A Comparative Study of Role of Flupirtine and Pregabalin as Pre-emptive Analgesic in Patients Undergoing Laparoscopic Cholecystectomy a Prospective, Randomised, Double Blind, Clinical Study

Neha Singh¹, Sanjeev Kumar², Ajit Gupta³

¹Resident, ²Additional Professor, ³Professor, Department of Anaesthesiology and Critical Care, Indira Gandhi Institute of Medical Sciences, Sheikhpura, Patna, India

DOI: 10.36347/sjams.2020.v08i01.020 | Received: 01.01.2020 | Accepted: 08.01.2020 | Published: 16.01.2020

*Corresponding author: Neha Singh

Abstract

**Introduction:** Pain shares its etymological origin with words punishment and penalty and is the most miserable symptom of disease presentation. Pre-emptive analgesia is used as a treatment that is initiated before surgery in order to prevent the establishment of central sensitization evoked by the incision and inflammatory injuries occurring during surgery and in the early postoperative period. Role of Pregabalin and Flupirtine as pre emptive analgesia has been documented. The present study was undertaken to compare the role of Flupirtine and Pregabalin as pre-emptive analgesic in patients undergoing laparoscopic cholecystectomy because of their documented efficacy, cost effectiveness, pharmacokinetics and minimal side effects or complication. **Material and Method:** The randomised, double blind, prospective study was carried out in 100 patients scheduled for laparoscopic cholecystectomy and fulfilling the inclusion criteria at Indira Gandhi Institute of Medical Sciences, Patna. Two randomised groups were administered Flupirtine and Pregabalin as pre emptive analgesia and the postoperative outcome were compared and analysed. **Results:** The study population of both the groups were comparable with respect to age, gender and mean body weight, and the differences were statistically not significant. The Flupirtine group of patients had low postoperative pain score (VAS) in the period of evaluation postoperatively except at 6th hour post operatively. The difference was statistically significant at 0 and 1 hours. The side effects were comparable among the two group and the difference was statistically not significant. **Conclusion:** Flupirtine in a single dose of 200 mg is better than single dose of 150 mg of Pregabalin when administered in the form of pre-emptive analgesia in patients undergoing laparoscopic cholecystectomy with lower VAS in immediate postoperative period and comparable side effects.

**Keyword:** Pre-emptive Analgesia, Flupirtine, Pregabalin, Postoperative Pain.

Copyright © 2020: This is an open-access article distributed under the terms of the Creative Commons Attribution license which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use (NonCommercial, or CC-BY-NC) provided the original author and source are credited.
In the past emphasis had been paid to treat postoperative pain after its onset however with better understanding of pain mechanism and related pain systemic implication of pain, the concept of pre-emptive analgesia is now emerging. Idea of pain prevention was initially introduced by Crile in 1913 and later developed by Wall and Woolf who suggested “simple changes in the timing of treatment can have profound effects on postoperative pain” [7-9]. Literature has termed pre-emptive analgesia as “taking possession (of the pain) before other (forces) can” or “seizing the initiative” in terms of prevention of pain [10].

Pre-emptive analgesia is defined as a treatment that is initiated before surgery in order to prevent the establishment of central sensitization evoked by the incision and inflammatory injuries occurring during surgery and in the early postoperative period [11]. Owing to the ‘protective’ effect on the nociceptive system, potentially pre-emptive analgesia is more effective than a similar post-operative analgesia treatment. Consequently, pre-emptive analgesia also reduces immediate post-operative pain and prevents chronic pain by modulating the altered central sensory processing [12].

A range of medications including non-steroids anti-inflammatory drugs (NSAIDS) and opioids both in enteral and parenteral form have been examined for possible pre-emptive analgesic effect [13, 14]. Overall choice of the drugs depends upon efficacy, cost effectiveness, pharmacokinetics and its side effects or complication.

Studies have demonstrated that post-operative pain is comparably reduced in laparoscopic cholecystectomy when compared to traditional open cholecystectomy but effective analgesic treatment following laparoscopic cholecystectomy remains a clinical challenge [15, 16]. Pain may occur in upper or lower abdomen, back or shoulder and may be transient or persist for at least 72 hours [17, 18]. Higher incidence is of pain is observed in upper abdomen [17]. The severity of pain is greatest after operation which decreases within 24 hours but might increase to second or even third peak later [17, 19, 20]. It has been demonstrated that following laparoscopic cholecystectomy, visceral origin pain dominates in initial 24 hours but subsides from a peak soon after surgery, on contrary shoulder pain, mild on first day, increases and becomes significant the next day [21]. In general post operative pain remains the main reason for staying overnight in the hospital on the day of surgery following laparoscopic cholecystectomy in 17-41% patients [22-26] and pain remains the most dominating complain and the primary reason of prolonged convalescence [16, 27]. Further it has also been hypothesized that acute intense pain following laparoscopic cholecystectomy may predict the development of chronic pain (e.g. post laparoscopic cholecystectomy syndrome) [6].

Recent review of use of gabapentin in procedure specific postoperative pain management has demonstrated a reduction in consumption of opioids in initial 24 hour post-operative period of abdominal hysterectomy and spinal surgeries [28]. Pregabalin, an analogue of gamma amino butyric acid, is characteristically similar to its predecessor, gabapentin, and though its mechanism of action is identical to gabapentin, yet it has better pharmacokinetic profile. Studies have already established its role in management of peripheral neuropathic pain and is claimed to be more effective in minimizing acute nociceptive pain of surgery and for amelioration of peri operative anxiety [29-31]. Several clinical trials have demonstrated the efficacy of Pregabalin in treatment of generalized anxiety disorder [32, 33].

Trials to establish role of Pregabalin as a drug for pre-emptive analgesia in patients undergoing laparoscopic cholecystectomy have demonstrated its efficacy in reducing postoperative pain and a decrease in requirement of post-operative analgesia besides no increase in frequency of side effects [34-36]. The pre-emptive analgesic effect of Pregabalin in patients of laparoscopic cholecystectomy is well documented at a dose of 150 mg and various comparative studies have demonstrated better efficacy with minimal or almost negligible side effect at such dose [34-37].

Flupirtine is centrally acting, non-opioid analgesic with N-methyl-D-aspartate (NMDA) receptor antagonist property, without antipyretic or antiphlogistic properties and has been shown to be effective in the management of post-operative pain. Flupirtine is effective in painful conditions where primary requirement for analgesia is without sedation or anti-inflammatory effects and it has been used in management of chronic pain as well. The drug constitutes a unique class within WHO-I group of analgesics and was first approved in Germany on a national level in 1989.

Flupirtine is generally well-tolerated, if administered on a short-term basis. Commonly observed side-effects include gastrointestinal upset, sedation, headache, disorientation, and hallucinations with continued administration.

Flupirtine can be used as pre-emptive analgesic, as it neither interacts with anaesthetic agents nor has side effects like respiratory depression & increased postoperative bleeding. Clinical study to ascertain the effectiveness of Flupirtine as pre-emptive analgesic in providing adequate analgesia during immediate postoperative period following laparoscopic cholecystectomy surgery has shown promising results [38].
The present study was hence undertaken to compare the role of Flupirtine and Pregabalin as pre-emptive analgesic in patients undergoing laparoscopic cholecystectomy because of their documented efficacy, cost effectiveness, pharmacokinetics and minimal side effects or complication.

**MATERIAL AND METHOD**

The randomised, double blind, prospective study was carried out in 100 patients between the age of 18-60 years, belonging to ASA physical status I and II, scheduled for laparoscopic cholecystectomy under general anaesthesia. The study was conducted after approval from the Institute Ethics Committee of Indira Gandhi Institute of Medical Sciences, Sheikhpura, Patna. A written informed consent was obtained from all the patients prior to the day of surgery.

**Sample Size Calculation**

Assuming p value <0.05 to be significant and considering effect to be two sided, Zα was calculated to be 1.96; and assuming power of study to be 80% we got Z1-β = 0.84. With reference to study done by Yadav G et al., [38] considering an effect size of 3 (Difference in VAS Score between the 2 groups) to be statistically significant, n was calculated to be 44, \[n > 2(Zα + Z1-β)2 x SD2/d2\] in each group. Hence 50 patients were taken in each group.

**Study Site and Time Frame**

The study was conducted at Department of Anaesthesiology, Indira Gandhi Institute of Medical Sciences, Patna over a period of one year from March 2016 to February 2017.

**Inclusion Criteria**

- Age 18 to 60 years.
- ASA physical status I and II.
- Patients of either gender.
- Patients undergoing laparoscopic cholecystectomy.

**Exclusion Criteria**

- History of drug / alcohol abuse or of smoking.
- History of chronic pain or daily intake of analgesics.
- NSAID intake within 24 hours pre-operatively.
- Patient with pregnancy.
- History of allergy to test drug.
- Surgery converted to open method.
- Patients who refuse consent to participate in the study.

**METHODOLOGY**

The study was carried out as prospective, double blind, randomised, controlled trial. Patients undergoing laparoscopic cholecystectomy and who gave written informed consent to participate in the trial were allocated into two groups (A and B) of 50 patients each using computer generated random numbers (Microsoft Office Excel 2010 Software). Group A patients received tablet Pregabalin 150 mg administered orally one hour prior to surgery and patients in Group B received capsule Flupirtine 200 mg orally two hours prior to surgery with sip of water by a staff nurse who was not involved with the study. In the preoperative ward, all patients were instructed regarding the proper use of visual analog score (VAS) and Ramsay sedation score (RSS) for assessing pain and sedation.

Premedication in all cases was omitted and uniform anaesthesia technique was used for all the patients. General anaesthesia was induced with Fentanyl (2 μg/kg, IV), and Propofol (2 mg/kg, IV). Endotracheal intubation was done using muscle relaxant, Vecuronium in the dose of 0.08 mg/kg, IV. Anaesthesia was maintained by means of Propofol infusion (100-200 μg/kg/min, IV) and Nitrous Oxide - Oxygen combination (70%:30%). Injection Fentanyl (1 μg/kg, IV) and Vecuronium (0.02 mg/kg, IV) were repeated as per requirement during surgery. At end of surgery, residual neuromuscular paralysis was reversed with Neostigmine (0.05 mg/kg, IV) and Glycopyrolate (0.01 mg/kg, IV). Hemodynamic variables i.e heart rate, NIBP, MAP, saturation, respiratory rate were recorded intraoperatively as per standard anaesthesia protocol.

Following reversal and after adequate recovery, all patients were extubated and shifted to the post anaesthesia care unit (PACU). In PACU patients were assessed for pain, sedation or any other complications. For any pain complaints (VAS > 3), a dose of 1 g Paracetamol IV was given on the first postoperative day, with minimum interval of 4 hours between each dose. If the patients complained of pain in between the Paracetamol dose, injection Tramadol 50 mg diluted in normal saline was administered over a period of 2 minute as rescue analgesia.

Acute postoperative pain was assessed using the 11-point VAS score on which 0 indicates “no pain” and 10 represents “worst imaginable pain.”
The sedation was assessed using the RSS (1 = Patient is anxious and agitated or restless, or both, 2 = Patient is cooperative, oriented, and tranquil, 3 = Patient responds to commands only, 4 = Patient exhibits brisk response to light glabellar tap or loud auditory stimulus, 5 = Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus, 6 = Patient exhibits no response).

Data for pain and sedation score were recorded at 0, 1, 2, 4, 6, 12, and 24 hours, postoperatively. The severity of post-operative nausea or vomiting (PONV) were assessed by four-point scale on which 1 indicates no PONV: Absence of any emesis or nausea, 2 indicates mild PONV: Patient having only mild nausea, or one emetic episode or nausea lasting for <10 min and where no anti emetic is required, 3 indicates moderate PONV: Patient has 1-2 emetic episodes or moderate to severe nausea and anti-emetic therapy is required and 4 indicates severe PONV. Patients received Ondansetron (0.1 mg/kg IV) as a rescue anti emetic if patient had >2 emetic episodes or was nauseated more than twice.

The study variables were recorded and the primary outcome that included the comparative outcome of severity of postoperative pain in terms of VAS score, time to first analgesic requirement in PACU, and total postoperative analgesic dose requirement in 24 hours were statistically evaluated whereas secondary outcome that included the comparison of the incidence of side-effects of the two group was statistically defined.

Patients who were unable to report VAS score, required re-exploration, converted to open cholecystectomy, or where surgery extended for more than one hour, were considered as drop out.

**Statistical Tools Employed**

**Categorical Variables:** Expressed as number of patients and percentage of patients were compared across the groups using Pearson’s Chi Square test for independence of attributes.

**Continuous Variables**

Expressed as Mean, Median and Standard Deviation and were compared across the 2 groups using Mann-Whitney U test.

Over time comparisons of variables were done using Wilcoxon Signed Ranks Test. The statistical software SPSS version 20 has been used for the analysis.

An alpha level of 5% has been taken, i.e. if any p value is less than 0.05 it has been considered as significant.

**RESULT**

Of the total 100 patients selected for the study, following randomization in two groups by computer generated random numbers, two patients from group A (Pregabalin group) and three patients from group B (Flupirtine group) were dropped from the study. As a result of which data of 48 patients of group A and 47 patients of group B was analyzed.
Table-1: Age, Sex and Weight Distribution of the patients

| Age Distribution | Group A (n=48) | Group B (n=47) | Total (N=95) |
|------------------|---------------|---------------|--------------|
| Age Group        | No | %   | No | %   | No | %   |
| Upto 30          | 8  | 16.67 | 12 | 25.53 | 20 | 21.05 |
| 31-40            | 14 | 29.17 | 13 | 27.66 | 27 | 28.42 |
| 41-50            | 23 | 47.92 | 17 | 36.17 | 40 | 42.11 |
| 51-60            | 3  | 6.25  | 5  | 10.64 | 8  | 8.42  |
| Total            | 41.15±8.44 | 39.49±8.34 | 40.33±8.38 |

P=0.563

| Gender Distribution | Group A (n=48) | Group B (n=47) | Total (N=95) |
|---------------------|---------------|---------------|--------------|
| Gender              | No | %   | No | %   | No | %   |
| Female              | 32 | 66.67 | 27 | 57.45 | 59 | 62.11 |
| Male                | 16 | 33.33 | 20 | 42.55 | 36 | 37.89 |
| p                   | 0.402 |

| Weight Distribution | No. of patients | Min. (in Kg) | Max. (in Kg) | Median (in Kg) | Mean (in Kg) | SD |
|---------------------|-----------------|--------------|--------------|----------------|--------------|----|
| Group A             | 48              | 56           | 103          | 69.50          | 71.88        | 10.83 |
| Group B             | 47              | 48           | 97           | 70.00          | 71.21        | 11.21 |
| Total               | 95              | 48           | 103          | 70.00          | 71.55        | 10.97 |

The patients in the two groups were identical in terms of age, sex and weight distribution with P value > 0.05.

At 0 and 1 hour post operation, mean VAS score of Pregabalin group (2.96±1.52) and (2.77±1.36) was found to be higher than that of Flupirtine group (2.00±1.20) and (1.96±1.43). These differences of mean VAS of Pregabalin group were found to be significantly higher than that of Flupirtine group, statistically. At 2, 4, 6, 12, 24 hour the mean VAS of pregabalin group was higher than Flupirtine group, however these differences were statistically not significant.

Mean Ramsay sedation score of patients of Pregabalin group was found to be higher than that of Flupirtine group at all the periods of observation. Statistically significant difference in mean sedation score was observed at 6 and 24 hours post-operative (2.44±0.87 vs.2.06±0.32) and (2.52±1.01 vs. 2.09±0.41).

Post-operative nausea and vomiting score of patients of Group A was found to be higher than that of Group B at all the periods of observation – 0 hour post operation (1.27±0.79 vs. 1.11±0.37), 1 hour (1.33±0.66 vs. 1.17±0.43), 2 hours (1.31±0.78 vs. 1.13±0.49), 4 hours post operation (1.29±0.58 vs. 1.21±0.59), 6 hours (1.40±0.94 vs. 1.26±0.64), 12 hours (1.25±0.60 vs. 1.19±0.50) and at 24 hours post operation (1.40±0.93 vs. 1.28±0.64). However the difference in post operative nausea and vomiting score between the two groups at any point of observation was statistically not significant.
Rescue analgesia was required in all 48 (100%) patients in Pregabalin group and in 46 (97.87%) patients in Flupirtine group. Requirement of first dose of rescue analgesia was earlier in patients of Pregabalin group (3.71±4.45 hours) as compared to Flupirtine group (4.13±5.00 hours) but difference in time of requirement of first dose of analgesia of both the groups was found not to be statistically significant (p=0.507).

The total dose of Paracetamol required by patients of Pregabalin group (2.02±0.76 g) was found to be higher than that of Flupirtine group (1.89±0.67 g) but the difference in requirement of Paracetamol among the patients of both the groups was found not to be statistically significant (p=0.564).

Inj Tramadol as rescue analgesia was required in 26 (54.17%) patients in Pregabalin group whereas in 21 (44.68%) patients in Flupirtine group. 2 (4.17%) patient in Pregabalin group required 2 doses of Inj Tramadol for effective pain control whereas 2nd dose of Tramadol was not required in Flupirtine group of patients. The difference in requirement of Inj Tramadol in patients of the two groups was found not to be statistically significant (p=0.340).

Rescue antiemetic in the form of Inj Ondansetron (0.1mg/Kg I.V.) was required in only 44 patients, however the requirement was in higher number in patients of Pregabalin group (54.17%) as compared to Flupirtine group (38.30%). The mean total dose of rescue antiemetic was higher in Pregabalin group (7.85±2.09 mg) as compared to Flupirtine group (7.16±1.69 mg). The difference in mean dose of antiemetic consumed among the two groups was statistically found to be insignificant (p=0.073).

**DISCUSSION**

The prospective, randomised, double blind, clinical study was conducted to compare the role of Pregabalin and Flupirtine as pre-emptive analgesia in patients undergoing laparoscopic cholecystectomy and to compare their side effects.

In our study, based on estimated sample size with α error of 0.05 & power of 80%, hundred patients planned for laparoscopic cholecystectomy satisfying the inclusion criteria were selected and randomised in two groups of 50 patients each. The two groups, A and B received Pregabalin and Flupirtine respectively as pre-emptive analgesia. Dose of Pregabalin 150 mg and Flupirtine 200 mg was selected for the study in agreement with results of other studies where different dose of the individual drugs were compared for maximum efficacy with minimal side effect [35, 37-40].

In group A (Pregabalin Group) two patients were dropped from the study (2 patients underwent procedure for more than 1 hour), whereas in group B (Flupirtine Group) three patients (1 patient underwent conversion from laparoscopic to open surgery and 2 patients underwent procedure for more than 1 hour) were dropped from the study. As a consequence of which 48 patients were included in group A and 47 patients were included in group B.

The study population of both the groups were comparable with respect to age, gender and mean body weight, and the differences were statistically not significant.

Post-operative pain score (VAS) of both the groups at 0, 1, 2, 4, 6, 12 and 24 hours were evaluated. In the study, it was observed that patients who had received Flupirtine as pre-emptive analgesia (group B) had significantly lower VAS compared to group A patients at 0 and 1 hour post-operative with p value <0.001 and 0.001 respectively. Throughout the duration of observation, VAS of Flupirtine group was lower than that of Pregabalin group except at 6th hour when Flupirtine group of patients reported higher VAS but the difference of which was statistically not significant (Figure-2). The variation in pain score were similar to those observed in the study done by Mishra R *et al.*, who evaluated postoperative analgesic benefit and efficacy in patients administered with oral gabapentin or Pregabalin as premedication for laparoscopic cholecystectomy under general anaesthesia and Yadav G *et al.*, who analyzed the role of Flupirtine as pre-emptive analgesic for postoperative pain relief in patients undergoing above surgery [37, 38].

On comparison of Ramsay sedation score of the two groups measured at 0, 1, 2, 4, 6, 12 and 24 hours post operatively, it was found that Pregabalin
group of patients had reported higher sedation than Flupirtine group, though the difference in sedative effect of Pregabalin was statistically not significant when compared to Flupirtine group except at 6\textsuperscript{th} and 24\textsuperscript{th} hour of observation [(2.44±0.87 vs. 2.06±0.32) and (2.52±1.01 vs. 2.09±0.41)]. Sedation has been a well-documented side effect of both Pregabalin and Flupirtine in various literature and the results of the present study are in sync with result of other investigators [37-41].

Yadav G \textit{et al.}, observed no significant side-effect except for increased sedation in Flupirtine group while comparing Flupirtine with placebo whereas in study by Thapa D \textit{et al.}, sedation was significantly higher in Flupirtine group in initial 4 hours after the surgery which was attributed to combined effect of Flupirtine as well as residual effect of anaesthetic agents [38, 41].

In a comparative study done by Mishra R \textit{et al.}, analyzing the effect of Pregabalin, Gabapentin and Placebo as pre-emptive analgesia in patients undergoing laparoscopic cholecystectomy, it was noted that the sedation was significantly more in Pregabalin group compared to the Gabapentin group and placebo group in early post-operative period, however the sedation score was never more than four [37]. Singh TH \textit{et al.}, compared two different dose of Pregabalin (150 and 300 mg) with placebo for post cholecystectomy pain relief and observed higher sedation in 300 mg Pregabalin group when compared to 150 mg Pregabalin and placebo group [40]. In a study done by Ali A \textit{et al.}, comparing preoperative dose of Pregabalin with Celecoxib for attenuation of postoperative pain after open cholecystectomy, it was observed that the frequency and severity of sedation was higher in Pregabalin group (P <0.05) in initial 12 hours but later no significant differences were observed between the groups [42].

In the present study, post-operative nausea and vomiting as a side effect was compared between the two group and the scores were comparable with no statistical difference at all instances of observation, though the mean post-operative nausea and vomiting score was higher throughout in Pregabalin group than Flupirtine group. Attributable factors for statistically non-significant but relatively higher score in Pregabalin group can be higher VAS and hence the increased incidence of use of Inj Tramadol, a weaker opioid as rescue analgesia to alleviate pain.

Incidence of post-operative nausea and vomiting has been reported to be low in several studies which have compared the pre-emptive analgesic effect of Pregabalin and Flupirtine with placebo or other drugs [43-45]. In a study done to evaluate the efficacy of pre-emptive Pregabalin for prolonging post-operative analgesia and for reducing post-operative opioid analgesic requirement and haemodynamic stability by Prashanth Gowtham Raj SK \textit{et al.}, the investigators noted increased incidence of post-operative nausea and vomiting in control group [43]. The finding was attributed to higher VAS in control group leading to increased requirement of rescue analgesic in the form of Inj Tramadol in control group. Tramadol being a weak opioid is not devoid of side effects and most commonly nausea and vomiting. Bekawi MS \textit{et al.}, evaluated the efficacy and tolerability of Pregabalin in postoperative pain management after laparoscopic cholecystectomy where three groups of patients receiving Pregabalin, Gabapentin and placebo were compared [44]. The investigator found significantly less (P<0.001) patients with postoperative nausea, vomiting, in the Pregabalin and gabapentin group versus control or the placebo group. Grant MC \textit{et al.}, performed a meta-analysis of randomized trials that report outcomes on the effect of preoperative Pregabalin on post-operative nausea and vomiting endpoints in patients undergoing surgery under general anaesthesia and concluded that preoperative Pregabalin administration caused significant reduction of post-operative nausea and vomiting and that it should not only be considered as part of a multimodal approach to postoperative analgesia but also for prevention of post-operative nausea and vomiting [45].

Yadav G \textit{et al.}, reported no difference of postoperative nausea or vomiting in Flupirtine group as compared to placebo group during the postoperative period of laparoscopic cholecystectomy whereas Thapa D \textit{et al.}, in their study comparing effect of Flupirtine with placebo, interpreted that the mean cumulative nausea/vomiting scores at 24\textsuperscript{th} and 48\textsuperscript{th} hour were significantly higher in the placebo group, a finding which was related to the significantly higher consumption of morphine for higher VAS in the group [38, 41].

In the present study, rescue analgesia was administered to all patients in Pregabalin group and in 97.87% (46 out of 47) patients in Flupirtine group. The requirement of first dose of rescue analgesia was found to be earlier in patients of Pregabalin group (3.71±4.45 hours) as compared to Flupirtine group (4.13±5.00 hours), though this difference in time of requirement of first dose of analgesia of both the groups was found not to be statistically significant (p=0.507). In a likewise manner the total dose of Paracetamol required by patients of Pregabalin group (2.02±0.76 g) was found to be higher than that of Flupirtine group (1.89±0.67 g) but the difference was not found to be statistically significant (p=0.564). The overall mean consumption of Inj Tramadol in the Pregabalin group was higher than that in Flupirtine group but this difference was also not significant statistically, similarly the incidence of requirement of Inj Tramadol was more in patients of Pregabalin group when compared to Flupirtine group however statistically this difference in requirement of...
Inj Tramadol was not significant. The above findings may be attributed to significantly high mean VAS observed in Pregabalin group at 0 and 1 hour and higher but statistically not significant difference in mean VAS of the two group at 2, 4, 12 and 24 hours.

The requirement of rescue antiemetic in the form of Inj Ondansetron (0.1mg/Kg I.V.) by the two groups was also analysed. Overall the rescue antiemetic was required in only 44 patients, though the requirement was in higher number of patients from Pregabalin group (54.17%) as compared to Flupirtine group (38.30%).

Although not significant statistically (p=0.698), the requirement of Inj Ondansetron was observed to be earlier in Flupirtine group (6.94±6.98 hours) as compared to Pregabalin group (7.69±8.68 hours). Contrary, the average dose of required rescue antiemetic was to some extent higher in Pregabalin group than Flupirtine group (7.85±2.09 vs. 7.16±1.69 mg), though the difference was statistically not significant (p = 0.073). The early requirement of Inj Ondansetron in Flupirtine group correlates with variance in post-operative nausea and vomiting grade in Flupirtine group than that at baseline (Figure-3), however these changes in baseline variance with respect to Pregabalin were not found to be statistically significant.

CONCLUSION
Flupirtine in a single dose of 200 mg is better than single dose of 150 mg of Pregabalin when administered in the form of pro-emptive analgesia in patients undergoing laparoscopic cholecystectomy with lower VAS in immediate post-operative period and comparable side effects.

REFERENCE
1. Bonica JJ. Postoperative pain. In Bonica JJ (ed). The management of pain 2nd ed. Lea & Febiger, Philadelphia, 1990:461-480.
2. Katz J, Kavanagh BP, Sandler AN, Nierenberg H, Boylan JF, Friedlander M, Shaw BF. Preemptive analgesia. Clinical evidence of neuroplasticity contributing to postoperative pain. Anesthesiology. 1992;77:439-446.
3. Raja SN, Meyer RA, Campbell JN. Peripheral mechanisms of somatic pain. Anesthesiology, 1998;88:571-590.
4. Woolf C J. Evidence for a central component of postinjury pain hypersensitivity. Nature 1983;306:686-688.
5. Woolf C J: Recent advances in the pathophysiology of acute pain. British Journal Anaesth 1989;63:139-147
6. Bisgaard T, Rosenberg J, Kehlet H. From acute to chronic pain after laparoscopic cholecystectomy: a prospective follow-up analysis. Scandinavian journal of gastroenterology. 2005 Jan 1;40(1):1358-64.
7. Crile GW. The kinetic theory of shock and its prevention through anoci-association. Lancet. 1913;185:7-16.
8. Wall PD. The prevention of postoperative pain. Pain 1988;June; 33(3):289-290
9. Woolf CJ. Central mechanisms of acute pain. In: Bond MR, Charlton JE, Woolf CJ, editors. Proc. 6th World Congress on Pain. Amsterdam: Elsevier. 1991:25-34.
10. Rowlingson JC. Pain relief before pain starts? APS Journal, 2(2):125-127.
11. Kissin I. Pre-emptive analgesia. Anaesthesiology. 2000; 93:1138-43.
12. Woolf CJ, Chong MS. Pre-emptive analgesia-treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg. 1993;77:362-79.
13. Bridgman JB, Gillgrass TG, Zacharias M. The absence of any pre-emptive analgesic effect for non-steroidal anti-inflammatory Br J Oral Maxillofac Surg. 1996;34:428-31.
14. Millar AY, Mansfield MD, Kinsella J. Influence of timing of morphine administration on postoperative pain and analgesic consumption. Br J Anaesth 1998;81:373-6.
15. Downs SH, Black NA, Devlin HB, Royston CMS, Russell RCG. Systematic review of the effectiveness and safety of laparoscopic cholecystectomy. Ann R Coll Surg Eng. 1996; 78:241-323.
16. Bisgaard T, Kehlet H, Rosenberg J. Pain and convalescence after laparoscopic cholecystectomy. Ann R Coll Surg Engl. 2001;167:84-96.
17. Dobbs FF, Kumar V, Alexander JI, Hull MGR. Pain after laparoscopy related to posture and ring versus clip sterilization. British journal of Obstetrics and Gynaecology 1987;94:262-266.
18. Rosenblum M, Weller RS, Conard P, Falvey EA, Gross JB. Ibuprofen provides longer lasting analgesia than fentanyl after laparoscopic surgery. Anesthesia and Analgesia 1991;73:255-259.
19. Alexander JI, Hull MGR. Abdominal pain after laparoscopy; the value of a gas drain. British Journal of Obstetrics and Gynaecology. 1987; 94:267-269.
20. Aanokar SM, Parulekar SV, Thatte UM, Dahanukar SA. A multiple dose comparison of ketorolac tromethamine with ibuprofen for analgesic activity. Journal of postgraduate medicine. 1993 Apr 1;39(2):74-76.
21. Joris J, Thiery E, Paris P, Lamy M. Pain after laparoscopic cholecystectomy: characteristic and effect of intraperitoneal bupivacaine. Anesthesia and Analgesia, 1995; 81:379-384.
22. Lau H, Brooks DC. Predictive factors for unanticipated admissions after ambulatory laparoscopic cholecystectomy. Arch Surg. 2001;136:1150-1153.
23. Callesen T, Klarskov B, Mogensen T, Kehlet H. Day case laparoscopic cholecystectomy: Feasibility and convalescence. Ugeskr Læger 1998; 160:2095-2100.

24. Fiorillo MA, Davidson PG, Fiorillo M, D'Anna JA, Sithian N, Silich RJ. 149 Ambulatory laparoscopic cholecystectomies. Surg Endosc 1996; 10:52-56.

25. Tuckey JP, Morris GN, Peden CJ, Tate JJ. Feasibility of day case laparoscopic cholecystectomy in unselected patients. Anaesthesia 1996; 51:965-968.

26. Bisgaard T, Klarskov B, Rosenberg J, Kehlet H. Characteristics and prediction of early pain after laparoscopic cholecystectomy. Pain. 2001 Feb 15;90(3):261-9.

27. Bisgaard T, Klarskov B, Rosenberg J, Kehlet H. Factors determining convalescence after uncomplicated laparoscopic cholecystectomy. Archives of Surgery. 2001 Aug 1;136(8):917-21.

28. Mathiesen O, Møiniche S, Dahl JB. Gabapentin and postoperative pain: a qualitative and quantitative systematic review, with focus on procedure. BMC anesthesiology. 2007 Dec;7(1):6.

29. Lesser H, Sharma U, LaMoreaux L, Poole RM. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. Neurology. 2003 Apr 22;60(8):1274

30. Dworkin RH, Corbin AE, Young JP, Sharma U, LaMoreaux L, Bockbrader H, Garofalo EA, Poole RM. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology. 2003 Apr 22;60(8):1274-83.

31. Crofford LJ, Rowbotham MC, Mease PJ, Russell IJ, Dworkin RH, Corbin AE, Young Jr JP, LaMoreaux LK, Martin SA, Sharma U. Pregabalin 1008-105 Study Group. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis & Rheumatism. 2005 Apr;52(4):1264-73.

32. Pande AC, Feltner DE, Jefferson JW, Davidson JR, Pollack M, Stein MB, Lydiard RB, Futterer R, Robinson P, Slomkowski M, DuBoff E. Efficacy of the novel anxiolytic pregabalin in social anxiety disorder: a placebo-controlled, multicenter study. Journal of Clinical Psychopharmacology. 2004 Apr 1;24(2):141-9.

33. Feltner DE, Crockatt JG, Dubovsky SJ, Cohn CK, Shrivastava RK, Targum SD, Liu-Dumaw M, Carter CM, Pande AC. A randomized, double-blind, placebo-controlled, fixed-dose, multicenter study of pregabalin in patients with generalized anxiety disorder. Journal of clinical psychopharmacology. 2003 Jun 1;23(3):240-9.

34. 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.

35. Agarwal A, Gautam S, Gupta D, Agarwal S, Singh PK, Singh U. Evaluation of a single preoperative dose of Pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy. Br J Anaesth. 2008;101:700-704.

36. Bartholdy J, Hilsted KL, Hjortsoe NC, Engbaek J, Dahl JB. Effect of Gabapentin on morphine demand and pain after laparoscopic sterilization using Filshie clips. A double blind randomized clinical trial. BMC Anesthesiol. 2006;6(12):36-45.

37. Mishra R, Tripathi M, Chandola HC. Comparative clinical study of gabapentin and Pregabalin for postoperative analgesia in laparoscopic cholecystectomy. Anesthesia, Essays and Researches. 2016;10(2):201-206.

38. Yadav G, Behera SS, Das SK, Jain G, Choupoo S, Raj J. Role of flupirtine as a preemptive analgesic in patients undergoing laparoscopic cholecystectomy. Journal of anaesthesiology, clinical pharmacology. 2015 Apr;31(2):169-173.

39. Malik A, Khatavkar SS, Kumar A, Vishnu A, Chaudhari S. Flupirtine for Pre-Emptive Analgesia Following Laparoscopic Gynaecological Surgeries. Indian journal of applied research. 2016 Jul;6(7):2249-555x.

40. Singh TH, Thokchom R, Rajkumar G, Singh YA, Meitei AJ, Singh NR, Singh LK. Pregabalin for postcholecystectomy pain relief-a study on the response of two different doses. IJHSR. 2014;4(5):159-168.

41. Thapa D, Ahuja V, Dass C, Gombar S, Huria A. Effect of preoperative flupirtine on postoperative morphine sparing in patients undergoing total abdominal hysterectomy. Saudi journal of anaesthesia. 2016 Jan;10(1):58-63.

42. Ali A, Babar KM. Comparison of preoperative dose of Pregabalin with celecoxib for attenuation of postoperative pain after open cholecystectomy. Anaesth Pain & Intensive Care. 2012;16(2):137-141.

43. Amingad B. Efficacy of Preemptive oral pregabalin for prolonging post-operative analgesia in modified radical mastectomies. Indian Journal of Clinical Anaesthesia. 2016;3(3):374-9.

44. Bekawi MS, Wakeel LM, Taher WM, Mageed WM. Clinical study evaluating Pregabalin efficacy and tolerability for pain management in patients undergoing laparoscopic cholecystectomy. Clin J Pain. 2014 Nov; 30(11):944-952.

45. Grant MC, Betz M, Hulse M, Zorrilla-Vaca A, Hobson D, Wick E, Wu CL. The Effect of Preoperative Pregabalin on Postoperative Nausea and Vomiting: A Meta-analysis. Anesth Analg. 2016 Nov;123(5):1100-1107.