

# Premedication with pregabalin 150mg versus 300mg for postoperative pain relief after laparoscopic cholecystectomy

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## Abstract

**Background and Aims:** Pregabalin has been used in various studies for postoperative pain relief in varying doses. However, there is no conclusive evidence to support a safe and effective dose of pregabalin. The present study was designed to compare the efficacy of two different preoperative doses of pregabalin (150 mg and 300mg) in patients undergoing laparoscopic cholecystectomy for postoperative pain relief.

**Material and Methods:** Ninety adult patients of either sex with American Society of Anesthesiologist physical status I and II scheduled for elective laparoscopic cholecystectomy under general anesthesia were randomized to receive pregabalin 150mg (group A), pregabalin 300mg (group B), or placebo (group C) orally 1 h before surgery. The pain was assessed using a visual analog scale (VAS) and a verbal rating scale (VRS) for the initial 24 h postoperatively. The primary outcome of our study was the comparative assessment of the severity of pain in the postoperative period in three groups. Postoperative analgesic consumption and incidence of side effects were assessed as secondary outcome measures.

**Results:** VAS score was significantly more in group C than group A and B ( $P$ -value  $<0.05$ ). The total amount of fentanyl required in 24 h was least in group B ( $228.33 \pm 42.41\mu\text{g}$ ) followed by group A ( $292.50 \pm 46.49\mu\text{g}$ ) and group C ( $322.50 \pm 39.58\mu\text{g}$ ) ( $P$ -value 0.0001). The incidence of sedation, dizziness, and visual disturbances was more in group B as compared to group A and was least in group C.

**Conclusions:** Pregabalin 150 mg is effective in decreasing postoperative pain after laparoscopic cholecystectomy with fewer incidences of adverse effects such as sedation and visual disturbances as compared to pregabalin 300 mg.

**Keywords:** Analgesia, fentanyl, laparoscopic cholecystectomy, pregabalin, postoperative pain, visual analog scale

## Introduction

The popular saying that there is no gain without pain is not true for acute postoperative pain. Postoperative pain if not relieved can lead to several complications. Pain results in physiological and psychological responses in the patient, which are detrimental to the postoperative outcomes. It, therefore, stands to reason that adequate relief of pain translates into better perioperative outcomes.<sup>[1]</sup>

Various drugs have been used preemptively to relieve postoperative pain and these include ketamine, ketorolac, lornoxicam, diclofenac

sodium, morphine, dexamethasone, gabapentin, and so on but consistent delivery of peri/postoperative analgesia is still a major challenge.<sup>[2-4]</sup> Opioids are associated with vomiting, urinary retention, and respiratory depression.<sup>[3-5]</sup> Local anesthetic techniques are either short-lived or require interventional procedures and the use of NSAIDs and COX 2 inhibitors is limited due to well-known complications and concerns.<sup>[5]</sup> Hence, there is a need for an ideal analgesic drug which provides good pain relief in the perioperative period with no/minimal adverse effects. Perioperative gabapentin has been found to decrease postoperative pain in patients undergoing laparoscopic cholecystectomy.<sup>[6]</sup> Pregabalin, an amino acid derivative of

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gamma-aminobutyric acid (GABA analog) is six times more potent successor to gabapentin. It has been used as a preemptive and postoperative analgesic in laparoscopic surgeries with variable results. Low-dose pregabalin has shown only a limited analgesic benefit. High-dose pregabalin though provides good analgesia but is associated with an increased incidence of side effects.<sup>[7-10]</sup>

This study was designed to compare 150mg and 300mg oral pregabalin premedication for postoperative pain relief. Primary outcome was the comparative assessment of the severity of pain in the postoperative period. Postoperative analgesic consumption and incidence of side effects (if any) were assessed as secondary outcome measures.

## Material and Methods

After approval from the institutional ethics committee and obtaining written informed patient consent, the study was conducted in a controlled, randomized, double-blind manner on 90 adult patients of either sex belonging to ASA grade I and II, scheduled for elective laparoscopic cholecystectomy under general anesthesia. Exclusion criteria included: a history of allergy to opioids or pregabalin, the patient's already taking gabapentinoids, history of drug abuse, morbidly obese patients (BMI >35), and severe kidney/liver disease. Uncooperative patients and patients with psychiatric illness or communication difficulties, who are unable to comprehend visual analog scale (VAS), were excluded from the study. Patients were randomly allocated into three groups of 30 patients each using computer-generated random numbers.

**Group A:** 150 mg of pregabalin was administered orally 1 h before surgery with a sip of water.

**Group B:** 300 mg of pregabalin was administered orally 1 h before surgery with a sip of water.

**Group C:** Control group – similar-looking sham capsule, administered orally 1 h before surgery with a sip of water.

## Blinding

All the study drugs were administered by a person who was blinded to the nature of the study groups. Intraoperatively and postoperatively, observations were made by an anesthesiologist who was also unaware of the group to which the patient belonged.

After shifting the patients to the operation theatre, standard monitoring including heart rate, noninvasive blood pressure, respiratory rate, temperature, end-tidal carbon dioxide, and oxygen saturation (SpO<sub>2</sub>) was started and baseline parameters were recorded. Injection (inj) glycopyrrolate 0.2 mg and inj fentanyl citrate 2 µgkg<sup>-1</sup> was given intravenously (i.v.). After preoxygenation with 100% oxygen for 3 min, patients were induced with thiopentone sodium (2.5%) 5mgkg<sup>-1</sup> i.v. slowly. Endotracheal intubation was facilitated by atracurium besylate

0.6 mgkg<sup>-1</sup> i.v. Anesthesia was maintained using controlled ventilation with nitrous oxide (N<sub>2</sub>O) 66% + oxygen (O<sub>2</sub>) 33% and propofol infusion at a dose of 100µgkg<sup>-1</sup> min<sup>-1</sup>. Injection fentanyl 1µgkg<sup>-1</sup> was repeated, if the patient developed signs of inadequate analgesia such as tachycardia and hypertension, tearing, and so on. Injection paracetamol 1 gm i.v. infusion and inj. ondansetron 8mg i.v. was given to all patients before extubation. After the surgery, neuromuscular blockade was reversed with inj. neostigmine 2.5 mg and glycopyrrolate 0.4 mg i.v. and extubation was done.

In the postoperative period, the pain was assessed using eleven-point (0–10) VAS as well as a verbal rating scale (VRS) to decrease the patient bias. Pain assessment was done hourly for the first 4 h and then 8<sup>th</sup>, 12<sup>th</sup>, and 24<sup>th</sup> hour postoperatively. As a part of a multimodal postoperative pain management strategy, all patients received inj. paracetamol 1g infusion 6 hourly. Any patient having a VAS >4 and/or VRS >2 or requesting analgesic was administered fentanyl 25 µg i.v. intermittent bolus. The pain was reassessed after 10 min of giving fentanyl bolus and a repeat dose of 25 µg administered up to a maximum of 150 µg fentanyl in 1 h. If the patient still complained of pain inj. diclofenac 50 mg slow infusion was given as a rescue measure. Time of administration of the first dose of supplemental analgesic and total fentanyl consumed in the first 24 h postoperatively was recorded.

Assessment of sedation was according to sedation score where 0 = alert, 1 = sleepy but arousable by verbal command, 2 = sleepy but arousable by the tactile stimulus, and 3 = sleepy but arousable by the painful stimulus. Patients were assessed for the occurrence of side effects like nausea, vomiting, itching, headache, visual disturbances, dizziness, and urinary retention in the initial 24 h postoperatively.

A post hoc power analysis was conducted using the software package, G\*Power (Faul and Erdfelder 1992). The alpha level used for this analysis was  $P < 0.05$  and beta was 0.20. The sample size was estimated from the results of the previous study by Anand *et al.* using the incidence of VAS at 4–8 h as the parameter.<sup>[7]</sup> Our sample size came out to be 30 subjects per group at the power of 0.91 and with an effect size of 0.90 with a 10% chance of error with  $\alpha = 0.05$ ,  $\beta = 0.20$ , and confidence interval of 95%. All results were tabulated and analyzed through analysis of variance (ANOVA) and Tukey's Post Hoc test. A  $P$  value of  $<0.05$  was considered significant. A Chi-square test was used for sex differences.

## Results

Assuming dropouts, a total of 111 patients were assessed for eligibility, of which 90 were randomized into three groups of

30 patients each [Figure 1- consort diagram]. All the groups were statistically comparable concerning age, sex distribution, body weight, height, BMI, ASA physical status, and duration of surgery ( $P > 0.05$ ) [Table 1].

Throughout 24 h, the mean pain score as depicted by VAS was found to be significantly higher at 0, 2, 4, 8, and 12 h ( $P < 0.05$ ) in group C as compared to the pregabalin groups. Amongst the pregabalin receiving groups, it was more in group A than group B at 0, 2, 3, 4, 8, and 12 h postoperatively [Table 2].

As shown in Table 3, the difference in VRS values was statistically significant between groups B vs C ( $P < 0.05$ ) and nonsignificant between groups A vs C ( $P > 0.05$ ) at 0 and 4 h postoperatively. The VRS score in group A was though higher than group B but it was not statistically significant ( $P > 0.05$ ).

The total amount of fentanyl consumed in 24 h was least in group B ( $228.33 \pm 42.41 \mu\text{g}$ ) followed by group A ( $292.50 \pm 46.49 \mu\text{g}$ ) and group C ( $322.50 \pm 39.58 \mu\text{g}$ ). These differences were statistically significant. ( $P$ -value 0.0001).

The maximum demand for analgesics was seen in the first 8 h postoperatively. The analgesic requirement in the first 8 postoperative hours was maximum in group C ( $245 \pm 32.43 \mu\text{g}$ ) followed by group A ( $219.17 \pm 29.86 \mu\text{g}$ ) and group B ( $158.33 \pm 23.97 \mu\text{g}$ ). The difference in analgesic consumption was statistically significant in first 8 h only, whereas as it was not statistically significant in the next 16 h [Table 4].

On the operation table, the baseline mean heart rate in group C ( $92.30 \pm 9.73 \text{bpm}$ ) was more than in groups A and B ( $90.67 \pm 9.15 \text{bpm}$  and  $85.53 \pm 9.80 \text{bpm}$ ). Intraoperatively and postoperatively mean heart rate

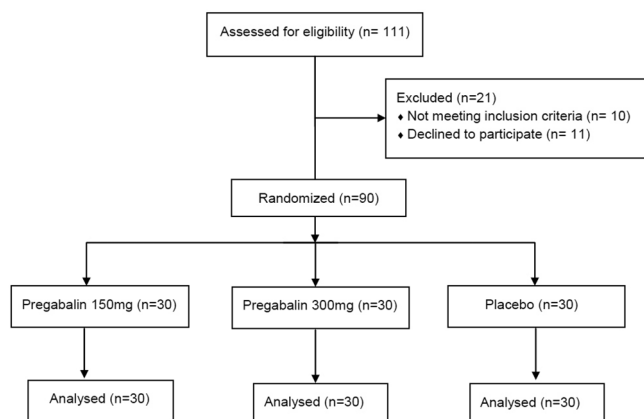


Figure 1: Consort diagram

was more in group C followed by group A and then group B at most of the time intervals [Figure 2]. Perioperatively systolic blood pressure, diastolic blood pressure, respiratory rate, and SpO<sub>2</sub> values were comparable in all the groups.

As shown in Table 5, the incidence of sedation, was significantly more in group B (56.67%) as compared to group A (16.67%) and group C (0%). The incidence of dizziness was also significantly more in group B (16.67%)

Table 1: Demographic characteristics of the patients and duration of surgery in three groups

	Group A	Group B	Group C	P
Age (years)	46.63±14.13	48.53±14.13	49.53±10.89	0.676
Sex (M/F)	14/16	10/20	8/22	0.102
Weight (kg)	68.67±7.76	67.47±7.85	66.73±6.49	0.595
Height (cm)	166.35±9.30	164.07±8.59	162.80±7.95	0.104
BMI (kg/cm <sup>2</sup> )	24.83±2.17	25.06±2.27	25.25±2.67	0.246
ASA PS (I/II)	15/15	16/14	17/13	0.46
Duration of surgery (min)	81.83±24.72	75.67±30.48	74.83±20.06	0.511

Data in the table are Mean±SD or number. BMI=Body mass index; ASA PS=American Society of Anesthesiologists'Physical Status. SD=Standard deviation

Table 2: Postoperative pain score on a visual analog scale

Period	Group-A	Group-B	Group-C	P
0h	7.07±1.11	6.72±0.69	7.30±0.65)	0.030
1h	5.58±1.08	5.63±0.85	5.77±0.90	0.741
2h	5.07±1.10)	4.82±0.93	5.60±0.77	0.006
3h	4.66±1.31)	4.28±1.07	4.87±0.73	0.098
4h	3.77±1.27	3.57±1.00	4.30±0.60	0.017
8h	2.67±1.35	2.50±1.33	3.47±0.68	0.004
12h	1.47±1.04	1.30±1.12	2.07±0.91	0.012
24h	0.53±0.63	0.57±0.73	0.87±0.51	0.083

Data in the table are Mean±SD. SD=Standard deviation

Table 3: Postoperative pain score on a verbal rating scale

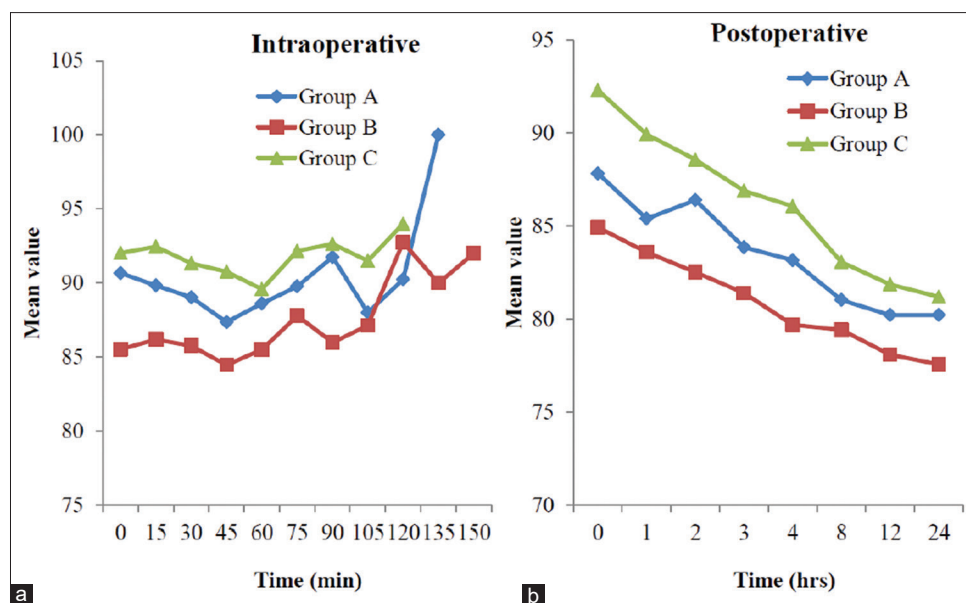
Period	Group-A	Group-B	Group-C	P
0h	3.93±0.45	3.70±0.47	4.03±0.18	0.004
1h	3.27±0.52	3.23±0.57	3.20±0.41	0.877
2h	3.10±0.55	2.83±0.59	3.00±0.37	0.132
3h	2.63±0.56	2.50±0.57	2.70±0.53	0.368
4h	2.07±0.69	1.93±0.58	2.37±0.56	0.023
8h	1.43±0.73	1.43±0.86	1.67±0.48	0.076
12h	0.77±0.57	0.70±0.65	1.00±0.45	0.092
24h	0.23±0.43	0.27±0.45	0.43±0.57	0.108

Data in the table are Mean±SD. SD=Standard deviation

Table 4: Mean amount of analgesic (in  $\mu\text{g}$ ) given in three time periods over 24 h in different groups

Period	Group-A	Group-B	Group-C	P
0-8h	219.17±29.86	158.33±23.97	245.00±32.43	0.0001
8-16h	54.17±18.67	49.17±17.96	55.83±10.75	0.3290
16-24h	19.17±14.21	20.83±11.53	21.67±10.85	0.217

Data in the table are Mean±SD. SD=Standard deviation,  $\mu\text{g}$ =microgram



**Figure 2:** (a) Intraoperative and (b) Postoperative trends in heart rate

as compared to group C (0%) ( $P$ -value 0.042) and group A (6.67%). The incidence of visual disturbance in group B (26.67%) was significantly more as compared to group C (0%) ( $P$ -value 0.008), and group A (10%).

The incidence of itching was significantly more in group C (20%) as compared to group A (0%) and group B (0%). No statistically significant difference was observed amongst patients in three groups concerning the incidence of nausea, vomiting, and headache [Table 5].

## Discussion

Gabapentin and pregabalin have been shown to possess antinociceptive and antihyperalgesic properties in experimental studies on neuropathic pain and inflammatory hyperalgesia.<sup>[11,12]</sup> Pregabalin decreases the discharge of neurotransmitters including glutamate, noradrenaline, serotonin, dopamine, and substance P by binding the  $\alpha 2-\delta$  subunit of calcium channels.<sup>[13]</sup>

In our study, we compared the efficacy of 150mg and 300mg doses of pregabalin in patients undergoing laparoscopic cholecystectomy for postoperative pain relief. The overall mean postoperative VAS score values in the control group (group C) were significantly higher as compared to the study groups A (150 mg pregabalin) and B (300 mg pregabalin). On arrival in the recovery room, high initial mean pain score values were observed in group C as compared to groups A and B. Amongst the pregabalin receiving groups, mean VAS values were more in group A as compared to group B, though their difference was not statistically significant.

**Table 5: Incidence of adverse effects in three groups**

Adverse Effect	Group-A n (%)	Group-B n (%)	Group-C n (%)	P
Sedation	5 (16.66)	17 (56.67)	0 (0.00)	0.005
Nausea	4 (13.33)	2 (6.67)	5 (16.67)	0.191
Vomiting	10 (33.33)	13 (43.33)	13 (43.33)	0.207
Itching	0 (0.00)	0 (0.00)	6 (20.00)	0.049
Headache	3 (10.00)	3 (10.00)	0 (0.00)	0.093
Visual disturbance	3 (10.00)	8 (26.67)	0 (0.00)	0.008
Dizziness	2 (6.67)	5 (16.67)	0 (0.00)	0.042
Urinary retention	0 (0.00)	1 (3.33)	0 (0.00)	0.164

N- Number of patients, %- the percentage

Agarwal *et al.*, Mishra *et al.*, and Anand *et al.* in their studies also have shown that postoperative pain was reduced with 150 mg pregabalin when compared with placebo ( $P < 0.05$ ) in patients undergoing laparoscopic cholecystectomy.<sup>[7,14,15]</sup> Entezary *et al.* and Sattari *et al.* in their studies have also shown that preemptive use of 300 mg of pregabalin reduced postoperative pain after abdominal hysterectomy and thoracotomy, respectively.<sup>[16,17]</sup>

However, Paech *et al.* in their study reported that a single preoperative dose of 100 mg pregabalin does not reduce postoperative pain after minor surgery involving the uterus.<sup>[18]</sup> Peng *et al.* also reported that pregabalin 75 mg provided only limited analgesic benefit in the postoperative period.<sup>[8]</sup> The possible reason for the difference in their results could be because of the lower doses of pregabalin used.

In our study, the maximum incidence of postoperative pain was reported in the first 8 h. During initial 8 h after surgery, patients in groups A and C reported more pain as compared to



patients in group B. Consequently, a higher amount of rescue analgesia (fentanyl) was consumed in the first 8 h in group A ( $219.166 \pm 29.86\mu\text{g}$ ) and group C ( $245 \pm 32.43\mu\text{g}$ ) as compared to group B ( $160 \pm 25.08\mu\text{g}$ ) [Table 4]. The VAS scores and VRS scores were comparable at 1, 2, and 3 in all three groups but at the cost of high consumption of fentanyl, which has its own set of risks and complications in patients with associated comorbidities and elderly population.

Joris *et al.* in their study also showed that after laparoscopic cholecystectomy, visceral, and parietal pain is maximum felt during the first 8 h postoperatively.<sup>[19]</sup> Pregabalin has an elimination half-life of 4.6–6.8 h after a single dose, so after an early postoperative period, the drug would have been eliminated out leading to almost the same amount of pain in all the groups after that 8 h period. This explains the comparable VRS score at 8, 12, and 24 h in all groups.

During the first 24 h postoperatively, the maximum amount of fentanyl was consumed by patients in group C ( $322.5 \pm 39.58\mu\text{g}$ ) and was significantly more than that required in groups A ( $292.5 \pm 46.49\mu\text{g}$ ) and B ( $228.33 \pm 42.41\mu\text{g}$ ). Entezary *et al.* and Mathiesen *et al.* also reported a decrease in opioid consumption postoperatively after premedication with 300 mg pregabalin as compared to placebo, in patients undergoing abdominal hysterectomy, and hip arthroplasty respectively.<sup>[16,20]</sup> Our findings also corroborate with those of Agarwal *et al.*, Mishra *et al.*, and Anand *et al.* who reported decreased postoperative opioid consumption after single oral 150 mg of pregabalin in patients undergoing laparoscopic cholecystectomy as compared to placebo.<sup>[7,14,15]</sup>

The hemodynamic parameters are an indirect reflection of pain control. Intraoperatively group C showed a mean HR which was more than that observed in groups A and B patients throughout the surgery. The lower heart rate in the groups A and B correlates well with the analgesic effects of pregabalin as compared to the placebo. Lower mean baseline heart rate observed in group A and B patients can also be attributed to the anxiolytic effect of pregabalin. Lower heart rate in group B as compared to group A which was seen throughout the surgery corresponds with the higher dose of pregabalin used in group B. Pande *et al.* and Gonano *et al.*, in their studies have also shown that pregabalin reduces anxiety in an effective and well-tolerated manner.<sup>[21,22]</sup>

Postoperatively, mean systolic blood pressure and mean diastolic blood pressure readings in our study were comparable in all groups and no significant difference was found. Mean respiratory rate and mean SpO<sub>2</sub> postoperatively in the recovery room were comparable in all the three groups

and no significant difference was found in these values. Our findings also correlate with those of Sahu *et al.* who found no statistically significant difference in mean systolic blood pressure, mean diastolic blood pressure, and mean respiratory rate in patients receiving two 150 mg pregabalin doses 12 h apart as compared to the placebo, in patients undergoing below umbilical surgeries under spinal anesthesia.<sup>[23]</sup>

In our study, the incidence of sedation, difficulty in vision and dizziness were highest in group B. Mathiesen *et al.* and Esmat *et al.* in their studies reported significantly higher 24 h sedation score with pregabalin 300 mg as compared with placebo in patients undergoing hip arthroplasty and laparoscopic cholecystectomy, respectively.<sup>[20,24]</sup> Agarwal *et al.* in their study on patients undergoing laparoscopic cholecystectomy reported that incidence and severity of sedation were comparable in patients taking either pregabalin 150 mg or placebo.<sup>[7]</sup> Paech *et al.* reported visual disturbance in 22% of patients taking 100 mg pregabalin as compared to 2% with placebo.<sup>[18]</sup> However, in a study by Gupta *et al.*, the incidence of dizziness with 150 mg and 300 mg pregabalin was negligible.<sup>[25]</sup>

In our study incidence of nausea, vomiting, and the headache was comparable in all the groups. Agarwal *et al.* and Paech *et al.* also have reported similar results.<sup>[7,18]</sup> Mathiesen *et al.* and Esmat *et al.* reported a higher incidence of nausea and vomiting with 300 mg pregabalin as compared to 150 mg pregabalin and placebo.<sup>[20,24]</sup>

In group C, 20% of patients reported itching, which was significantly more than that seen in group A and B patients. This can be explained by the low consumption of fentanyl due to the opioid-sparing effect of pregabalin. Jokela *et al.* in their study reported that incidence of pruritus was 5% in subjects taking 600 mg pregabalin in two divided doses, which was much less than the incidence (29%) in patients taking 300 mg pregabalin in two divided doses.<sup>[9]</sup>

### Limitations

Limitations of our study include a small sample size of only 30 patients in each group. We evaluated pain during rest only and the pain after mobilization and deep breathing was not assessed. As the side effects like dizziness and sedation can occur with both pregabalin and fentanyl, the actual incidence of side effects caused exclusively by pregabalin could not be assessed.

### Conclusions

Analyzing the results of our study, we opine that perioperative pregabalin has a definitive role in reducing postoperative pain and analgesic requirements in patients undergoing laparoscopic cholecystectomy. The analgesic efficacy of 300 mg pregabalin

is more than 150 mg, but a dose of 300 mg pregabalin is associated with an increased incidence of adverse effects such as sedation, dizziness, and visual disturbances. Hence, 150 mg pregabalin can be safely used as an optimal dose in patients undergoing laparoscopic cholecystectomy for postoperative pain relief with minimal side effects.

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### Conflicts of interest

There are no conflicts of interest.

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