < 0.001)

and vomiting. There was no difference in the incidence of side effects between pregabalin and gabapentin groups. The incidence of somnolence was 40% in pregabalin group, 33.3% in gabapentin group, 3.3% in control group ($P=0.002$). Twenty-nine patients in control group had nausea and vomiting compared to 11 in pregabalin group and 21 patients in gabapentin group ($P<0.001$). Six patients reported dizziness in pregabalin group, eight in gabapentin group and one in control group ($P=0.093$). The incidence of headache, blurred vision, peripheral edema and skin rash was comparable in all the groups. Respiratory depression was not observed in any patient. Figures 1 and 2 display postoperative pain scores over time at rest and on cough, respectively. Patients in pregabalin and gabapentin groups had lower mean pain scores than placebo in the initial hour of recovery. However, pain scores were subsequently similar in all the groups.

DISCUSSION

The present study reveals that pregabalin 300 mg, given orally 1–2 hours before abdominal hysterectomy, resulted in significantly reduced postoperative analgesic requirement compared with gabapentin 900 mg and placebo. There were reduced pain scores, both at rest and on cough in the first hour of recovery. During the later hours of recovery, there

Table 3: Sedation score at different time intervals postoperatively (mean±SD)

Group	1 hour	2 hour	6 hour	12 hour
P	2.07±0.25	2.00	1.90±0.31	1.27±0.52
G	1.87±0.35	1.97±0.18	1.90±0.31	1.37±0.49
C	1.40±0.62*	1.47±0.57*	0.63±0.49*	0.17±0.38*

*III versus II, I (P value <0.001)

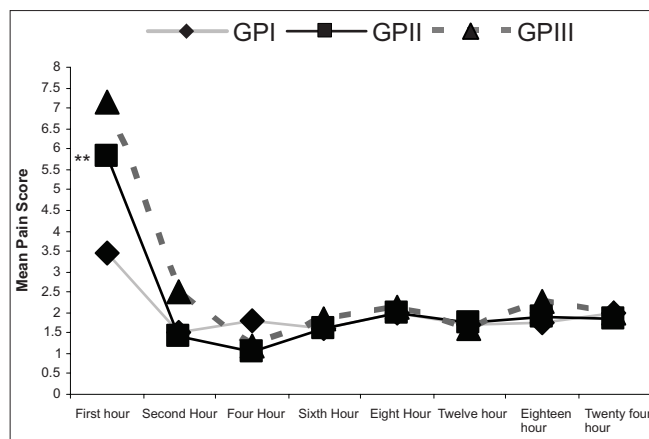


Figure 1: Visual analogue scale (VAS) scores for pain at rest postoperatively in different time intervals. Time 0 is taken as admission to the recovery. Results are expressed as mean (SD). Patients in pregabalin and gabapentin groups had lower mean pain scores in the initial hour of recovery than placebo group. However, pain scores were subsequently similar in all the groups

was no difference in pain scores between the groups. This finding is in accordance with the pharmacokinetic profile of both the drugs as they have short elimination life (6–8 hours) after a single dose.

Pregabalin, like gabapentin, is an amino acid derivative of gamma-aminobutyric acid (GABA analogue). It is pharmacologically active *S*-enantiomer of 3-aminomethyl-5-methyl-hexanoic acid, and has a similar pharmacological profile to gabapentin. Pregabalin has been found to have distinct pharmacokinetic advantages over gabapentin.

It probably shares the same mechanism of action with gabapentin but has a predictable and linear pharmacokinetic profile. It is associated with fewer dose-related adverse events as lower dosages can be used to treat neuropathic pain. Though it has been used in dosages starting from 150 mg and increasing to 600 mg a day in neuropathic pain, the commonly used dosage has been 300 mg for control of pain. The 300 mg dose of pregabalin used in our study was considered on the basis of previous studies.^[18,21,22] Gabapentin has been used preoperatively in varying dosages from 300 to 1200 mg, but 1200 mg has been the common, single highest safe dose used in previous trials on postoperative pain.^[10-13,16,17] This dose has been well tolerated except for minor side effects like dizziness and sedation.^[12] Our purpose of choosing 900 mg was also to find whether a dose below the already tested dose of 1200 mg could be equally efficacious at the cost of less side effects as the absorption of gabapentin is limited by saturable, active, dose-dependent transport in the gastrointestinal tract due to which absorption of gabapentin is 60% with 300 mg dose and decreases to 40% with 600 mg. This decreases to 35% at steady state with

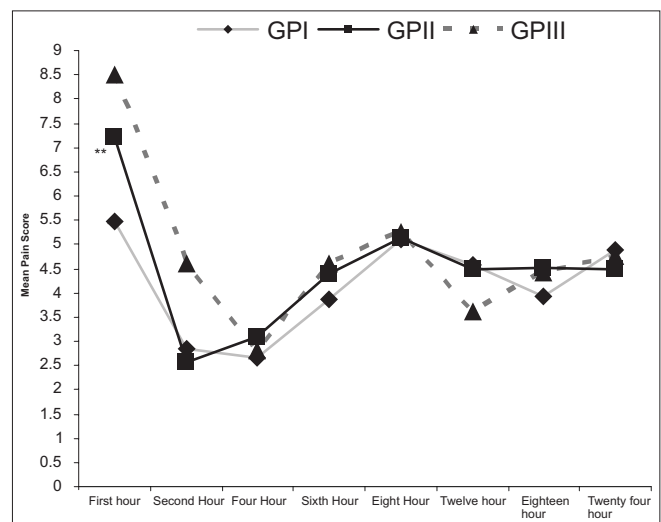


Figure 2: Visual Analogue Score on cough over the 24 hour postoperative period. Group receiving pregabalin experienced least amount of pain during (06 hour) time interval. Data is expressed as mean±SD, * I vs II, III ($P=0.000$), ** II vs III ($P=0.000$)

1600 mg.^[9] Based on the above observations, the absorption of 900 mg should vary somewhere between 35 and 40%, which would amount to 315–360 mg, whereas 300 mg pregabalin would give plasma levels of 270 mg considering 90% bioavailability. Moreover, the antihyperalgesic effects of pregabalin have been observed at dosages twofold to fourfold lower than that of gabapentin in rodent models of neuropathic pain.^[5,23] Based on this fact, we could consider a dose of gabapentin between 600 and 1200 mg. We opted to select a dose in between these two dosages, i.e., threefold higher (900 mg). Also, this dose has not been studied in earlier trials. Further, pregabalin has been found to be approximately 2.5 times more potent than gabapentin.^[24,25] All these trials justified the equipotent doses of pregabalin and gabapentin used in the present study. Their administration 1–2 hours prior to surgery appeared rational in order to attain maximal plasma concentration at the time of surgical stimuli though pregabalin is rapidly absorbed (peak: within 30 minutes to 2 hours) and gabapentin is slowly absorbed (peak: 2 hours). Two hours lapsed easily by the time patient received the drug and skin incision was given, which gave sufficient time to achieve peak effect of both the drugs. Though our main aim was to compare pregabalin and gabapentin, we thought it worthwhile to add a placebo group for some additional inferences as it could help in comparison of each drug to placebo as well. There are sufficient data supporting the evidence of gabapentin in postoperative pain relief in various surgical procedures, but there is paucity of literature regarding placebo-controlled studies of pregabalin in acute pain states. None of the trials available in literature have assessed the efficacy of pregabalin in abdominal hysterectomy.

Hill *et al.* found 300 mg pregabalin to be more effective than 50 mg pregabalin or 400 mg ibuprofen in attenuating pain after dental extraction.^[18] Paech *et al.* did not observe improvement in analgesia with a single preoperative dose of 100 mg pregabalin before minor gynecological surgery involving uterus and cervix.^[19] Also, Jokela *et al.* reported that premedication with pregabalin 150 mg in day-case gynecological laparoscopic surgery did not reduce fentanyl consumption.^[20] Since the doses of 100 and 150 mg were ineffective in day care surgeries, a higher dose was considered in our study for abdominal hysterectomy taking into consideration the more intense surgical stimulus. In contrast to the above trials, premedication with 150 and 300 mg pregabalin reduced analgesic consumption in laparoscopic hysterectomy.^[21] Pain scores were decreased with a single preoperative dose of gabapentin and pregabalin in the initial hour of recovery in our study which is consistent with previous studies.^[16,17] There was no difference after the initial hour. It may be due to the fact that both the drugs have a relatively short half-life and were administered as a single preoperative dose. Time to

first request for analgesia was longest in pregabalin group which could be explained due to its quicker onset of action than gabapentin. The incidence of side effects did not differ among all the groups except sedation, somnolence and vomiting. Sedation with their use has been reported in previous studies also, but it had no effect on ambulation and discharge.^[16,17] The increased vomiting observed in the control group could be due to more tramadol consumption.

Pregabalin was well tolerated in a single dose of 300 mg in our study. We used 600 mg pregabalin in 12 initial cases when research was being planned, which was associated with excess somnolence up to 18–24 hours after surgery. Further cases were abandoned with 600 mg though most of these cases did not require any analgesic in the first 24 hours. Limitations in our study were administration of these drugs in a single dose, which may have resulted in decreased effect over time. Two different analgesics were used at the same time. It would have been much better to use a single drug and also to use a patient-controlled analgesia machine (not available at that time). Future studies should investigate a range of doses and with Patient controlled analgesia (PCA) machine. Also, more controlled studies are required to define benefits and outcomes with different dosages of pregabalin. Although pregabalin was found more effective than gabapentin in the present study, usage of both was associated with decreased analgesic consumption.

To conclude, postoperative analgesia was better with 300 mg pregabalin than 900 mg gabapentin and placebo during the early recovery after abdominal hysterectomy. Gabapentinoids are an effective tool in the treatment of postoperative pain.

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How to cite this article: Ghai A, Gupta M, Hooda S, Singla D, Wadhwa R. A randomized controlled trial to compare pregabalin with gabapentin for postoperative pain in abdominal hysterectomy. *Saudi J Anaesth* 2011;5:252-7.

Source of Support: Nil, **Conflict of Interest:** None declared.