ORIGINAL ARTICLE

Comparative study between paracetamol and two different doses of pregabalin on postoperative pain in laparoscopic cholecystectomy

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ABSTRACT

Background: Postoperative pain is the primary reason for prolonged hospital stay after laparoscopic cholecystectomy. This study compared the effect of a single oral preoperative administration of paracetamol (1 g) with 2 different doses of pregabalin (150 or 300 mg) for attenuating postoperative pain and analgesic consumption. **Materials and Methods:** Seventy-five patients, aged 18-60 years, American Society of Anesthesiologists' physical status I and II undergoing elective laparoscopic cholecystectomy were included in this randomized controlled study. Patients were divided into three groups, 25 each to receive either oral paracetamol 1 g (group I, control group) or pregabalin 150 (group II) or 300 mg (group III), 2 h before surgery. Postoperative pain was evaluated based on visual analog scale over a period of 6 h and 1st time for rescue analgesia. Postoperative sedation, hemodynamic changes, serum cortisol level, and side effects were also evaluated. **Results:** There was a significant decrease in mean heart rate, mean systolic blood pressure, sedation score, pain score, and delayed the first request for analgesics postoperatively in group (II) and group (III) compared to group (I) 2 h postoperatively. There was no significant difference in group (III) compared to group (II) postoperatively. The incidence of postoperative side effects was more in group (III). **Conclusion:** The single oral preoperative dose administration of pregabalin had significant opioid-sparing effect in the first 6 h after surgery, whereas side effects were more common with administration of pregabalin 300 mg.

Key words: *Analgesia, cholecystectomy, pain, paracetamol, pregabalin*

INTRODUCTION

"Freedom from pain should be a basic human right, limited only by our knowledge to achieve it."[1] Recent advances in the pathophysiology of pain have suggested that it is possible to prevent or to attenuate the central neural hyperexcitability that contributes to enhanced postoperative pain.[2] Early postoperative pain is the most common complaint after elective laparoscopic cholecystectomy. In 17-41% of the patients, pain is the main reason for overnight hospital stay after day case surgery.[3] Intense acute pain after laparoscopic cholecystectomy might predict the development of chronic pain (e.g., postlaparoscopic cholecystectomy syndrome).[4]

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Pregabalin is a structural analog of γ-aminobutyric acid, which shows the analgesic, anticonvulsant, and anxiolytic effects. In many countries, it is approved for the treatment of neuropathic pain.[5] Like its predecessor, gabapentin, it binds to the α-2-d subunit of voltage-gated calcium channels, reducing the release of several excitatory neurotransmitters (including glutamate, norepinephrine, substance P, and calcitonin gene-related peptide) and blocking the development of hyperalgesia and central sensitization.[6] Pregabalin is more potent than the similar drug, gabapentin. It is rapidly absorbed orally with >90% bioavailability, achieves peak plasma levels within 30 min to 2 h. and shows linear pharmacokinetics.[7] The most common adverse events are dizziness and somnolence, and pregabalin has no effect on arterial blood pressure or heart rate.[8]

Paracetamol (acetaminophen; N-acetyl-p-aminophenol) is well-absorbed from the proximal small bowel and is not

subject to significant first-pass metabolism in the liver, with oral bioavailability estimated at between 63% and 89% in adults.[9] The minimum plasma paracetamol level required for analgesia and antipyresis is thought to be 10 μg/ml, and the therapeutic range is usually stated to be 10-20 μg/ml.[10] 150 μg/ml is considered to be the threshold for potential hepatotoxicity.[11] Peak plasma concentration (Cmax) is achieved approximately 45 min after 1 g orally.[12] Paracetamol inhibits both isoforms of cyclooxygenase (COX); the constitutive COX-1 and the inducible COX-2. Paracetamol displays weak anti-inflammatory activity, few or no gastrointestinal side effects and only a small dose-dependent alteration of platelet function. Current evidence points to multisite activity in the central nervous system, involving inhibition of prostaglandin synthesis and interaction with both serotonergic and cannabinoid pathways.[13]

The stress response to surgery is characterized by increased secretion of pituitary hormones and activation of the sympathetic nervous system. The changes in the pituitary secretions have secondary effects on hormone secretion from target organs (increased secretion of cortisol from the adrenal cortex).[14]

The present study was therefore designed to evaluate the role of a preoperative single oral dose of paracetamol (1 g) in comparison to preoperative single oral dose of two different doses of pregabalin (150 mg or 300 mg) for attenuating postoperative pain and analgesic consumption in patients undergoing laparoscopic cholecystectomy.

MATERIALS AND METHODS

This randomized controlled study was conducted on 75 patients aged between 18 and 60 years old of both sex of American Society of Anesthesiologists (ASA) physical status I and II of 70-90 kg body weight and height 160-180 cm undergoing elective laparoscopic cholecystectomy under general anesthesia. 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 cardiac or central nervous system disease, 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 nonsteroidal anti-inflammatory drugs within 24 h before surgery or allergy to the used medications, and duration of operation >90 min were excluded from the study.

Patients meeting the inclusion criteria during the preanesthetic evaluation were randomly assigned into three groups of 25 each to receive1 g paracetamol (group I, control group) or pregabalin 150 mg (group II) or pregabalin 300 mg (group III) orally 2 h before induction of anesthesia with sips of water. Assessment of postoperative pain, sedation, postoperative monitoring of heart rate, mean systolic and mean diastolic blood pressure, and side effects (e.g., vomiting, blurring of vision, and excessive sedation) were done every 30 min for 2 h and after 6 h.

Postoperative pain was evaluated based on visual analog scale (VAS), 1st time to ask for rescue analgesia administered over a period of 6 h postoperatively. Before the surgery, patients were instructed in the use of VAS for pain assessment postoperatively where 0 cm defines no pain, and 10 cm defines the maximum intolerable pain. Patients with (VAS) >3 were given extra-analgesic doses in the form of 0.5 mg/kg pethidine intramuscularly. Assessment of sedation was according to sedation score where 0 = alert, 1 = sleepy and arousable by verbal command, 2 = sleepy and arousable by tactile stimulation and 3 = sleepy and arousable by painful stimulation.

Serum cortisol was measured by a fluorescence polarization immunoassay technology by the Abbott AxSYM system with the following reference ranges (morning serum cortisol 4.2-38.4 μg/dl) and evening serum cortisol 1.7-16.6 μg/dl). Serum cortisol level was measured 1 h postoperatively.

The general anesthesia technique was standardized for all the patients as well as monitors including 5 lead electrocardiography (ECG), noninvasive blood pressure (NIBP) monitor, pulse oximetry, and capnography after intubation using Datascope monitors. Neuromuscular function was also monitored using a peripheral nerve stimulator. After establishing an intravenous (IV) line, induction of general anesthesia with fentanyl (2 μg/dl) and sleeping dose of propofol followed by rocuronium (0.6 mg/kg) to facilitate orotracheal intubation was done. Anesthesia was maintained using sevoflurane in oxygen and air. Granisetron (1 mg IV) was given as a prophylactic antiemetic. At the end of the surgery, the residual neuromuscular paralysis was antagonized with neostigmine (0.05 mg/kg) and atropine (0.01 mg/kg). After satisfactory recovery, patients were extubated and transferred to the postanesthesia care unit where they were monitored with ECG, NIBP, and pulse oximetry.

RESULTS

Analysis of data

Using PASS for sample size calculation, it was calculated that a sample size of 22 patients per group will achieve

80% power to detect differences in the mean-time to 1st rescue analgesia of 90 min between the three groups with a standard deviation (SD) within a group assumed to be 41.77 using an *F* test with a 0.05000 significance level. Data were analyzed using SPSS 18.0 for Windows (SPSS, Chicago, IL, USA). Analysis of variance was used to compare the three groups for quantitative parametric data and if there was a significant difference among the groups, a *post-hoc* Tukey's test was performed. Kruskal-Wallis test was used for quantitative nonparametric data. Chi-square test was used for comparison of qualitative data. Continuous parametric data were presented as mean ± SD, nonparametric data as median (interquartile range) and categorical data were presented as number of patients. $P < 0.05$ were considered significant and < 0.001 highly significant.

A total of 85 patients were assessed for eligibility from March 2008 to April 2009 [Figure 1], out of which 78 patients received study medication after randomization and 75 patients completed the study (25 patients for each group) [Figure 1]. Seven patients were not included in this study on account of patient's refusal (4 patients) and history of chronic analgesic consumption (3 patients). Three patients were considered as drop-outs after initial randomization and were therefore not subjected to further statistical analysis (two patients underwent conversion to open cholecystectomy, and one patient needed re-exploration on account of the postoperative bleed).

Results of the current study did not show significant difference in the demographic data of the groups of patients as regard age, height, body weight, male to female ratio, ASA physical status and the length of surgery in minutes as shown in Table 1.

There was a significant decrease in the mean heart rate in the group (II) and group (III) compared to group (I) 30 min, 1 h, 1.5 h, and 2 h postoperatively as shown in Table 2. There was not a significant difference in the mean heart rate in the group (III) compared to group (II) at any time postoperatively and there was not a significant difference in the mean heart rate between the three groups 6 h postoperatively.

There was a significant decrease in the mean systolic blood pressure in the group (II) and group (III) compared to group (I) 30 min, 1 h, 1.5 h, and 2 h postoperatively as shown in Table 3. There was not a significant difference in the mean systolic blood pressure in the group III compared to group (II) at any time postoperatively and there was no statistically significant difference between these groups of patients 6 h postoperatively.

There was no significant difference between the three groups 30 min, 1 h, 1.5 h, 2 h, and 6 h postoperatively as regard the mean diastolic blood pressure ($P > 0.05$).

Sedation score was significantly higher in group (II) and group (III) than in group (I) in the first 2 h postoperatively as shown in Figure 2. Sedation score was significantly higher in group (III) than in group (II) in the first 2 h postoperatively.

There was a significant reduction in VAS in group (II) and group (III) in comparison to group (I) at

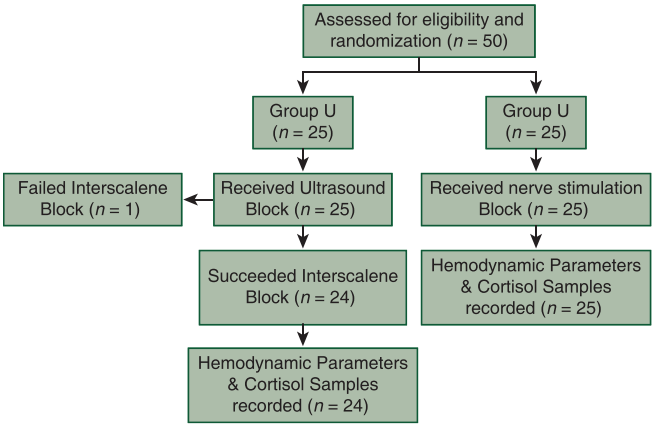

Figure 1: Flow chart of patients (study design)

Table 1: The demographic data

Parameters	Group (I) Paracetamol (1 g) (*n* = 25)	Group (II) Pregabalin (150 mg) (*n* = 25)	Group (III) Pregabalin (300 mg) (*n* = 25)	*P*
Age (year)	45.5±5.1	47±4.12	44.6±2.2	0.117
Weight (kg)	77.68±6.2	79.2±4.9	79.3±4.1	0.17
Gender (female/male)	18/7	19/6	14/11	0.08
Height (cm)	169.4±5.5	170.9±3.3	168.5±4.9	0.078
ASA (I/II)	20/5	21/4	21/4	0.49
Duration of anesthesia (min)	67.2±4.5	68.8±5	68.7±6.2	0.48

Values are mean ± SD for age, weight, height, duration of anesthesia and number of patients for gender and ASA; $P > 0.05$ was considered statistically nonsignificant. ASA: American Society of Anesthesiologists; SD: Standard deviation

Table 2: The heart rate changes (beats/min)

Time points	Group (I) Paracetamol (1 g) (*n* = 25)	Group (II) Pregabalin (150) (*n* = 25)	Group (III) Pregabalin (300) (*n* = 25)	*P*
30 min	82.7±5.2†	79.2±4.9	79.3±4.1	<0.001*
1 h	81.2±4.3†	74.6±2.3	71.7±3	<0.001*
1.5 h	82.5±4.5†	74.2±2	75±5.1	<0.001*
2 h	84±4.3†	78.4±2.6	75.9±3.7	<0.001*
6 h	85±3.82	82.9±2.7	80.6±3.3	0.7

Values were mean ± SD; *$P < 0.001$ was considered statistically significant between the three groups; †$P < 0.001$ was considered statistically significant between group (I) compared to groups (II) and (III); SD: Standard deviation

the first 30 min to 2 h postoperatively as shown in Figure 3. Pain score was lower in group (III) compared to group (II) 2 h postoperatively and this was not significant.

There was significant reduction as regards the time for first requirement for analgesia postoperatively between group (II) and group (III) in comparison to group (I) at the first 30 min to 2 h postoperatively [Table 4].

Table 3: The systolic blood pressure changes (mmHg)

Time points	Group (I) Paracetamol (1 g) (n = 25)	Group (II) Pregabalin (150 mg) (n = 25)	Group (III) Pregabalin (300 mg) (n = 25)	P
30 min	124.6±4†	112.6±4.9	110.6±3	<0.001*
1 h	122.4±5†	111.3±2.3	110.1±2.4	<0.001*
1.5 h	120.2±3.5†	115.5±2	113.7±2.5	<0.001*
2 h	120.9±3.3†	116.1±2.1	118.5±2.6	<0.001*
6 h	122.4±3	117.6±2.3	116±2.3	0.78

Values were mean ± SD; *P<0.001 was considered statistically significant between the three groups; †P < 0.001 was considered statistically significant between group (I) compared to groups (II) and (III); SD: Standard deviation

Table 4: The time for the first requirement for analgesia (min) and serum cortisol changes (in µg/dl) postoperatively

Parameters	Group I	Group II	Group III	P
Time for 1st rescue analgesic (min)	26.7±34†	164.2±22	166±20	<0.001*
Serum cortisol 1 h postoperative (in µg/dl)	32±4.4†	21.3±3.3	21.2±3.6	<0.001*

Values were mean ± SD; *P < 0.001 was considered statistically significant between the three groups; †P < 0.001 was considered statistically significant between group (I) compared to groups (II) and (III); SD: Standard deviation

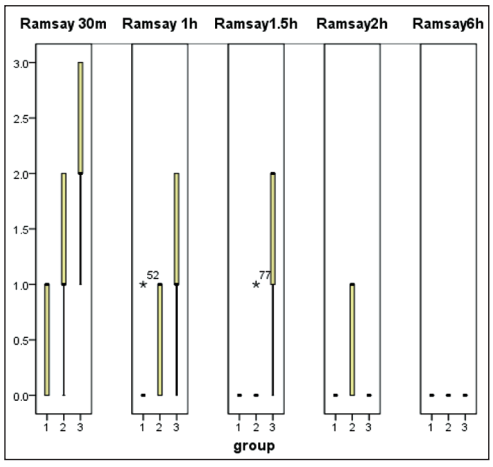

Figure 2: Comparison between the three groups of patients as regard sedation score. The middle line in each box represents the median, the outer margins of the box represent the interquartile range, and whiskers represent minimum and maximum

As regard serum cortisol level, there was a significant difference postoperatively between group (II) and group (III) in comparison to group (I) at 1 h postoperatively [Table 4].

There was no significant difference between group (II) and group (III) 1 h postoperatively as regards the time for the first requirement for analgesia and serum cortisol level [Table 4].

The occurrence of postoperative vomiting was significant (P < 0.01) in group (III) (9 patients) while it was absent in group (I) and group (II), in spite of premedication by granisetron (IV). There was significant excessive sedation and blurring of vision (P < 0.001) in group (III) (12 patients).

DISCUSSION

Optimal pain relief postoperatively is important as it may reduce postoperative complications and encourage early discharge from hospital. The ideal method for postoperative pain relief should be simple to perform, inexpensive, and causes minimal morbidity.[15]

The results of the present study demonstrated that the single preoperative oral dose of pregabalin (150 mg or 300 mg) had delayed the first request for analgesics postoperatively compared to the group with single preoperative oral dose of paracetamol (1 g).

These results are in agreement with the findings of Girija *et al.* who reported that the administration of single preoperative dose of oral pregabalin 150 or 300 mg was effective in reducing postoperative pain and total fentanyl consumption in patients undergoing lumbar laminectomy and discectomy.[16]

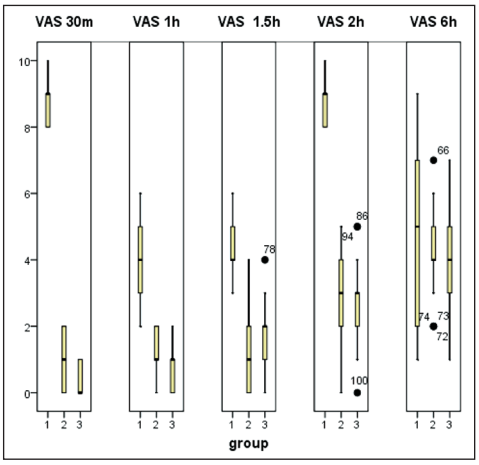

Figure 3: The visual analog scale. The middle line in each box represents the median, the outer margins of the box represent the interquartile range, and whiskers represent minimum and maximum

Agarwal *et al.* also reported that oral pregabalin 150 mg administered before the operation was effective in reducing postoperative pain and the postoperative patient-controlled fentanyl requirement in patients undergoing laparoscopic cholecystectomy.[17]

Paech *et al.* found that no better pain relief than placebo and an increase in side effects, after a single preoperative dose of pregabalin 100 mg in patients have day-case uterine surgery.[18]

These results were partially consistent with Peng *et al.* who reported that multiple doses of pregabalin resulted in superior analgesia only in the first 90 min over placebo. Pregabalin 75 mg offered better analgesia compared with pregabalin 50 mg. However, pregabalin did not result in a reduction in opioid consumption, clinical meaningful side effects or an improvement in quality of recovery.[19]

In this study, sedation score was significantly higher in group (II) and group (III) than in group (I) in the first 2 h postoperatively.

This result was supported by the study of Girija *et al.* who reported that the sedation score was higher postoperatively in patients received single preoperative dose of oral pregabalin 300 mg than patients received single preoperative dose of oral pregabalin 150 mg undergoing lumbar laminectomy and discectomy.[16]

Hill *et al.*, Chang *et al.* and Kim *et al.* had evaluated postoperatively the undesirable side effects of preoperative oral pregabalin 300 mg, e.g., excessive sedation, blurring of vision, dizziness, and postoperative nausea and vomiting.[20-22]

CONCLUSION

The single preoperative dose administration of pregabalin (150 or 300 mg) had a significant opioid-sparing effect in the first 2 h after surgery. The postoperative undesirable side effects of preoperative oral pregabalin 300 mg, e.g., excessive sedation, blurring of vision, and postoperative nausea and vomiting were significantly common. The use of preoperative oral pregabalin 150 mg was an effective and a safe adjuvant for acute pain after surgery.

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