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+ORIGINAL RESEARCH

Effect of preoperative administration of oral pregabalin on postoperative pain intensity and analgesic requirement following laparoscopic cholecystectomy

[1]Dr Swati Gupta, [2]Dr. Ganesh Ramaji Nimje, [3]Dr. Kalpana Verma, [4]Dr. Vishnu Kumar Garg, [5]Dr. Ayush Gupta, [6]Dr. Shubham Jain

[1,5,6]MBBS, Junior Resident, Department of Anaesthesia, Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan, India
[2]Assistant Professor, Department of Organ Transplant Anaesthesia & Critical Care, Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan, India
[3] Associate Professor, Department of Anaesthesia, Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan, India
[4]Associate Professor, Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan India

Corresponding author: Dr. Ganesh Ramaji Nimje
ganesh.nimje8@gmail.com

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Abstract
Background: The present study was conducted to evaluate the clinical efficacy of preoperative administration of pregabalin on postoperative pain and analgesic requirement in patients undergoing elective laparoscopic cholecystectomy.
Methods: The prospective, randomized, comparative, hospital-based study was conducted in 60 patients who were divided into two groups: Group 1 (n=30) received oral placebo capsule two hours before surgery and Group 2 (n=30) received oral pregabalin 150 mg two hours before surgery. Along with demographic and vital parameters, visual analogue scale (VAS) scores at rest & at movement at 0, 8, 16 and 24 hours postoperatively, analgesic requirement and complications were compared between the groups.
Results: The mean VAS score at rest & at movements are significantly lower in pregabalin group than in placebo group at all intervals ($p<0.05$). Although post operative requirement of rescue analgesic and complications like sedation, nausea and vomiting were comparatively lesser in pregabalin group than in placebo group, this difference was not statistically significant.
Conclusion: Preoperative administration of oral pregabalin is effective in reducing postoperative pain, postoperative requirement of analgesics and incidence of postoperative complications in patients undergoing laparoscopic cholecystectomy.
Keywords: Analgesic, cholecystectomy, pain, pregabalin,

Introduction

Laparoscopic cholecystectomy is one of the most common surgical procedure; however, pain after this surgery remains a major challenge. Earlier reports revealed that approximately 80% of patients undergoing the procedure experience moderate to severe postoperative pain.[1]For many decades, the treatment of acute postsurgical pain has been essentially limited to three classes of medications: opioids, cyclo-oxygenase inhibitors, and local anesthetics. These medications are usually effective in the routine care of patients, although side effects, which range from inconvenient to life-threatening, can be limiting their use. Multimodal analgesia

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techniques have been studied widely during the past decade as a way of enhancing analgesia and minimizing side effects, primarily of opioids.[2]

These regimens have added medications such as ketamine, acetaminophen, tramadol, and the anticonvulsant medications: gabapentin and pregabalin. To achieve effective postoperative pain relief, multimodal therapy with 2 or more analgesics and modalities that work by different mechanisms to improve analgesia and reduce the severity of adverse effects have become quite popular. For surgery, operatively induced neuroplastic changes may provoke sensitization and cause postoperative hyperalgesia or allodynia. Therefore, an optimal multimodal analgesic regimen, including anti hyperalgesia drugs to attenuate central sensitization, may have beneficial effects for pain control after surgery.[3]

Pregabalin, a ligand to alpha2-delta subunit of the presynaptic N-type voltage-dependent calcium channels that are found in high densities in the dorsal horn. It's up-regulation may contribute to the hypersensitivity associated with pain.[4] Binding of pregabalin to the alpha2-delta subunit has been shown to decrease the depolarization induced influx of calcium at nerve terminals, resulting in decreased release of neurotransmitters such as glutamate, substance P, calcitonin-gene-related peptide, and norepinephrine. This modulation is probably responsible for the analgesic property of pregabalin.[5]

The present study was aimed to evaluate the clinical efficacy of preoperative administration of pregabalin in postoperative pain and analgesic requirement in patients undergoing elective laparoscopic cholecystectomy.

Materials and methods

Sampling

This double blind, prospective, randomized, comparative, hospital-based study was conducted in a tertiary care centre in Western India. Patients of American society of anaesthesiologist grade I and II in the age group of 18-65 years, scheduled for elective laparoscopic cholecystectomy were randomly allocated with their consent in one of the two groups. Randomisation was done according to computer generated random number table, where each number will refer to one of the two groups. Unwilling patient, pregnant and lactating female patient and patient with history of allergy to study drug, impaired liver or kidney function, history of chronic pain or daily intake of analgesics, history of chronic use of central nervous system depressant drugs and anticonvulsant, morbid obesity, inability to comprehend or participate in pain scoring system were excluded from the study. A total of 60 patients were included in the study with 30 patients in each group. Group 1 received oral placebo capsule two hours before surgery and Group 2 received oral Pregabalin 150 mg two hours before surgery

Methodology

The study was conducted after the approval of the institutional ethical committee. On the day of surgery on arrival in the operating room, standard monitors like non-invasive blood pressure, pulse oximetry, Electrocardiogram was connected, and intravenous line were secured, and fluid was started. A uniform anaesthetic technique was maintained in all the patients. Patient was induced with fentanyl 2mcg/kg and propofol 1.5-2.5mg/kg; orotracheal intubation was facilitated by intravenous injection of atracurium (0.5mg/kg) and anaesthesia was maintained with isoflurane 1% in a mixture of O_2 and air. At the end of surgery, residual neuromuscular paralysis was antagonized with neostigmine 0.04 mg/kg and glycopyrrolate 0.01 mg/kg. Injection of paracetamol (15mg/kg) was administered to all the patients.

After satisfactory recovery, patients were extubated and shifted to the post-anaesthetic care unit (PACU) for observation. Postoperative nausea/ vomiting was assessed using PONV scores and postoperative level of consciousness was monitored continuously according to Ramsay

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Sedation Score. The presence and severity of pain at rest and at movement using the visual analogue scale (VAS)and rescue analgesia requirement were assessed postoperatively at 0, 8, 16 and 24 hours. If the VAS score was more than 4, then rescue analgesia was administered in the post-operative period with injection of Diclofenac 1mg/kg. If the score did not decrease to desired level, then was supplemented with injection of Tramadol 1mg/kg. Time for first request of rescue analgesia and total dose of analgesia requirement in first 24 hours were also noted.

Statistical analysis

The data were tabulated in Microsoft excel and analysed with SPSS V.24 software. The continuous variables were presented with mean and standard deviation. The categorical variables were presented with frequency and percentage. Independent t test and chi square test were used for the comparisons. The p value ≤0.05 is considered statistically significant.

Results

A total of 60 patients were assessed for eligibility and 60 of them consented and were randomized. The flow of the patients through the trial summarized in Figure 1.

Figure 1: CONSORT flow diagram of the study

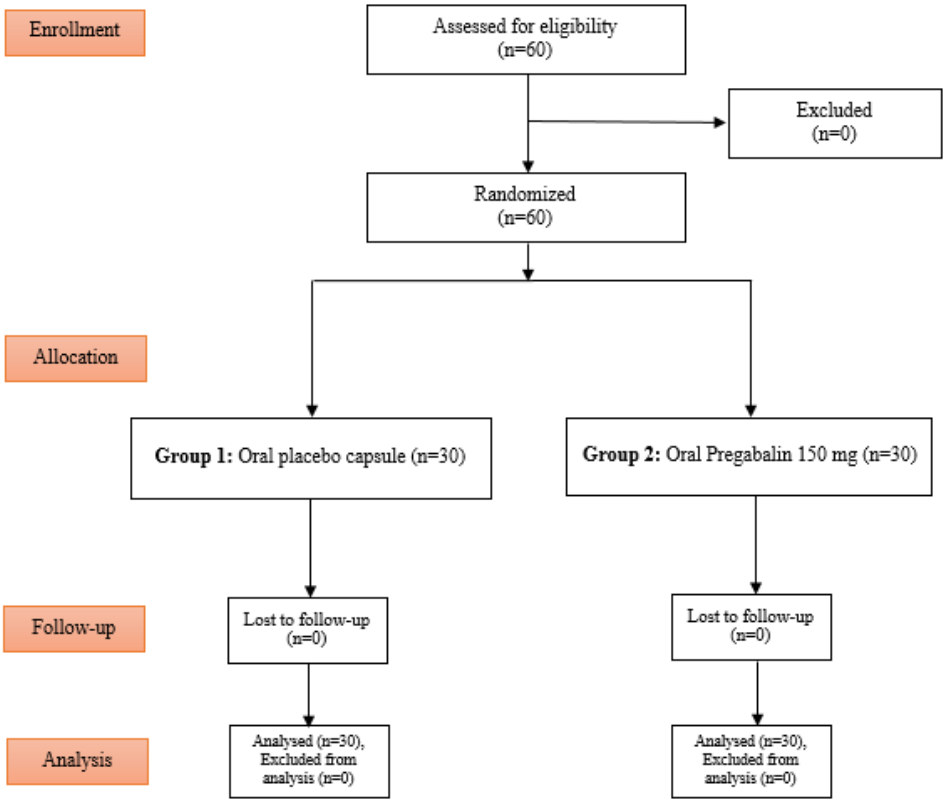

Table 1: Demographic and clinical characteristics

Characteristics	Pregabalin group (n = 30)	Placebo group (n = 30)	P value
Age (years)	45.6±8.1	46.2±8.5	0.724
Sex (Male/Female)	17/13	16/14	0.795
Duration of surgery (min)	89.3±18.6	92.5±20.7	0.261
Duration of anesthesia (min)	112.9±31.7	115.2±33.5	0.448
Heart rate (bpm)	72.4±6.4	72.7±6.5	0.992
Systolic blood pressure (mmHg)	118.2±13.7	119.5±14.1	0.803

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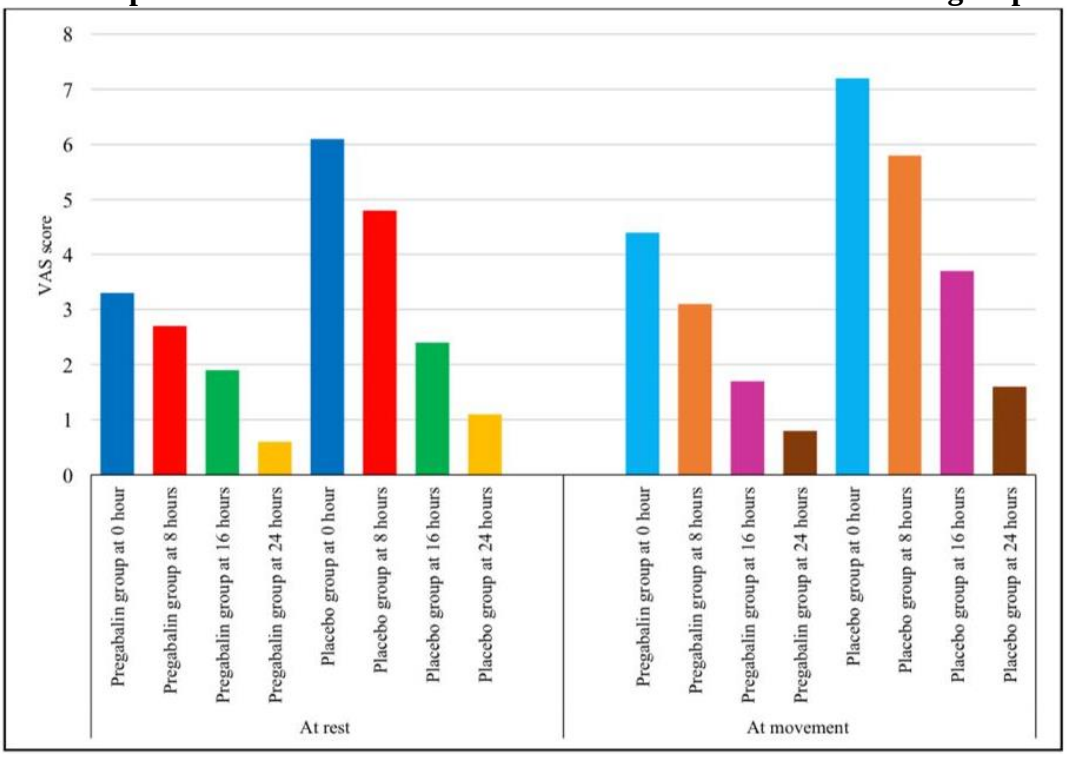
Diastolic blood pressure (mmHg)	79.1±9.3	80.6±10.1	0.915

Table 1 shows the distribution of demographic and clinical characteristics of both the groups. There were no statistically significant differences between the groups in terms of age, sex, duration of surgery and anaesthesia (p>0.05). The vital parameters (heart rate, systolic blood pressure and diastolic blood pressure) were slightly higher in placebo group than pregabalin group without any statistically significant differences (p>0.05).

Figure 2: Comparison of VAS scores at rest and at movement between the groups.



VAS: Visual analogue scale

Figure 2 shows the comparisons of VAS scores at rest and at movement respectively at four intervals (postoperative 0, 8, 16 and 24 hours).

The mean VAS score at rest & at movements were significantly lower in pregabalin group than in placebo group at all intervals (p<0.001).

Although post operative requirement of rescue analgesic and complications like sedation, nausea and vomiting were comparatively lesser in pregabalin group than in placebo group, this difference was not statistically significant. (Table 2).

Table 2: Analgesic requirement and complications

Parameters	Pregabalin group (n = 30)	Placebo group (n = 30)	P value
Rescue analgesic used	4	10	0.07
Sedation	3	5	0.45
Nausea	8	9	0.77
Vomiting	2	3	0.64

Discussion

The present study was conducted to evaluate the effect of preoperative administration of oral pregabalin on postoperative pain intensity and analgesic requirement following laparoscopic cholecystectomy. The average age of patients included in our study was 45.6±8.1years in

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pregabalin group and 46.2±8.5 years in placebo group. There were no significant differences in age or sex distribution between the two groups. This is important because it has implications in the difference of perception of pain. These findings are supported by studies done by Eidyet al and Agarwal et al. [6,7]

The comparisons of VAS scores at rest and at movement were done at four intervals (postoperative 0, 8, 16 and 24 hours). The mean VAS score at rest & at movements are significantly lower in pregabalin group than placebo group at all intervals ($p<0.001$).

Gurusamy K in a 2014 Cochrane meta-analysis studied the various pharmacological interventions for prevention or treatment of postoperative pain in people undergoing laparoscopic cholecystectomy. The authors found that the pain at 4 to 8 hours was generally reduced by about 1 to 2 on the visual analogue scale of 1 to 10 in the comparisons involving the different pharmacological agents and inactive controls (low or very low-quality evidence). The pain at 9 to 24 hours was generally reduced by about 0.5 (a modest reduction) on the visual analogue scale of 1 to 10 in the comparisons involving the different pharmacological agents and inactive controls (low or very low-quality evidence).[8]

Assessment of pain only at rest will not reveal differences between more potent pain relieving methods, such as optimal thoracic epidural analgesia, compared with less effective epidurals or systemic opioid analgesia: systemic opioids can make the patient comfortable, even after major surgery, when resting in bed.[9] However, dynamic pain provoked by movements necessary to get the patient out of bed, and mobilizing bronchial secretions by forceful coughing, cannot be relieved by systemically administered potent opioids without causing unacceptable adverse effects.[10]

Findings similar to our study have been previously reported in a few earlier studies. Agarwal et al in 2008 reported a statistically significant decrease in pain intensity (static and dynamic) with pregabalin 150 mg.[7] Similarly, Balaban et al showed a decrease in pain scores with pregabalin 150 and 300 mg compared to placebo and a dose of 300mg pregabalin offered better analgesia than placebo 2 hours post-surgery, and 300 mg offered better analgesia than 150 mg 1 hour after the procedure.[11]Sarakatsianou in 2013 demonstrated similar reduction in pain scores with 300mg pregabalin administered twice before surgery.[12] Peng et al in 2010 showed that pain after laparoscopic cholecystectomy was significantly decreased with 75 mg pregabalin but not with 50 mg pregabalin.[13] However analgesia was superior to placebo only in the first 90 minutes after the procedure in their study. Singh et al in 2016 also showed efficacy of 150 and 300 mg pregabalin in decreasing pain scores.[14] Contradictory results have been seen in a study by Chang et al in 2009 where they found that that perioperative use of pregabalin in two doses of 150mg 1 hour before surgery and then 12 hours after the first dose did not decrease the frequency or severity of shoulder pain as well as the severity of pain after laparoscopic cholecystectomy.[15]

Although in our study, VAS pain scores were significantly less across all time intervals in the first 24 hours with 150 mg oral pregabalin, we did not find a significant difference in opioid consumption between the placebo and pregabalin groups. Ten patients out of 30 required rescue analgesia in the form of tramadol in the placebo arm compared to only four patients in the pregabalin arm. This can be explained by the relatively modest reduction in pain scores between the groups. Although pain was decreased with pre-emptive pregabalin, this did not translate into a net clinical benefit in the form of decrease in rescue analgesic requirement. This is also because pain is a subjective feeling but requirement of analgesic is a hard end point and was negative in our study. This might be one of the reasons why in spite of multiple studies showing decrease in pain, it has not become a routine practice to use pre-emptive pregabalin.

Similar to our study, Peng et al in 2010 also found that although 50 mg and 75 mg oral pregabalin was able to decrease pain scores ,however, pregabalin did not result in a reduction in opioid consumption.[13]Chang et al also showed that pain scores, time for first rescue

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analgesia and additional need of ketorolac consumption did not differ significantly in pregabalin vs placebo.[15]This is in contrast to other studies by Agarwal, Balaban, Sarakatsianou, and Singh et al.[7,10,11]

One interesting finding was the very low requirement of rescue analgesia in our study in almost both the groups. This could be related to either surgical technique or the efficacy of intra-operative anaesthesia. Bekawi et al had reported very different results than all previous studies. They had showed that 150 mg pregabalin perioperatively is effective in reducing postoperative pethidine consumption without increasing the side effect profile, although it has failed to reduce postoperative pain (VAS scores). Authors' explanation for this was that they had used an intermediate dose of pregabalin over an extended period and a single dose in order to decrease the side effect potential.[16]

Incidences of nausea and vomiting were nearly similar in our two groups of patients. Pregabalin arm showed similar incidence of nausea and vomiting compared to placebo. This may be explained on association of greater VAS scores in control group with increased demand of rescue opioid analgesic.

In the study by Singh et al, the incidence of side effects such as nausea and vomiting were minimal in the two pregabalin groups as compared with the control group which recorded increased incidence.[14] Similar findings have been reported in thes tudies of Paul FW et al and Wichai I et al. [17,18]Bekawiet al. reported less postoperative nausea and vomiting (PONV) in the intervention group (150 mg pregabalin) compared to the placebo group.[16]

Similar to postoperative nausea and vomiting, we did not find significant difference in sedation between pregabalin or placebo arms. This translates into almost similar side effect profile with pregabalin compared to placebo and shows the safety of this intervention in decreasing postoperative pain in patients undergoing laparoscopic cholecystectomy. Balaban et al. and Chang et al. reported increased postoperative sedation early (at 15 min and 2 h, respectively) in the intervention group (300 mg pregabalin). [11,15] No other trial showed any statistically significant difference in the incidence or severity of sedation at any time point.In a study by Esmatet al, sedation score was significantly higher in groups receiving 150 mg and 300 mg pregabalin in the first 2 hours postoperatively.[19]This result was supported by the study of Girija et al. who reported that the sedations 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.[20]

Conclusion

From the findings of our study, we can conclude that, preoperative administration of oral pregabalin is effective in reducing post-operative pain, postoperative requirement of analgesic and incidences of postoperative complications in patients undergoing laparoscopic cholecystectomy. Further research on larger samples and with lower doses of pregabalin is recommended.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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