

Evaluation of a single preoperative dose of pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy

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Background. Postoperative pain is the dominating complaint and the primary reason for prolonged convalescence after laparoscopic cholecystectomy. We have evaluated the efficacy of a single preoperative dose of pregabalin for attenuating postoperative pain and fentanyl consumption after laparoscopic cholecystectomy.

Methods. Sixty adults (16–60 yr), ASA physical status I and II, of either sex undergoing elective laparoscopic cholecystectomy were included in this prospective, randomized placebo controlled, double-blind study. Subjects were divided into two groups of 30 each to receive either a matching placebo or pregabalin 150 mg, administered orally 1 h before surgery. Postoperative pain (static and dynamic) was assessed by a 100 mm visual analogue scale, where 0, no pain; 100, worst imaginable pain. Subjects received patient-controlled i.v. fentanyl analgesia during the postoperative period. Results were analysed by Student's *t*-test, χ^2 test, Mann–Whitney *U*-test, and Fisher's exact test.

Results. Postoperative pain (static and dynamic) and postoperative patient-controlled fentanyl consumption were reduced in the pregabalin group compared with the placebo group ($P < 0.05$). Side-effects were similar in both groups.

Conclusions. A single preoperative oral dose of pregabalin 150 mg is an effective method for reducing postoperative pain and fentanyl consumption in patients undergoing laparoscopic cholecystectomy.

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Pain is thought to be inadequately treated in one-half of all surgical procedures.¹ Recent advances in the pathophysiology of pain have suggested that it is possible to prevent or attenuate the central neural hyperexcitability that contributes to enhanced postoperative pain.^{2,3}

Early postoperative pain is the most common complaint after elective laparoscopic cholecystectomy.⁴ In 17–41% of the patients, pain is the main reason for overnight hospital stay after day care surgery.^{5–7} Postoperative pain is the dominating complaint and the primary reason for prolonged convalescence after laparoscopic cholecystectomy.^{8,9} Intense acute pain after laparoscopic cholecystectomy might predict the development of chronic pain (e.g. post-laparoscopic cholecystectomy syndrome).¹⁰

Pregabalin and its developmental predecessor gabapentin were originally developed as spasmolytic agents and adjuncts for the management of generalized or partial epileptic seizures resistant to conventional therapies.¹¹ Gabapentin has been found to be useful for neuropathic pain¹² and postoperative pain after breast surgery,¹³ spinal surgery,¹⁴ and laparoscopic cholecystectomy.¹⁵ Similarly, pregabalin has a proven role in treating neuropathic pain;¹¹ however, evidence supporting the postoperative analgesic efficacy of pregabalin is limited to randomized controlled trials in patients undergoing dental surgery,¹⁶ spinal fusion surgery,¹⁷ laparoscopic hysterectomy¹⁸ and day-case gynaecological laparoscopic surgery.¹⁹ None of these trials has investigated the role of preoperative single-dose administration of pregabalin in

attenuating postoperative pain after laparoscopic cholecystectomy. The present study was therefore designed to evaluate the role of preoperative single dose of pregabalin for attenuating postoperative pain and analgesic consumption in patients undergoing laparoscopic cholecystectomy.

Methods

This prospective, randomized, double-blind, and placebo controlled clinical study was designed to include 60 adult patients (16–60 yr) of either sex, ASA physical status I and II, undergoing laparoscopic cholecystectomy under general anaesthesia. The study protocol was approved from the institutional ethical committee and written informed consent was obtained from all the patients.

Patients with impaired kidney or liver functions, history of drug or alcohol abuse, history of chronic pain or daily intake of analgesics, uncontrolled medical disease (diabetes mellitus and hypertension), history of intake of non-steroidal anti-inflammatory drugs within 24 h before surgery, and inability to operate patient-controlled analgesia (PCA) device were excluded from the study.

Patients meeting the inclusion criteria during the pre-anaesthetic evaluation were randomly assigned into two groups of 30 each with the help of a computer-generated table of random numbers, to receive either a matching placebo or pregabalin 150 mg. All the medications were provided by hospital pharmacy, were identical, and were administered orally, 1 h before the induction of anaesthesia with sips of water by a staff nurse who was not involved in the study.

Anaesthesia technique was standardized in all the groups. Patients were induced with fentanyl $3 \mu\text{g kg}^{-1}$ and propofol 2 mg kg^{-1} ; orotracheal intubation was facilitated by vecuronium $0.08 \mu\text{g kg}^{-1}$. Anaesthesia was maintained with $100\text{--}200 \mu\text{g kg}^{-1} \text{ min}^{-1}$ propofol infusion and 66% nitrous oxide in oxygen. At the end of surgery, residual neuromuscular paralysis was antagonized with neostigmine 0.05 mg kg^{-1} and glycopyrrolate 0.01 mg kg^{-1} . After satisfactory recovery, the patients were extubated and shifted to the post-anaesthesia care unit (PACU). In the PACU, patients received i.v. fentanyl via PCA with patient activated dose of $20 \mu\text{g}$, lockout interval of 5 min, with a maximum allowable fentanyl dose being $2 \mu\text{g kg}^{-1} \text{ h}^{-1}$.

Primary outcomes were severity of postoperative pain and postoperative fentanyl requirement. Secondary outcomes were incidence and severity of side-effects such as postoperative nausea and vomiting (PONV), headache, sedation, and respiratory depression if any. Both these outcomes were assessed by an independent anaesthesia registrar (S.K.G.) blinded to group allocation.

Assessment of pain both at rest (static) and during coughing (dynamic) was done by a 100 mm visual analogue scale (VAS); 0, no pain; 100, worst imaginable pain. Assessment of pain was done on arrival of patient to the PACU (0) and

then every 2 h till the end of the study, that is, 24 h after operation. From these data, the maximum pain scores at different time intervals (0, 0–4, 4–8, 8–12, and 12–24 h) for each patient were considered for statistical analysis. The severity of PONV was graded on a four-point ordinal scale (0, no nausea or vomiting; 1, mild nausea; 2, moderate nausea; and 3, severe nausea with vomiting). Rescue anti-emetic ondansetron 4 mg i.v. was given to all patients with PONV of grade ≥ 2 . The Ramsay sedation scale (awake levels were: 1, anxious, agitated, or restless; 2, cooperative, oriented, and tranquil; 3, responds to command; asleep levels were dependent on patient's response to a light glabellar tap or loud auditory stimulus; 4, brisk response; 5, a sluggish response; and 6, no response) was used to assess the sedation;²⁰ patients with a sedation scale of ≥ 4 were considered as sedated. Respiratory depression was defined as ventilatory frequency ≤ 8 bpm and oxygen saturation $< 90\%$ without oxygen supplementation.

Calculation of sample size was based on the presumption that postoperative VAS scores after preoperative administration of pregabalin 150 mg would be 30 mm when compared with 45 mm in the placebo group with a standard deviation of 20 mm at all time points. For the results to be of statistical significance with $\alpha=0.05$ and $\beta=0.80$, one needed to recruit 25 patients in each group. To take care of any drop outs, we enrolled 30 patients in each group. The method of analysis was decided prospectively and incorporated the intention-to-treat principle. Patient characteristic data were analysed with one-way ANOVA for continuous variables and χ^2 test for categorical variables. Postoperative PCA fentanyl consumption was analysed with Student's *t*-test. The VAS pain scores were analysed with Mann–Whitney *U*-test; the incidences of side-effects were analysed with Fisher's exact test. The package SPSS 14.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. $P < 0.05$ was considered significant.

Results

A total of 84 patients were assessed for eligibility from January 2007 to April 2008 (Fig. 1), out of which 60 subjects received study medication after randomization and 56 subjects (94%) completed the study (Fig. 1). Twenty-four patients were not included in this study on account of patient's refusal (16 patients), history of chronic analgesic consumption (two patients), and inability to operate PCA device (six patients). Four subjects were considered as drop-outs after initial randomization and were therefore not subjected to further statistical analysis (three subjects underwent conversion to open cholecystectomy and one subject needed re-exploration on account of postoperative bleed).

There was no substantial difference among the groups with regard to age, weight, sex, duration of anaesthesia, duration of surgery, and intraoperative fentanyl consumption ($P > 0.05$) (Table 1). Postoperative pain (static and

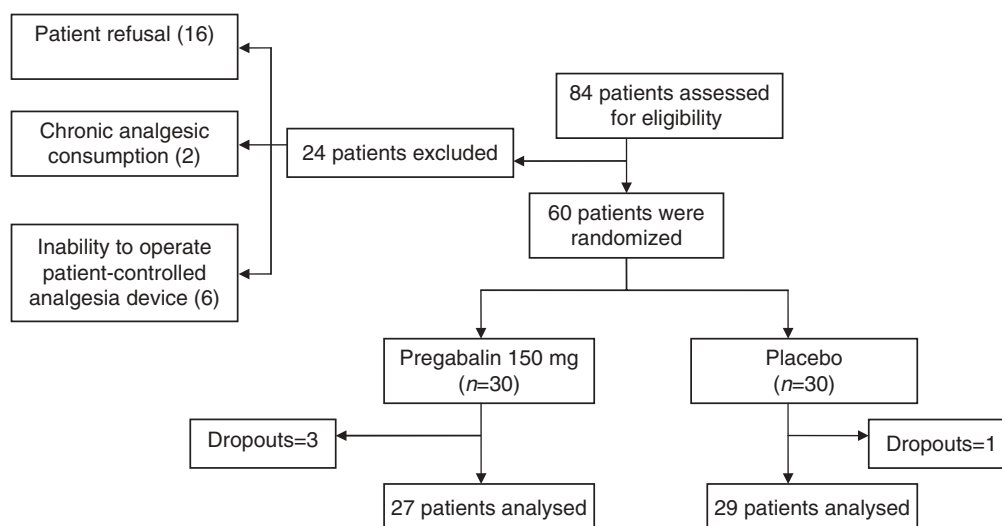


Fig 1 Study design.

dynamic) and postoperative patient-controlled fentanyl consumption were reduced in the pregabalin group when compared with placebo ($P < 0.05$) (Figs 2 and 3) (Table 2). Incidence and severity of sedation were comparable between two groups ($P < 0.05$) (Table 3). Incidence and severity of PONV, number of patients requiring antiemetics, incidence of headache, and respiratory depression were similar among the groups ($P > 0.05$) (Table 4).

Discussion

We observed that preoperative single-dose pregabalin (150 mg) was effective in reducing both the static and the dynamic components of postoperative pain along with postoperative patient-controlled fentanyl consumption in subjects undergoing laparoscopic cholecystectomy.

Experimental models of neuropathic pain and inflammatory hyperalgesia have shown that γ -aminobutyric acid analogues such as gabapentin and pregabalin have antinociceptive and antihyperalgesic properties.²¹ The pharmacological effects of pregabalin are believed to result from its action as a ligand at the alpha-2-delta binding site, which is associated with the voltage-gated calcium channels in

the central nervous system.²² Potent binding of pregabalin at alpha-2-delta site has been shown to reduce the depolarization-induced calcium influx at nerve terminals with a consequential reduction in the release of several excitatory neurotransmitters, including glutamate, norepinephrine, substance P, and CGRP.^{22–24} It is probable that this modulation of neurotransmitter release by pregabalin contributes to the drug's anticonvulsant, analgesic, and anxiolytic effects.

Gabapentin has also been found to have antinociceptive activity that translates into the management of postoperative pain.²⁵ Animal models of surgical pain and clinical studies of inflammatory pain in adults demonstrate that these conditions provoke allodynia and hyperalgesia, which are modified by gabapentin, independent of opioid receptor activation.²⁵ However, pregabalin appears to be a better option when compared with gabapentin, as it exhibits greater analgesic efficacy in rodent models of neuropathic pain²⁶ and better pharmacokinetic profile across its therapeutic dose range with low inter-subject variability.²² The side-effect profile of pregabalin is also very promising

Table 1 Patient characteristic data presented as mean (range), mean (SD) or numbers. No significant differences between the groups by one-way ANOVA for continuous variables and χ^2 test for categorical variables ($P > 0.05$)

Variables	Groups	
	Placebo (n=30)	Pregabalin (n=30)
Age (yr)	44.6 (22–69)	46.6 (25–76)
Weight (kg)	55.7 (9.1)	56.2 (10.1)
Sex (M/F)	18/12	23/7
Duration of anaesthesia (min)	120.5 (20.3)	118.5 (19.5)
Duration of surgery (min)	91.3 (22.9)	88.7 (22.7)
Intraoperatively fentanyl consumption (μ g)	212.6 (27.4)	218.7 (30.3)

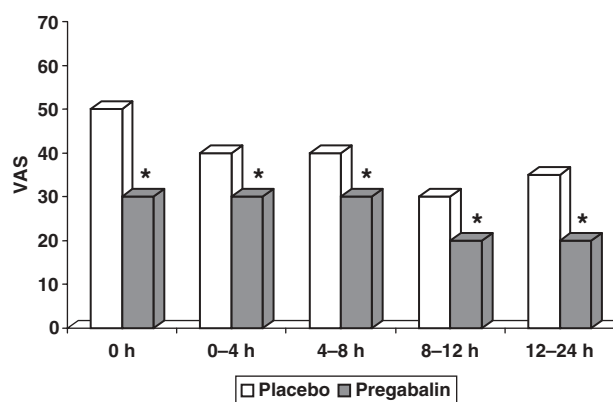


Fig 2 Postoperative pain (static); pain is expressed as median VAS scores. * $P < 0.05$ vs placebo by Mann–Whitney U -test.

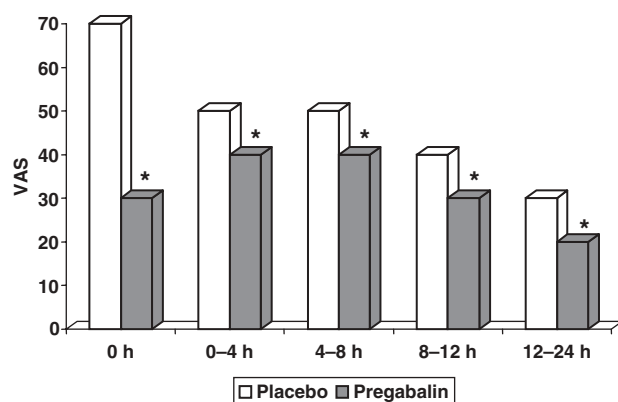


Fig 3 Postoperative pain (dynamic); pain is expressed as median VAS scores. * $P < 0.05$ vs placebo by Mann–Whitney U -test.

with the most common adverse events being dizziness and somnolence;²⁷ in addition, pregabalin has no effect on arterial pressure or heart rate.¹⁷

Pregabalin demonstrates highly predictable and linear pharmacokinetics, a profile that makes it easy to use in clinical practice. It is rapidly and extensively absorbed after oral dosing in the fasted state, with maximal plasma concentration occurring ~ 1 h after single or multiple doses, and steady state being achieved within 24–48 h after repeated administration.²² It can be started at an effective dose of 150 mg day⁻¹,²² the dose of pregabalin used in the present study. The oral bioavailability of pregabalin is high at $\geq 90\%$ and is independent of dose.²² Furthermore, the administration of pregabalin with food has no clinically relevant effect on the amount of pregabalin absorbed,²² thus providing for a dosing regimen that is uncomplicated by meals.

Table 2 Postoperative pain and fentanyl consumption; pain was assessed by 100 mm VAS; 0, no pain; 100, worst imaginable pain and expressed as median VAS scores (inter-quartile range) whereas, postoperative PCA fentanyl consumption is presented in μg . * $P < 0.05$ vs placebo for pain scores analysed by Mann–Whitney U -test and postoperative fentanyl consumption by Student's t -test

Variables	Groups	
	Placebo (n=29)	Pregabalin (n=27)
0 h		
Static	50 (28)	30 (20)*
Dynamic	70 (20)	30 (25)*
0–4 h		
Static	40 (38)	30 (20)*
Dynamic	50 (28)	40 (20)*
4–8 h		
Static	40 (10)	30 (10)*
Dynamic	50 (30)	40 (20)*
8–12 h		
Static	30 (18)	20 (10)*
Dynamic	40 (10)	30 (15)*
12–24 h		
Static	35 (40)	20 (20)*
Dynamic	30 (30)	20 (10)*
Total postoperative fentanyl consumption (μg)	757.5 (99.3)	555.2 (124.8)*

Table 3 Sedation score (Ramsay sedation score); data are presented as numbers and median (inter-quartile range). No significant differences between the groups by Fisher's exact test ($P > 0.05$)

Sedation score	Groups	
	Placebo (n=29)	Pregabalin (n=27)
1	2	1
2	14	11
3	13	13
4	0	2
5	0	0
6	0	0
Median (inter-quartile range)	2 (1)	3 (1)

The use of pregabalin in acute postoperative pain management has been evaluated in recent studies. These studies sought to determine whether perioperative pregabalin was effective in reducing postoperative pain and whether it had opioid-sparing effects. However, differences in the pregabalin dosages and types of surgery have yielded contrasting results. A study investigating pain relief after dental extraction showed that 400 mg pregabalin administered after operation was more effective than ibuprofen in attenuating acute post-procedural pain.¹⁶ Reuben and colleagues¹⁷ observed that in patients undergoing lumbar laminectomy, pregabalin 150 mg before and after surgery was as effective as celecoxib in reducing postoperative pain and patient-controlled morphine consumption and the combination of both drugs was the most effective. In another clinical trial, Jokela and colleagues¹⁸ observed that perioperative administration of pregabalin 300 mg before and after laparoscopic hysterectomy decreases oxycodone consumption, but is associated with an increased incidence of adverse effects. Jokela and colleagues¹⁹ in another study observed that analgesia was better after premedication with pregabalin 150 mg in patients undergoing day-case gynaecological laparoscopic surgery.

On the contrary, in a recently published article, Paech and colleagues²⁸ reported that a single preoperative dose of 100 mg pregabalin was ineffective in reducing acute postoperative pain or improving recovery after minor surgery involving only the uterus. The difference in the results from our study could possibly be because Paech

Table 4 Incidence of side-effects; data are presented as numbers. No significant differences between the groups by Fisher's exact test ($P > 0.05$)

Variables	Groups	
	Placebo (n=29)	Pregabalin (n=27)
PONV		
No	14	13
Mild	2	4
Moderate	6	4
Severe	7	6
Patients requiring antiemetic	7	6
Headache	6	8
Respiratory depression	0	1

and colleagues administered a smaller dose (100 mg) against the recommended starting dose of 150 mg²² or because of the difference in the nature of surgery. Limitations of the present study are that we did not evaluate the dose–response or the effect of continuation of therapy. Further studies are suggested in these areas.

In conclusion, oral pregabalin 150 mg administered before operation was effective in reducing postoperative pain and postoperative patient-controlled fentanyl requirement in patients undergoing laparoscopic cholecystectomy. The side-effect profiles were similar in both the groups. We therefore suggest that oral preoperative single dose of pregabalin 150 mg is an effective method for reducing postoperative pain and fentanyl consumption in patients undergoing laparoscopic cholecystectomy.

References

- Gottschalk A, Smith DS. New concepts in acute pain therapy: preemptive analgesia. *Am Fam Physician* 2001; **63**: 1979–84
- Woolf CJ. Evidence for a central component of postinjury pain hypersensitivity. *Nature* 1983; **306**: 686–8
- Wall PD. The prevention of postoperative pain. *Pain* 1988; **33**: 289–90
- Dubois F, Icard P, Berthelot G, Levard H. Coelioscopic cholecystectomy. Preliminary report of 36 cases. *Ann Surg* 1990; **211**: 60–2
- Lau H, Brooks DC. Predictive factors for unanticipated admissions after ambulatory laparoscopic cholecystectomy. *Arch Surg* 2001; **136**: 1150–3
- Callesen T, Klarskov B, Mogensen TS, Kehlet H. Ambulatory laparoscopic cholecystectomy. Feasibility and convalescence. *Ugeskr Laeger* 1998; **160**: 2095–100
- Bisgaard T, Klarskov B, Rosenberg J, Kehlet H. Characteristics and prediction of early pain after laparoscopic cholecystectomy. *Pain* 2001; **90**: 261–9
- Bisgaard T, Kehlet H, Rosenberg J. Pain and convalescence after laparoscopic cholecystectomy. *Eur J Surg* 2001; **167**: 84–96
- Bisgaard T, Klarskov B, Rosenberg J, Kehlet H. Factors determining convalescence after uncomplicated laparoscopic cholecystectomy. *Arch Surg* 2001; **136**: 917–21
- Bisgaard T, Rosenberg J, Kehlet H. From acute to chronic pain after laparoscopic cholecystectomy: a prospective follow-up analysis. *Scand J Gastroenterol* 2005; **40**: 1358–64
- Bryans JS, Wustrow DJ. 3-substituted GABA analogs with central nervous system activity: a review. *Med Res Rev* 1999; **19**: 149–77
- Kong VK, Irwin MG. Gabapentin: a multimodal perioperative drug? *Br J Anaesth* 2007; **99**: 775–86
- Fassoulaki A, Patris K, Sarantopoulos C, Hogan Q. The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. *Anesth Analg* 2002; **95**: 985–91
- Turan A, Karamanlioglu B, Memis D, et al. Analgesic effects of gabapentin after spinal surgery. *Anesthesiology* 2004; **100**: 935–8
- Pandey CK, Priye S, Singh S, Singh U, Singh RB, Singh PK. Preemptive use of gabapentin significantly decreases postoperative pain and rescue analgesic requirements in laparoscopic cholecystectomy. *Can J Anaesth* 2004; **51**: 358–63
- Hill CM, Balkenohl M, Thomas DW, Walker R, Mathe H, Murray G. Pregabalin in patients with postoperative dental pain. *Eur J Pain* 2001; **5**: 119–24
- Reuben SS, Buvanendran A, Kroin JS, Raghunathan K. The analgesic efficacy of celecoxib, pregabalin, and their combination for spinal fusion surgery. *Anesth Analg* 2006; **103**: 1271–7
- Jokela R, Ahonen J, Tallgren M, Haanpää M, Korttila K. A randomized controlled trial of perioperative administration of pregabalin for pain after laparoscopic hysterectomy. *Pain* 2008; **134**: 106–12
- Jokela R, Ahonen J, Tallgren M, Haanpää M, Korttila K. Premedication with pregabalin 75 or 150 mg with ibuprofen to control pain after day-case gynaecological laparoscopic surgery. *Br J Anaesth* 2008; **100**: 834–40
- Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone–alphadolone. *Br Med J* 1974; **2**: 656–9
- Wolf CJ, Chong MS. Pre-emptive analgesia treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg* 1993; **77**: 362–79
- Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. *Epilepsia* 2004; **45**: 13–8
- Dooley DJ, Donovan CM, Pugsley TA. Stimulus-dependent modulation of [(3)H] norepinephrine release from rat neocortical slices by gabapentin and pregabalin. *J Pharmacol Exp Ther* 2000; **295**: 1086–93
- Fink K, Dooley DJ, Meder WP, et al. Inhibition of neuronal Ca(2+) influx by gabapentin and pregabalin in the human neocortex. *Neuropharmacology* 2002; **42**: 229–36
- Dahl JB, Mathiesen O, Møiniche S. 'Protective premedication': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in the treatment of post-operative pain. *Acta Anaesthesiol Scand* 2004; **48**: 1130–6
- Frampton JE, Scott LJ. Pregabalin in the treatment of painful diabetic peripheral neuropathy. *Drugs* 2004; **64**: 2813–20
- Kavoussi R. Pregabalin: from molecule to medicine. *Eur Neuropsychopharmacol* 2006; **16**: S128–33
- Paech MJ, Goy R, Chua S, Scott K, Christmas T, Doherty DA. A randomized, placebo-controlled trial of preoperative oral pregabalin for postoperative pain relief after minor gynecological surgery. *Anesth Analg* 2007; **105**: 1449–53