Original Article

Role of flupirtine as a preemptive analgesic in patients undergoing laparoscopic cholecystectomy

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Abstract

Background and Aims: Postsurgical pain is the leading complaint after laparoscopic cholecystectomy that may delay the postoperative recovery and hence we undertook a prospective randomized trial to analyze the role of flupirtine as a preemptive analgesic for postoperative pain relief in patients undergoing above surgery.

Material and Methods: A total of 66 cases were randomly assigned to two groups to receive capsule flupirtine (200 mg) or capsule vitamin B complex administered orally, 2 h before the laparoscopic cholecystectomy surgery. Time to first analgesic requirement, assessment of postoperative pain in terms of visual analog score, and analgesic requirement postoperatively were measured as a primary outcome.

Results: Time to first analgesic requirement was significantly prolonged in the flupirtine group as compared with the placebo group. There was significant pain reduction in early postoperative period (up to 4 h), but no changes occurred thereafter. Total analgesic requirement (including rescue analgesia) and side-effects were comparable between the groups except for higher sedation in flupirtine group.

Conclusions: Flupirtine is effective as a preemptive analgesic in providing adequate pain relief during the immediate postoperative period after laparoscopic cholecystectomy surgery. However, continuation of drug therapy postoperatively could possibly delineate its optimal analgesic profile more profoundly.

Key words: Flupirtine, laparoscopic cholecystectomy, preemptive analgesia

Introduction

Acute postoperative pain is a major health concern, which augments postsurgery complications, depending upon the extent of the procedure.[1] There is a growing evidence that acute postoperative pain also influences the development of chronic pain through central or peripheral sensitization of receptors.[2] These observations have prompted the research on preemptive analgesia. It is a preventive measure to avoid such hypersensitization caused by incision and inflammatory injuries, through chronic activation of nociceptors.[3] A wide range of medications have been examined for their possible preemptive analgesic effects, including opioids, and nonsteroidal anti-inflammatory drugs (NSAIDS), through systemic or oral route.[4,5] The choice of analgesic depends upon its efficacy, pharmacokinetics, complications, and cost-effectiveness.

Flupirtine is a nonopiate, nonNSAID, centrally acting analgesic, with N-methyl-D-aspartate (NMDA) receptor antagonistic properties. Its relative advantages are preservation of respiratory functions and better gastric tolerability profile. Various studies have investigated its analgesic effect on acute as well as chronic pain. However, its efficacy as a preemptive analgesic has not been the primary stand point in any trial. Therefore, we undertook this study to evaluate the preemptive efficacy of flupirtine in reducing acute postoperative pain after laparoscopic cholecystectomy surgery.

Material and Methods

After Ethical Committee approval and written/informed consent, 80 American Society of Anesthesiologists physical

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Status I or II patients of either sex, aged 18-70 years, posted for laparoscopic cholecystectomy, between August 2012 and April 2013, were included in this trial. Patients with a history of psychiatric disorder or presently on psychotropic, analgesics, or opioid medications within 28 days of scheduled surgery, any end organ dysfunction, pregnancy, alcohol abuse or smoking habit, chronic pain, and drug allergies, were excluded.

The study was designed in a double-blinded, prospective fashion. All patients were randomly assigned to flupirtine group (F group) or the control group (C group) to receive either capsule flupirtine 200 mg or physically similar capsules of vitamin B complex, respectively. Two consecutive patients formed a set and each set had two unique numbers indicating, which group the patient would be allocated. We took total 30 sets. Then groups and sets were randomized using online randomization software (http://www.randomizer.org/). An anesthesia resident, who was not part of the study, administered one capsule to all patients with sips of water 2 h before surgery. Neither patients nor the observer was aware of the type of medications.

Premedication was omitted. In the preoperative ward, all patients were instructed on the proper use of visual analog score (VAS) and Ramsay sedation score (RSS) for assessing pain and sedation. General anesthesia was induced with lidocaine (1 mg/kg, intravenous [IV]), fentanyl (2 μg/kg, IV), and propofol (2 mg/kg, IV). Endotracheal intubation was facilitated with vecuronium (0.08 mg/kg, IV). Anesthesia was maintained with 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 and when required during surgery. At the end of surgery residual, neuromuscular paralysis was reversed with neostigmine (0.05 mg/kg, IV) and glycopyrrolate (0.01 mg/kg, IV). After adequate recovery, all patients were extubated and shifted to the postanesthesia 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 the shortest interval of at least 4 h between each dose. If the patients complained of pain in between the paracetamol dose, injection tramadol 50 mg diluted with 4 ml normal saline and was given over a period of 2 min as a rescue analgesia.

Acute postoperative pain was assessed, using the 11-point VAS score on which 0 indicated "no pain" and 10 represented "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).[6] Data for pain and sedation score were recorded at 0, 1, 2, 4, 6, 12, and 24 h, postoperatively. The severity of postoperative nausea or vomiting (PONV) was assessed by four-point scale on which 1 indicated no. PONV: Absence of any emesis or nausea, 2 indicated mild PONV: Patient having only mild nausea, or one emetic episode or nausea lasting for <10 min and where no antiemetic is required, 3 indicated moderate PONV: Patient has 1-2 emetic episodes or moderate to severe nausea and antiemetic therapy is required and 4 indicated severe PONV: Patients received ondansetron (0.1 mg/kg IV) as a rescue antiemetic if patient had >2 emetic episodes or is nauseated more than twice and more than one antiemetic required.[7] Patients received ondansetron (0.1 mg/kg IV) for any such episodes as a rescue antiemetic. Liver function test was performed in all patients on the 2nd postoperative day.

Primary outcome was the severity of postoperative pain in terms of VAS score, time to first analgesic requirement in PACU, and postoperative analgesic dose requirement, whereas secondary outcomes included the incidence of side-effects. Statistical analysis was performed using SPSS 17.0 statistical software (SPSS Inc., 233 South Wacker Drive, 11th Floor, Chicago, IL). The continuous variables were compared using the one-way analysis of variance test. *Post-hoc* testing was done using Bonferroni's method. Discrete variables were compared using Fisher's exact test/Chi-square test, whichever was appropriate. $P < 0.05$ was considered as significant.

The superiority sample size calculation was based on self-reported VAS score for pain assessment before the commencement of this study. To detect a 30% difference in the postoperative VAS score among the groups with a standard deviation of 30% estimated from previous studies, with 80% power and 5% alpha error, we need to enroll 27 patients/group.[1] We selected 30 patients/group to compensate for any dropouts in the study. Patients who were unable to report VAS score, requiring re-exploration, converted to open cholecystectomy, or surgery extending >1 h, were considered as dropped out.

Results

After assessing 80 patients, posted for laparoscopic cholecystectomy, 66 patients meeting the eligibility criteria received the studied medication. Six patients from F group and 5 patients from C group dropped out. Therefore, total 55 patients completed the study successfully [Figure 1].

There were no significant differences regarding demographics, duration of anesthesia, total intra-operative dose of fentanyl, total

rescue analgesic (tramadol) requirement and the requirement of paracetamol in first postoperative day [$P > 0.05$; Table 1]. The VAS (median ± interquartile range), was significantly lower in F group when compared with the C group ($P < 0.0001$) for the first 4 postoperative hours [$P > 0.05$; Figure 2]. Time to first analgesic requirement was significantly longer in F group as compared with C group [$P = 0.001$; Figure 3]. Side-effects did not vary significantly between the groups except for sedation, which was greater in F group [$P = 0.879$; Figure 4].

Discussion

The current study indicates that 200 mg flupirtine administered orally before incision has preemptive analgesic effect in patient undergoing laparoscopic cholecystectomy surgery. This is most convincingly shown by the observation that patients who received flupirtine before the surgical stimulus had lower VAS scores during the entire postoperative period. In contrast, VAS scores were significantly higher in C group

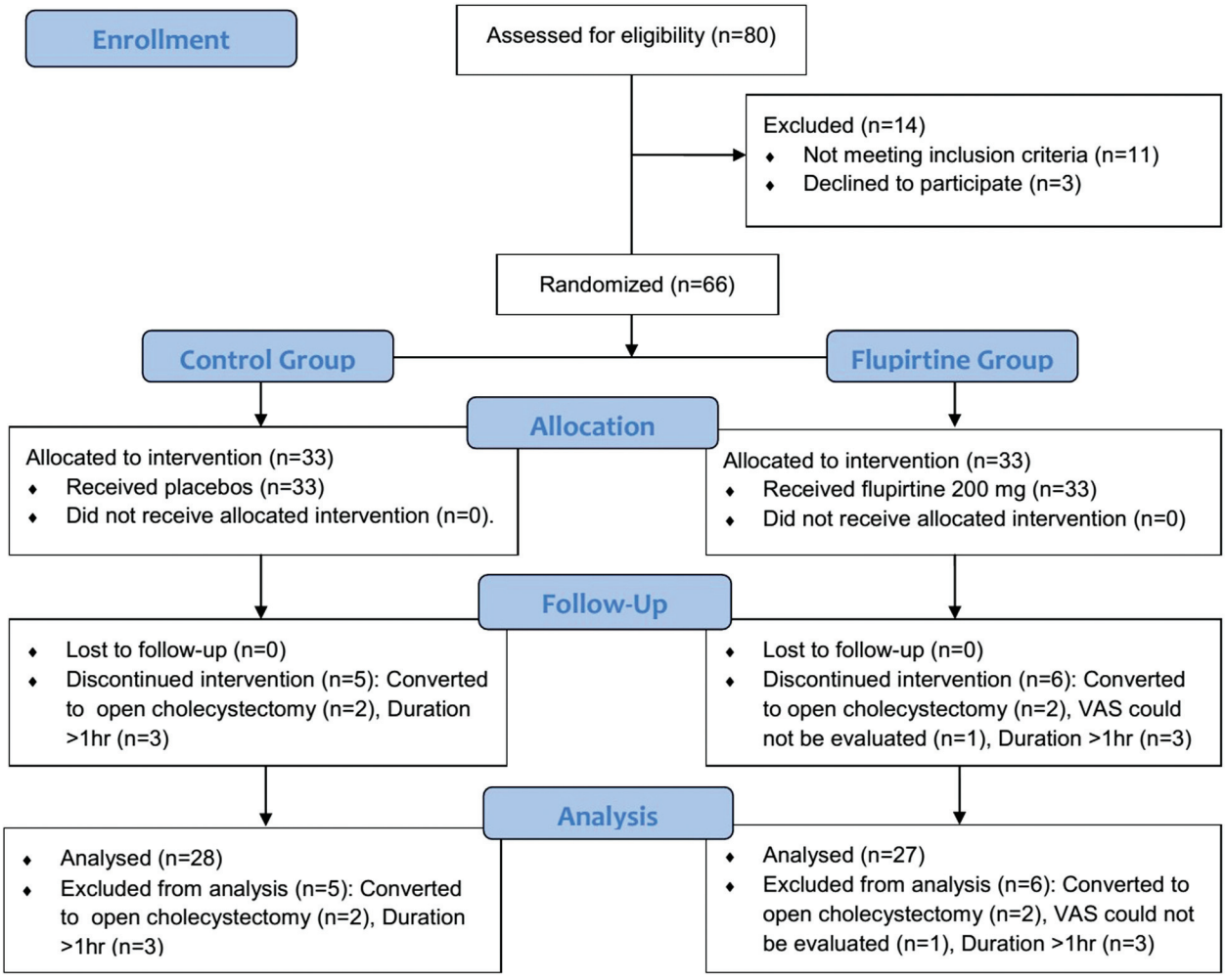

Figure 1: Flow chart of patient distribution

Table 1: Comparison of demographic and treatment characteristics among the groups

Parameters	Control group (n=28)	Flupirtine group (n=27)	P value
Age (years)	42.85±15.93	43.3±13.45	0.321
Sex (female:male)	15:12	16:12	—
Weight (kg)	57.25±8.14	56.14±6.66	0.579
Duration of anesthesia (min)	33.88±14.28	35.64±13.32	0.868
Intraoperative fentanyl requirement (μg)	120.70±20.23	115.53±14.68	0.597
No. of paracetamol injections (POD1)	3.28±0.72	3.12±0.68	0.490
Total rescue analgesic requirement (mg)	19.68±8.73	15.92±7.51	0.062

SD = Standard deviation, POD = Postoperative day. Data are presented as mean ± SDs or ratio.

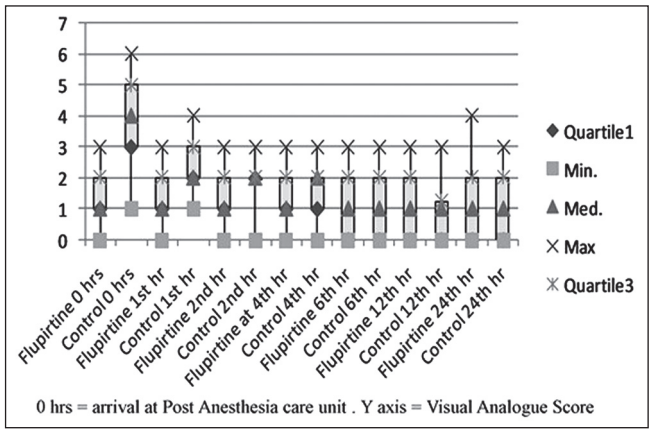

Figure 2: Significantly high visual analog score in control group during 0, 1st, 2nd and 4th h postoperatively when compared to flupirtine group

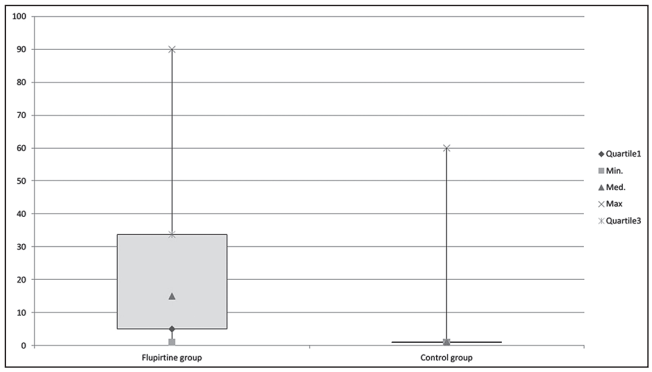

Figure 3: Significantly prolong first analgesic requirement in flupirtine group as compared to control group

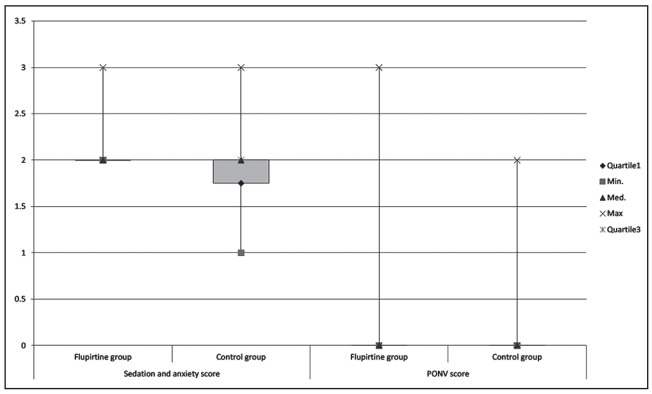

Figure 4: Significantly high incidence of sedation and no difference of postoperative nausea or vomiting in flupirtine group as compared to control group during the postoperative period

during the early postoperative period. Longer time to first analgesic requirement also indicates a preemptive analgesic effect of flupirtine.

Flupirtine maleate, a water soluble compound, undergoes rapid gastric absorption (bioavailability 90%) after oral administration, with a peak plasma concentration of approximately 0.8-2 mg/L, achieved in about 1.6-2 h.[8,9] We chose to administer the selected doses, 2 h before skin incision, with a target to maximize the analgesic effect for the duration of surgery. This methodology is further supported by observation of decreased intraoperative fentanyl requirement in our study. The analgesic activity of flupirtine has been measured in various experimental models. The analgesic effects are dose dependent, but not in a linear fashion for the whole range of therapeutic doses (100-400 mg).[8,9] Previous studies show that analgesic efficacy of flupirtine is best achieved at a dose of 200 mg. Further increase in oral dose increases the side-effects such as drowsiness, muscle relaxation and concentration impairment effects, least desirable during the immediate postoperative period.[8,9] Considering this, we chose a therapeutic dose of flupirtine (200 mg) with maximum therapeutic analgesia, but insignificant sedation related side-effects.

Previous data indicate that flupirtine exerts its analgesic activity at both spinal and supra-spinal levels. Primary site of action appears to be descending adrenergic pathways, by an indirect action on NMDA receptors through activation of G-protein coupled inward rectifying potassium channels.[10] By acting as potassium channel opener, flupirtine reduces glutamate mediated rise in intracellular calcium concentration, leading to hyperpolarization of neuronal membrane.[11-14] Furthermore, it may suppress the opening of NMDA channel by acting as an oxidizing agent at the redox site of the receptor. Flupirtine has been utilized for various painful conditions including postoperative pain. Moore *et al.* showed equivalent postoperative pain relief when flupirtine (100 mg) was compared with dihydrocodeine (60 mg) in patients undergoing hysterectomy.[15] Another study also showed similar results when flupirtine was compared with pentazocine.[16] When compared with NSAIDs, flupirtine exhibited better analgesic profile in comparison to diclofenac sodium.[17] We chose to compare flupirtine with the C group to fully quantify its analgesic activity, and any possible side-effects, as compared to placebos.

Various studies indicate that flupirtine is well-tolerated, if administered on a short term basis. Commonly observed side-effects with continued administration include sedation, gastrointestinal upset, headache, disorientation, and hallucinations.[8,9] We observed no significant side-effects except for excess sedation in the F group. Noncontinued administration of flupirtine doses during the postoperative period might have prevented the development of other side-effects in our study.

Limitations of our study included a relatively small sample size in proportion to the burden of this postoperative morbidity.

The results of our study may not coincide with studies done on other ethnic groups owing to variations in body surface area and pain tolerance. Moreover, performing a dose-response study could have better delineated its optimal analgesic profile and the corresponding increase in the side-effects more profoundly. Future studies can investigate on these aspects or the effect of continuation of drug therapy during the postoperative period.

We conclude that flupirtine is as effective preemptive analgesic to settle the pain in postsurgical cases. The preemptive analgesic effect of flupirtine is more acceptable as it lacks the typical side-effects of continued administration.

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