Original Research Article

Comparative study to evaluate the analgesic efficacy of pregabalin versus gabapentin in patients undergoing laparoscopic cholecystectomy

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Abstract

Background: Laparoscopic cholecystectomy results in less postoperative pain and/or reduced analgesic consumption as compared with open cholecystectomy. Nonetheless, pain after laparoscopy may be moderate or even severe for some patients, and may require opioid treatment. The present study was designed in view of evaluating analgesic efficacy of pregabalin versus gabapentin in patients undergoing laparoscopic cholecystectomy. **Material and Methods:** Present study was hospital based, double blind, randomized, prospective, comparative clinical study, conducted patients 18-70 years, of either sex, with ASA grade I-II, undergoing Laparoscopic cholecystectomy surgery. The patients were randomly divided in two groups as - Gabapentin group (receiving Capsule Gabapentin 600 mg orally with sips of water, two hours prior to surgery) and Pregabalin group (receiving Capsule Pregabalin 150 mg orally with sips of water, one hour prior to surgery). **Results:** In present study, there was no substantial difference among the two groups with regard to age, weight, sex and ASA grade. In present study, patients receiving Pregabalin (14.7 ± 4.1) had a statistically significant lower mean first hour post operative visual analogue scale score as compared to patients receiving Gabapentin (32.8 ± 9.6). The mean time of rescue analgesia in the pregabalin group was 4.33 hours and that in the gabapentin group was 1.75 hours and difference was statistically significant. Pain, as measured by the visual analogue scale score was always found to be lower in the Pregabalin group when compared with the Gabapentin group, during the entire observation period. We noted a significant difference in the total number of analgesic doses required in gabapentin group compared to the pregabalin group. **Conclusion:** Pregabalin (150 mg) decreases post operative pain for the first 24 hours, reduces the requirement of rescue analgesia and had low incidence of side effects as compared to gabapentin (600 mg).

Keywords: Pre-emptive analgesia, pregabalin, gabapentin, laparoscopic cholecystectomy.

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INTRODUCTION

The international association for the study of pain (IASP) defines pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[1] Pain causes an increase in sympathetic response of the body with subsequent increase in the heart rate, cardiac work and oxygen consumption. Prolong pain can reduce physical activity and lead to venous stasis and an increase risk of deep vein thrombosis and consequent pulmonary embolism.[1] Pre-emptive analgesia is defined as an antinociceptive treatment that prevents establishment of

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altered central processing of afferent input from injuries. Acute postoperative pain is dependent on the surgical procedure, extent and nature of tissue damage, duration of surgery, timing of pre-emptive treatment relative to incision, pharmacokinetics of the agent(s) used pre-emptively, presence or absence of additional analgesia intraoperatively, nature of postoperative analgesia, and a host of other variables.[2] Laparoscopic cholecystectomy results in less postoperative pain and/or reduced analgesic consumption as compared with open cholecystectomy.[3,4,5] Nonetheless, pain after laparoscopy may be moderate or even severe for some patients, and may require opioid treatment. Interestingly, the type of pain after laparoscopy differs considerably from that seen after laparotomy. The present study was designed in view of evaluating analgesic efficacy of pregabalin versus gabapentin in patients undergoing laparoscopic cholecystectomy

MATERIAL AND METHODS

Present study was hospital based, double blind, randomized, prospective, comparative clinical study, conducted in Department of Anaesthesia, Dr.Vasantrao Pawar Medical College, Hospital And Research Centre, Adgaon,, India. Study duration was of 2 years (July 2018 to June 2019). Study was approved by institutional ethical committee.

INCLUSION CRITERIA: Patients 18-70 years, of either sex, with ASA grade I-II, undergoing Laparoscopic cholecystectomy surgery.

EXCLUSION CRITERIA: Patients with known history of hypersensitivity to the drug. History of ischemic heart disease. Patient refusal to participate. Patients with uncontrolled concomitant medical disorders. History of peptic ulcer or of bleeding diathesis or taking antacids. Impaired kidney or liver functions. Ingestion of analgesics within 24 hours before scheduled surgery. Antidepressant and calcium channel blocker use.

After getting approval from the ethical committee the study was started. The patients in the study group were explained about nature of study and informed consent was obtained for participation in the study. Patients were educated about Visual Analogue Scale (V.A.S.) for grading of pain. All patients were investigated including Hemoglobin, Complete blood counts, Urine analysis, Bleeding time, Clotting time, Liver function tests, Renal function tests, Chest X-Ray and ECG as appropriate.

The patients were randomly divided in two groups as -

Gabapentin group - Patients receiving Capsule Gabapentin 600 mg orally with sips of water, two hours prior to surgery.

Pregabalin group – Patients receiving Capsule Pregabalin 150 mg orally with sips of water, one hour prior to surgery. On the day of the surgery, patients were administered the drug (either gabapentin or pregabalin) orally with sips of water according to the number allocated to the patient approximately two hours and one hour prior to surgery respectively. Once inside the operation theatre, routine monitors were attached using cardioscope, non-invasive blood pressure monitoring, pulse oximeter and capnometer. Preoxygenated with 100% oxygen with face mask for three minutes. Premedication was done with Inj. Glycopyrrolate 0.004 mg/kg, Inj. Ranitidine 1 mg/kg, Inj. Ondansetron 0.08mg/kg, Inj. Midazolam 0.03 mg/kg and Inj. Fentanyl 1-2mg/kg intravenously. Anaesthesia was then induced with Inj. Propofol 2-3 mg/kg IV in titrated doses. Intubation was facilitated with Inj. Atracurium 0.5 mg/kg. Anaesthesia was maintained with 50% air with 50 % oxygen and inhalational isoflurane(0.8-1%) and infusion of atracurium 25 mg /hr to maintain adequate depth of anaesthesia. Normocapnia was maintained. Intra operatively additional analgesia was provided with Inj. Diclofenac 75 mg immediately after intubation. After completion of surgery Inj. Neostigmine 0.05 mg/kg with Inj. Glycopyrrolate 0.01 mg/kg was given to reverse neuromuscular blockade. Tracheal extubation was performed after adequate and regular spontaneous ventilation was established and adequate tone, power and reflexes were regained. Postoperatively patients were observed in recovery room where monitoring was done for a period of 24 hours by an anaesthesiologist blinded for the drug. The anaesthesiologist recorded vital parameters, V.A.S. score on arrival in recovery room(immediately after the surgery=0 hour) and every 2 hourly till 24 hours. V.A.S. score of pain was used where 100 mm scale marked with ‘0’ at one end represented ‘no pain’ and marked ‘100’ at other end represented ‘worst possible pain’. When asked, patient was told to point out his assessment of pain at that time on the multiple points of this visual analogue scale. When V.A.S. score was ≥30 , rescue analgesia was given with Inj. Diclofenac 1.5 mg/kg IV. The time to first rescue analgesia was recorded and total analgesic requirement over 24 hours was assessed. The side effects of the drugs were also studied. Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi- square test or Fisher exact test as applicable. P value less than 0.5 was considered as statistically significant.

RESULTS

In present study, there was no substantial difference among the two groups with regard to age, weight, sex and ASA grade.

Table 1: Demographic Data

Parameters	Gabapentin (n=30)	Pregabalin (n=30)	' p' Value	Significance
Age(Yrs)	47.2 ± 10.8	52.7 ± 10.3	0.058	Not significant
Weight (Kgs)	70.0 ± 8.0	70.3 ± 9.9	0.157	Not significant
Sex (M/F)	14/16	15/15	0.796	Not significant
ASA Grade(I/II)	17/13	13/17	0.302	Not significant

In present study, patients receiving Pregabalin (14.7 ± 4.1) had a statistically significant lower mean first hour post operative visual analogue scale score as compared to patients receiving Gabapentin (32.8 ± 9.6). Patients requiring rescue analgesia during the first postoperative hour was found to be of reduced magnitude in the pregabalin group as compared to the gabapentin group (10 vs. 0) and difference was statistically significant. The mean time of rescue analgesia in the pregabalin group was 4.33 hours and that in the gabapentin group was 1.75 hours and difference was statistically significant.

Table 2: Comparison post operative visual analog scale (VAS) score

	Gabapentin (n=30) Mean ± SD	Pregabalin (n=30) Mean ± SD	' p' Value	Significance
First (0) post operative hour VAS score	32.8 ± 9.6	14.7 ± 4.1	< 0.001	Significant
No. of patients requiring rescue analgesia in first post operative	10	0	0.033	Significant
Time of first rescue analgesia	1.75 ± 1.800	4.33 ± 1.670	< 0.001	Significant

Pain, as measured by the visual analogue scale score was always found to be lower in the Pregabalin group when compared with the Gabapentin group, during the entire observation period.

Table 3: Comparison of mean vas scores at various time periods

Time (Hours)	Gabapentin (n=30) Mean ± SD	Pregabalin (n=30) Mean ± SD	' p' Value	Significance
0	32.8 ± 9.6	14.7 ± 4.1	< 0.001	Significant
2	31.0 ± 8.2	16.5 ± 4.4	< 0.001	Significant
4	30.0 ± 7.1	25.5 ± 6.1	0.010	Significant
6	26.0 ± 6.6	25.2 ± 7.7	< 0.001	Significant
8	24.3 ± 6.8	24.0 ± 5.8	< 0.001	Significant
10	25.6 ± 7.2	24.5 ± 3.8	< 0.001	Significant
12	27.3 ± 6.7	24.2 ± 5.4	0.048	Significant
14	24.8 ± 5.5	19.2 ± 6.8	0.001	Significant
16	27.2 ± 6.1	18.0 ± 4.7	< 0.001	Significant
18	25.3 ± 5.4	22.8 ± 4.9	< 0.001	Significant
20	24.3 ± 5.0	22.7 ± 5.2	< 0.001	Significant
22	23.5 ± 6.5	20.2 ± 7.9	< 0.001	Significant
24	17.7 ± 5.2	17.3 ± 6.3	< 0.001	Significant

We noted a significant difference in the total number of analgesic doses required in gabapentin group (24) compared to the pregabalin group (11).

Table 4: Comparison of total doses of rescue analgesic used between two groups

Total Doses used over 24 hrs.	Gabapentin	Pregabalin	'p' Value	Significance
1	15	11		
2	7	0		
3	1	0		
4	1	0		
Total	**24**	**11**	**< 0.001**	**Significant**

There was no significant difference in the individual incidences of dizziness, nausea and sedation between the comparison groups. A significant difference does exist if the total incidence of all the side effects is considered.

Table 5: Comparison of side effects between two groups

Adverse Effect	Gabapentin (n=30)	Pregabalin (n=30)	'p' Value	Significance
Dizziness	4	2	0.667	Not significant
Nausea	4	0	0.121	Not significant
Sedation	4	0	0.121	Not significant
Total	**12**	**2**	**0.006**	**Significant**

DISCUSSION

Acute pain after laparoscopic cholecystectomy is complex in nature. The pain pattern does not resemble the pain after other laparoscopic procedures, suggesting that the analgesic treatment might be procedures specific and multimodal.[6] Pre-incisional preemptive analgesia has been shown to be more effective in control of post operative pain by protecting the central nervous system from deleterious effects of noxious stimuli and resulting allodynia, and increased pain.[7,8] Gabapentin and pregabalin both have antiallodynic and anti-hyperalgesic properties useful from treating neuropathic pain and may also be beneficial in acute postoperative pain. Pregabalin and gabapentin share a similar mechanism of action, inhibiting calcium influx and subsequent release of excitatory neurotransmitters; however, the compounds differ in their pharmacokinetic and pharmacodynamic characteristics.[9] Gabapentin is absorbed slowly after oral administration, with maximum plasma concentrations attained within 3-4 hours. Orally administered gabapentin exhibits saturable absorption--a nonlinear (zero-order) process--making its pharmacokinetics less predictable.[9] Plasma concentrations of gabapentin do not increase proportionally with increasing dose. In a large randomized control trial, Pandey *et al.*,[10] studied effect of 300 mg gabapentin, 100 mg tramadol or placebo in a double-blind manner on postoperative pain and rescue analgesic requirements after laparoscopic cholecystectomy under general anesthesia. Patients in the gabapentin group had significantly lower pain scores at all time intervals in comparison to tramadol and significantly less fentanyl was consumed in the gabapentin group than in the tramadol and placebo groups. Ho *et al.*,[11] in their systematic review suggested that perioperative administration of gabapentin was effective in reducing pain scores, opioid requirements and opioid-related adverse effects in the first 24 hours after surgery. Their analysis also demonstrated a statistically significant prolongation to the time of first request for rescue analgesics. The incidence of postoperative vomiting and pruritus were also found to be significantly lower in the gabapentin group. Though sedation was associated with the use of gabapentin, no serious adverse effects were observed. Agrawal *et al.*,[12] evaluated the efficacy of a single preoperative dose of pregabalin for attenuating postoperative pain and fentanyl consumption after laparoscopic cholecystectomy. 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. 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. Chang *et al.*,[13] evaluated the efficacy of two perioperative doses of pregabalin 300 mg 12 h apart for preventing and attenuating post laparoscopic shoulder pain(PLSP) after laparoscopic cholecystectomy. In both groups, the overall incidence of PLSP did not differ significantly, and the pain score for PLSP, time to first rescue analgesia, and cumulative ketorolac consumption were similar at each time point. However, the 2-h postoperative incidence of oversedation was higher with pregabalin. Vishal Arora *et al.*,[14] (2009), (113) designed compared the efficacy of gabapentin versus pregabalin with respect to increase in duration of analgesia, reduction in total post- operative requirements of analgesics. The total postoperative analgesic time was 6.14hrs in Group G, 7.31hrs in Group P (HS, P < 0.001) and 4.13hrs in group M. Dizziness and somnolence were the only side effects noticed in both groups. Thus they concluded that pregabalin is more effective than gabapentin in prolongation of post spinal analgesia with decreased rescue analgesic requirements. Pregabalin is several times more potent than similar drug gabapentin due to rapid absorption orally with more than 90% bioavailability, achieves peak plasma levels within 30-60 minutes, had linear pharmacokinetics with low inter-subject variability including dose independent absorption, after single or multiple dosing, the maximal plasma concentration is dose proportional and absorption is independent of food intake.[15] Present study, results suggested that preemptive oral Pregabalin (150 mg) as compared to oral Gabapentin (600 mg) had significant effect on reducing postoperative pain in patients undergoing laparoscopic cholecystectomy surgeries. Also it was observed that time for first rescue analgesia and the total number of rescue analgesic doses over 24 hrs. was significantly less in pregabalin group compared to gabapentin group. Slightly increased incidence of sedation and dizziness was noted in gabapentin compared to pregabalin receiving patients, which did not require any further treatment. Present study was small sample, single center study, further larger studies are recommended to confirm present study findings.

CONCLUSION

Pre-emptive analgesia with Pregabalin (150 mg) is superior to gabapentin (600 mg) in cases of laparoscopic cholecystectomy. Pregabalin (150 mg) decreases post operative pain for the first 24 hours, reduces the requirement of rescue analgesia and had low incidence of side effects as compared to gabapentin (600 mg).

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