PREEMPTIVE SINGLE-DOSE PREGABALIN IN MODULATION OF POSTOPERATIVE PAIN AND OPIOID REQUIREMENT AFTER LAPAROSCOPIC CHOLECYSTECTOMY- A RANDOMIZED CLINICAL STUDY

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ABSTRACT

BACKGROUND

With the enormous advancement in the field of laparoscopic cholecystectomy, postoperative pain has substantially reduced as compared to open procedures. However, postoperative pain is still the most frequent complaint, which can hamper recovery, mandate inpatient admission and thereby increase the cost of such care. Preemptive analgesia attenuates sensitisation of pain before surgery so as to reduce postoperative hyperalgesia and allodynia. Pregabalin is a structural analog of γ-aminobutyric acid, which shows analgesic, anticonvulsant, and anxiolytic effects.

The aim of the present study was to evaluate the effectiveness of preemptive oral pregabalin on postoperative pain and opioid consumption in patients undergoing laparoscopic cholecystectomy.

MATERIALS AND METHODS

Eighty adult patients of ASA I and II undergoing laparoscopic cholecystectomy were randomly divided into two groups to receive either pregabalin 150 mg capsule or a matching placebo (vitamin B complex capsule) 1 hour before surgery. Anaesthesia technique was standardised in both the groups. Postoperative pain was assessed at 0, 1, 2, 3, 6, 9, 12, 18 and 24 hours period postoperatively by a 10 cm visual analogue scale, where 0, no pain; 10, worst imaginable pain. Subjects received Inj. Tramadol hydrochloride (1 mg/kg IV) as a rescue analgesic whenever VAS score was ≥4. Occurrence of any side effects like nausea, vomiting, sedation, headache and dizziness was also noted.

Statistical Analysis Used- Data analysis was done using PASW 18.0 software. Results were analysed by Mann-Whitney U-test, large sample difference in proportion test and Fisher's Exact test.

RESULTS

Patients in the pregabalin group had significantly lower pain scores at all the time intervals in comparison to placebo group ($p<0.05$). Total postoperative tramadol consumption in the pregabalin group was statistically significantly lower than in the control group ($p<0.05$) and also time to first request for rescue analgesic was significantly prolonged in the pregabalin group ($p<0.05$). Incidence of nausea/vomiting was greater in the placebo group than in the pregabalin group ($p<0.05$).

CONCLUSION

Pre-emptive oral administration of pregabalin 150 mg in patients undergoing laparoscopic cholecystectomy is an effective and safe method of analgesia with a low incidence of PONV and reduces postoperative opioid consumption.

KEYWORDS

Preemptive Analgesia, Pregabalin, Laparoscopic Cholecystectomy.

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BACKGROUND

Anaesthesia as a subject by itself had originated in an endeavour to offer pain relief to the patient during surgical procedures. Pain after surgery is a significant concern with poor perioperative pain management associated with an increased risk of morbidity and mortality. The practice of treating pain only after it has been established is slowly being supplanted by a preventive approach. In recent years, studies have shown that taking control over postoperative pain starting during the preoperative period is an important factor for reducing surgery-related stress, which brought about the idea of preemptive analgesia. Sensitisation of dorsal horn neurons after tissue damage has been demonstrated to lead to hyperalgesia or allodynia.[1] Thus, this process is considered to play a key role in chronification of pain after a noxious stimulus.[2] Reducing hyperexcitability

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of dorsal horn neurons by initiating analgesic treatment before tissue damage is pivotal in preventing central nervous upregulation. Postoperative pain is not purely nociceptive in nature and may consist of inflammatory, neurogenic and visceral components. Therefore, multimodal analgesic techniques utilising a number of drugs acting on different analgesic mechanisms are becoming increasingly popular.[3] Although traditionally, the mainstay of postoperative analgesia is opioid based, increasingly more evidence exists to support the multimodal approach with the intent to reduce opioid side effects (such as postoperative nausea and vomiting, somnolence, constipation and respiratory depression) and improve pain scores. Pregabalin is a structural analogue of the inhibitory neurotransmitter, GABA- gamma-aminobutyric acid with anticonvulsant, antihyperalgesic and anxiolytic properties such as gabapentin, but with a more favourable pharmacokinetic profile,[4,5] it binds to the α-2-δ subunit of voltage-gated calcium channels reducing the release of several excitatory neurotransmitters and blocking the development of hyperalgesia and central sensitisation.[6,7] There are several reports for the use of pregabalin in the management of postoperative pain with a positive result in a variety of surgical models.[8,9,10] This study evaluated the effects of pregabalin on postoperative pain in patients undergoing laparoscopic cholecystectomy and compared them with a placebo group.

MATERIALS AND METHODS

The present study used a prospective, randomised, patient and observer blinded, placebo controlled design. After approval from the institutional ethical committee, the clinical study was conducted under the Department of Anaesthesiology and Critical Care at Gauhati Medical College and Hospital.

Inclusion Criteria

1. American Society of Anaesthesiologists physical status class (ASA) I or II.
2. Age between 18 to 60 years.
3. Belonging to any gender.

Exclusion Criteria

1. Any emergency operation.
2. Patients with impaired kidney or liver functions.
3. History of drug or alcohol abuse.
4. History of chronic pain or chronic use of analgesics.
5. Uncontrolled concomitant medical diseases like diabetes mellitus and hypertension.
6. Pregnant or lactating.
7. Any case converted to open cholecystectomy.
8. History of allergy or contraindication to pregabalin.

Using block randomisation, 80 patients satisfying the inclusion criteria were randomly assigned to one of the two treatment groups- drug (pregabalin) or a control (placebo) group. On the morning of the surgery, patients received either pregabalin capsule 150 mg or a matching placebo (vitamin B complex capsule) orally with sips of water, 1 hour before induction of anaesthesia by staff nurses who were not involved in the study.

In the operation theatre, intravenous infusion line was secured and standard monitoring devices measuring Non-Invasive Blood Pressure (NIBP), Pulse Rate (PR), Percentage Oxygen Saturation (SPO2) and Continuous Electrocardiograph (ECG) were attached and baseline recordings were taken before induction of anaesthesia. In both groups, anaesthesia procedures were standardised according to departmental protocol. All patients were premedicated with injection glycopyrrolate (0.004 mg/kg body weight) and injection fentanyl (2 µg/kg body weight), which were given intravenously approximately 3 minutes prior to endotracheal intubation. Anaesthesia was induced with propofol titrated to loss of consciousness after preoxygenation for 3 minutes and endotracheal intubation facilitated by vecuronium bromide (0.08 mg/kg body weight). Anaesthesia was maintained with nitrous oxide in oxygen (66% + 33%) and isoflurane with intermittent dosage of vecuronium. After intubation, a gastric tube was inserted to deflate the stomach and the tube was aspirated and removed before extubation.

Intraoperative monitoring consisted of ECG, NIBP, SPO_2, pulse rate and end-tidal CO_2 (ETCO2). Ventilation was adjusted to maintain $ETCO_2$ within 30-40 mm of Hg. All patients received injection ondansetron (4 mg) approximately 30 minutes before extubation. At the end of surgery, residual neuromuscular paralysis was antagonised with neostigmine (0.05 mg kg^{-1} body weight) and glycopyrrolate (0.01 mg kg^{-1} body weight). Pharyngeal suctioning was done and when adequate spontaneous ventilation was established, patients were extubated. Subsequently, patients were shifted to recovery room. Upon arrival to recovery room, the pulse rate, respiratory rate, SpO_2, BP, pain score (on visual analogue scale) and sedation score (Ramsay sedation score) was assessed and recorded by a blinded observer and the time was designated as T_0, and later after stabilisation, they were sent to their respective wards.

In the wards, the pain and sedation scores along with pulse rate, BP, respiratory rate and SPO_2 were continuously recorded at 1^{st}, 2^{nd}, 3^{rd}, 6^{th}, 9^{th}, 12^{th}, 18^{th}, 24^{th} hours and the times were designated as T_1, T_2, T_3, T_6, T_9, T_{12}, T_{18} and T_{24}.

Assessment of pain was done using a 10 cm Visual Analogue Scale (VAS) where 0 is no pain and 10 worst imaginable pain.

No pain 0 1 2 3 4 5 6 7 8 9 10 worst pain.

Patients were explained about this method of pain scoring on the preoperative visit and they were asked to make a mark on the line, which represented their level of perceived pain severity and the scale was scored by measuring the distance from the no pain end to the point marked by the patient measured in centimetres with a standard scale. Injection tramadol hydrochloride (1 mg/kg) IV was given as a rescue analgesic whenever the pain score was ≥4 or if the patient demand so.

Time to first dose of rescue analgesic and the total amount consumed by the patients in each group over 24 hours was recorded. Sedation score was assessed at same interval postoperatively using Ramsay sedation scale (1- Anxious, agitated or restless; 2- Cooperative, oriented and tranquil; 3- Semi asleep, but responds to command; 4- Asleep, but has a brisk response to light glabellar tap or loud auditory stimulus; 5- Asleep, but has a sluggish response to light glabellar tap or loud auditory stimulus; 6- Asleep, no response). Patients with a sedation score of more than 3 were considered as sedated.

Any incidence of adverse effect like nausea, vomiting, headache or dizziness were recorded in both groups during the first 24 hours and treated accordingly, if present.

Outcome- In this study, we evaluated the efficacy of single oral dose of pregabalin 150 mg in patients undergoing LC for postoperative pain relief and analgesic consumption as primary outcomes.

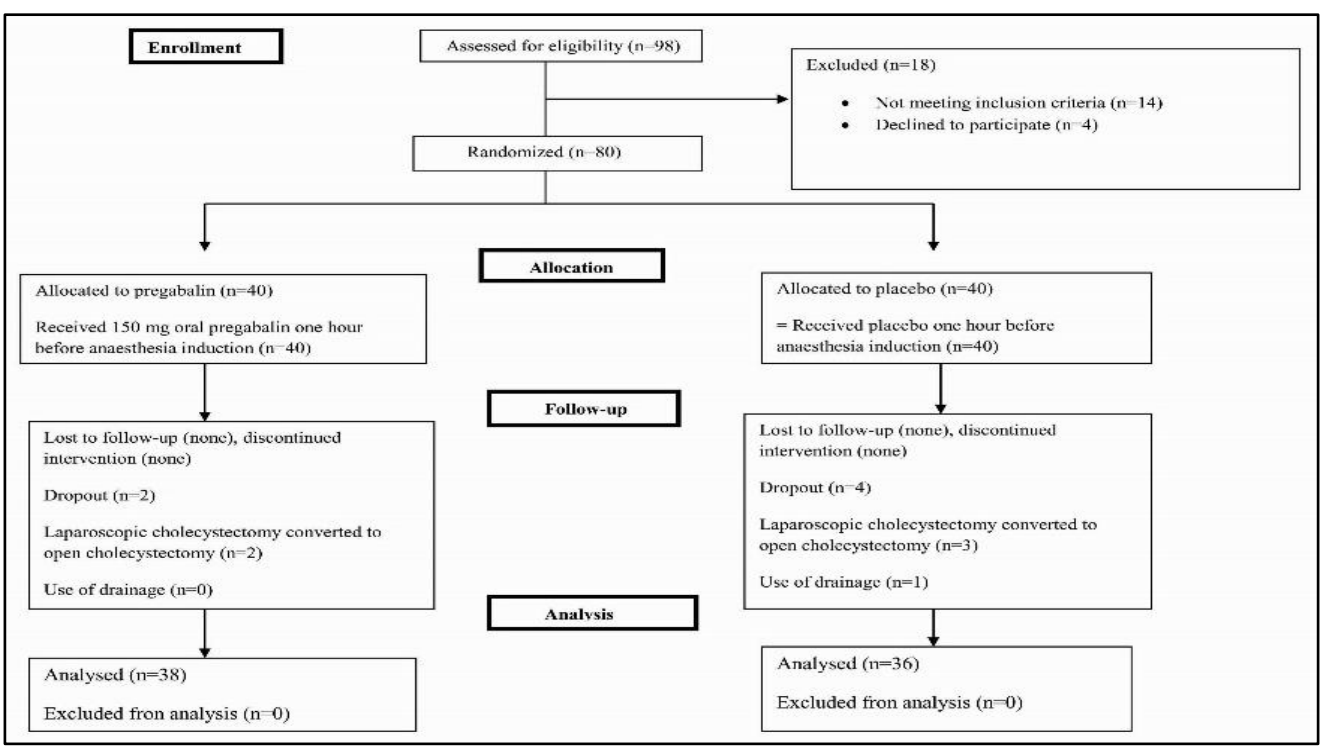
Secondary outcomes were incidence and severity of side-effects such as Postoperative Nausea and Vomiting (PONV), headache, sedation and dizziness, if any.

Sample Size Calculation- Considering the reported mean VAS score of 5.5 and standard deviation of 2.2 in the placebo group to detect a difference of VAS of 1.5 with similar standard deviation, 35 samples were required in each group to achieve a power of 80% at significance level of 0.05.[11] Considering a dropout of 10%, 40 patients in each group were included in this study.

Statistical Analysis- Results were analysed by Mann-Whitney U test, large sample difference in proportion test and Fisher's exact test. The software PASW 18.0 has been used to carry out the analysis and the graphs were generated using the Microsoft Excel 2007. A p-value less than 0.05 has been considered to be significant.

RESULTS

Ninety eight patients scheduled for laparoscopic cholecystectomy were screened for eligibility of whom 80 fulfilled the inclusion criteria. 18 patients were not included in this study on account of patient's refusal (4 patients), history of chronic analgesic consumption (4 patients), diabetes mellitus (4 patients), alcohol abuse (3 patients) and impaired kidney function (3 patients). Treatments were successfully administered to all patients in both the group, however, 2 surgeries in the pregabalin group and 3 surgeries in the placebo group were converted to open cholecystectomy. In addition, one subject in the placebo group needed drainage, which was excluded resulting in a total of 74 patients; 38 in pregabalin and 36 in placebo group, which underwent statistical analysis. The patients' recruitment and allocation flowchart, according to the Consort guideline is shown in Figure below.



Variable	Drug	Placebo	p-value
Age	36 ± 12	35 ± 10	>0.05
Sex (M/F)	14/24	10/26	>0.05
ASA I/II	32/6	35/1	>0.05
Weight (kg)	60 ± 12	54 ± 10	>0.05
Height (cm)	163.09 ± 6.39	163.06 ± 6.32	>0.05
Surgery time (minutes)	70 ± 8	70 ± 9	>0.05
Anaesthesia time (minutes)	85 ± 8	83 ± 10	>0.05

Table 1. Demographic Data and Timing

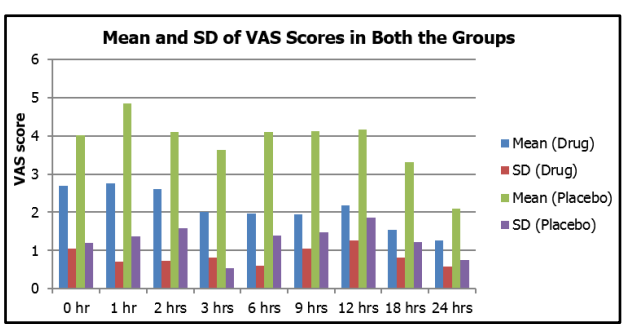
Data are presented as the mean ± standard deviation, unless otherwise denoted.

The VAS scores of the patients of the drug group were significantly lower as compared to the placebo group at all the observed time intervals.

Time Interval	Drug Group	Placebo Group	p-value
0 hour	2.69 ± 1.04	4.02 ± 1.19	0.023 <0.05
1 hour	2.76 ± 0.70	4.85 ± 1.36	0.015 <0.05
2 hours	2.61 ± 0.73	4.10 ± 1.58	0.018 <0.05
3 hours	2.02 ± 0.81	3.64 ± 0.53	0.038 <0.05
6 hours	1.97 ± 0.61	4.10 ± 1.40	0.003 <0.05
9 hours	1.95 ± 1.05	4.13 ± 1.48	0.002 <0.05
12 hours	2.19 ± 1.27	4.16 ± 1.86	0.017 <0.05
18 hours	1.53 ± 0.81	3.31 ± 1.22	0.034 <0.05
24 hours	1.27 ± 0.57	2.10 ± 0.75	0.045 <0.05

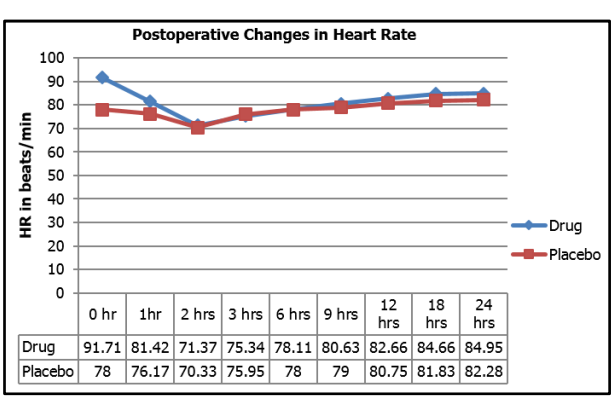
Table 2. Postoperative Pain VAS* Scores

Data are presented as the mean ± standard deviation.
*VAS = Visual analogue scale.



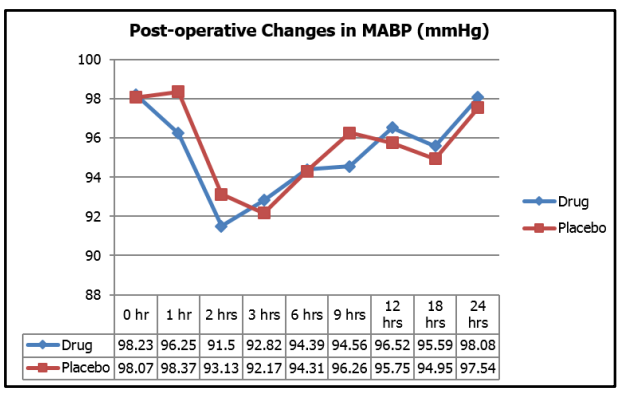
Graph 1. Mean and SD of VAS Scores in Both the Groups

Haemodynamic parameters like MABP and HR was comparable in both the group.



	0 hr	1hr	2 hrs	3 hrs	6 hrs	9 hrs	12 hrs	18 hrs	24 hrs
Drug	91.71	81.42	71.37	75.34	78.11	80.63	82.66	84.66	84.95
Placebo	78	76.17	70.33	75.95	78	79	80.75	81.83	82.28

Graph 2. Postoperative Changes in Heart Rate



	0 hr	1 hr	2 hrs	3 hrs	6 hrs	9 hrs	12 hrs	18 hrs	24 hrs
Drug	98.23	96.25	91.5	92.82	94.39	94.56	96.52	95.59	98.08
Placebo	98.07	98.37	93.13	92.17	94.31	96.26	95.75	94.95	97.54

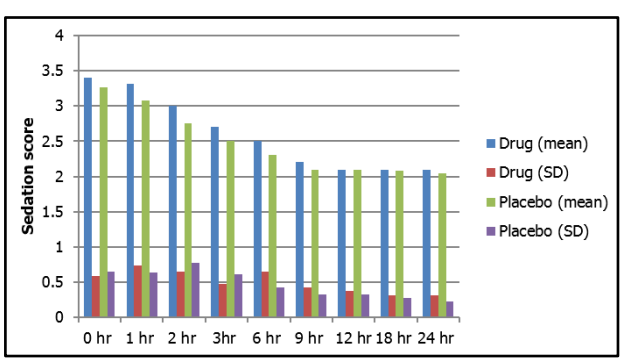
Graph 3. Postoperative Changes in MABP (mmHg)

No significant difference between the sedation scores of both the groups (p>0.05) at all the observed time intervals.

Time Interval	Drug Group	Placebo Group	p-value
0 hour	3.4 ± 0.59	3.27 ± 0.65	0.149 >0.05
1 hour	3.32 ± 0.73	3.08 ± 0.64	0.120 >0.05
2 hours	3 ± 0.65	2.75 ± 0.77	0.079 >0.05
3 hours	2.7 ± 0.48	2.5 ± 0.61	0.414 >0.05
6 hours	2.5 ± 0.65	2.3 ± 0.43	0.137 >0.05
9 hours	2.2 ± 0.43	2.1 ± 0.32	0.158 >0.05
12 hours	2.1 ± 0.37	2.1 ± 0.32	0.59 >0.05
18 hours	2.1 ± 0.31	2.08 ± 0.28	0.749 >0.05
24 hours	2.1 ± 0.31	2.05 ± 0.23	0.437 >0.05

Table 3. Postoperative Sedation Score at Different Time Points

Data are presented as the mean ± standard deviation.



Graph 4. Postoperative Sedation Score at Different Time Points

The time to first rescue analgesic (tramadol) was significantly prolonged in the pregabalin group compared to the placebo group.

The mean tramadol consumed over a period of 24 hours was found to be significantly less in the pregabalin group compared to the placebo group.

Group	Time to First Rescue Analgesic Dose (in minutes)	Total Rescue Analgesic in 24 Hours (in mg)
Drug	581.05 ± 352.26	94.21 ± 51.86
Placebo	55.25 ± 40.63	149.72 ± 34.70
P value	0.000 <0.05 (Significant)	0.000 <0.05 (Significant)

Table 4. Rescue Analgesic (Tramadol) Consumed

Data are presented as the mean ± standard deviation.

Number of patients requiring rescue analgesic at different time intervals was significantly less in drug group compared to the placebo group.

Time Interval (minutes)	Drug Group		Placebo Group		P value
	Number of Patients	Percentage	Number of Patients	Percentage	
0-120	6	10.34	29	29.29	0.010
120-240	4	6.90	8	8.08	0.045
240-480	2	3.45	7	7.07	0.044
480-720	14	24.14	13	13.13	0.048
720-1080	21	36.21	14	14.14	0.025
1080-1440	11	18.97	28	28.28	0.012

Table 5. Number of Patients Receiving Rescue Analgesic at Various Time Intervals

Pregabalin group had significantly lesser incidence of nausea and vomiting than the placebo group. Incidence of other side effects like headache and dizziness were found to be similar between the two groups.

Adverse Effect	Drug Group		Placebo Group		P value
	Number of Patients	Percentage	Number of Patients	Percentage	
Nausea	19	50%	33	91.67%	0.0007 <0.05 (Significant)
Vomiting	7	18.42%	23	63.89%	0.0001 <0.05 (Significant)
Dizziness	6	15.79%	5	13.89%	0.98 >0.05 (Not significant)
Headache	3	7.89%	1	2.78%	0.96 >0.05 (Not significant)

Table 6. Incidence of Adverse Effects

DISCUSSION

Prevention and treatment of postoperative pain continues to be a major challenge in the postoperative period upon, which early mobilisation and well-being of the surgical patients depend. Pregabalin has some proven role in the control of anxiety and postoperative pain either singly or in combination with other antinociceptive drug for synergistic effects; various clinical studies with the drug for postoperative analgesia and analgesic consumption have shown promising result.[8,12] Pregabalin has been investigated in laparoscopic surgery patients for postoperative pain relief and analgesic consumption with variable results.

We used a single preoperative dose of pregabalin 150 mg as studies using low dose of pregabalin (50-75 mg) shows limited analgesic benefit as reported by Peng et al (2010)[13] and those with higher (≥300 mg) combination, found it to have an analgesic and opioid sparing effect, but associated with an increased incidence of side effects as seen in individual studies by Jokela R et al (2008),[14] Chang S et al (2009)[15] and Farag H et al (2015).[16] The dose in our study is similar to the dose used by Agarwal et al (2008)[8] and Mishra et al (2016)[17] who have shown better postoperative pain scores with pregabalin 150 mg.

Premedication, anaesthetic drugs and techniques were kept constant in both the groups to exclude any variation in responses due to a variety of drugs and technique. There were no substantial difference among the groups with regards to duration of surgery, duration between oral dose and anaesthesia induction, duration of anaesthesia, intraoperative propofol and fentanyl consumption (P>0.05). Other authors have reported similar findings in their studies like Agarwal et al (2008)[8] and Mishra et al (2016).[17]

Both the group were found to be homogeneous with respect to preoperative, intraoperative and postoperative changes in haemodynamic parameters. This indifferent haemodynamic might be seen because of the fact that there is no effect of pregabalin on cardiovascular or respiratory system. In both the groups throughout the study, the pain score were also not much higher so as to cause haemodynamic changes, viz. rise in pulse rate or mean arterial pressure and also patients were given rescue analgesics as soon as they complained of pain or VAS score was more than 4. Our findings are consistent with that of the independent studies conducted by Singh et al (2014),[18] Tarangini et al (2017)[19] and Eman A et al (2014),[20] thus supporting the findings that pregabalin has no action on haemodynamic parameters.

Postoperatively, VAS score were significantly reduced in pregabalin group when compared with placebo group at different time interval, i.e. 0 hour, 1 hour, 2 hours, 3 hours, 6 hours, 9 hours, 12 hours, 18 hours and 24 hours as described by 'p' value <0.05. Findings similar to this study

are in agreement with individual studies conducted by Agarwal A et al (2008)[8] and Surana R et al (2017)[21] where they compared pregabalin 150 mg with placebo for postoperative analgesia after laparoscopic cholecystectomy and found a significant low VAS score in pregabalin group compared to placebo group.

Contradictory results have been seen in a study by Chang et al (2009).[15] They found that perioperative use of pregabalin in two doses of 150 mg 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 surgical pain after laparoscopic cholecystectomy. In another study conducted by Paech et al (2007)[22] comparing preoperative pregabalin (100 mg) in minor gynaecological surgeries did not find any significant difference in postoperative pain intensity in pregabalin group as compared to placebo. The finding in our study was in contrast to this study. The possible cause of it maybe because of the lower dose (100 mg) of pregabalin used and evaluation of analgesia in visceral pain model.

It is observed that the mean timing of first postoperative rescue analgesic requirement in this study was significantly more in pregabalin group (581.05 minutes) compared to placebo (55.25 minutes) group. The mean total rescue analgesic consumed in postoperative period was found to be significantly less in pregabalin group (94.21 mg) as compared to placebo group (149.72 mg). Moreover, the number of patients receiving rescue analgesic at various time intervals was found to be significantly less in pregabalin group compared to placebo group. Findings similar to our study are further supported by individual studies by Agarwal A et al (2008),[8] Balaban F et al (2012),[23] Sarakatsianou et al (2013)[24] and Singh TH et al (2014).[18]

This is in contrast to a study by Peng et al (2010)[13] where they found that although 50 and 75 mg oral pregabalin were able to decrease pain scores in patients undergoing laparoscopic cholecystectomy, analgesic requirement in the form of fentanyl was not decreased. In comparison to our study, limited duration of analgesic benefit from low dose of pregabalin used by them would have probably resulted in increase in rescue analgesic consumption.

Pregabalin is generally well tolerated[25] and associated with transient mild-to-moderate adverse effects, which are dose dependent. Sedation score in this study is found to be higher in pregabalin group than the placebo group in the first few hours after surgery though statistically insignificant. The sedation gradually decreases in pregabalin group in subsequent readings and all patients were free of sedation at 3 hours and thereafter. Probably, in our study, the sedative effects of opioid, which was required in larger amount in the placebo group was countered by the sedative effects of pregabalin in the treatment group, which might have resulted in the nonsignificant difference in the sedation scores between the groups. Slightly higher sedation though statistically not significant seen in initial postoperative period with pregabalin might be beneficial as it reduces the postoperative stress and anxiety without causing any untoward events like respiratory depression.

In several studies, a significantly higher sedation score had been reported with pregabalin in a dose greater than 150 mg, more than the one used in this study. Such findings are corroborated with that of independent studies by Farag H et al (2015),[16] Girija et al (2012),[26] Tarangini D et al (2017)[19] and Balaban F et al (2012).[23]

PONV is a usual complication of surgery and anaesthesia. Although, it is rarely fatal, it is unpleasant, associated with patient discomfort and dissatisfaction with perioperative management.[27] In this study, nausea and vomiting was significantly lower in the pregabalin group. This might be related to the decreased use of opioids after surgery and the consequent decrease in opioid-related adverse effects.

CONCLUSION

Present study showed that preemptive single oral dose of pregabalin 150 mg in patients undergoing laparoscopic cholecystectomy was effective in reducing postoperative pain, tramadol consumption, as well as nausea and vomiting without any untoward side effects.

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