Original Article

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Comparison of Analgesic Efficacy of Oral Flupirtine Maleate and Ibuprofen in Patients Undergoing Laparoscopic Cholecystectomy: A Randomized Control Trial

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Abstract

Aims and Objective: To evaluate the efficacy of Flupirtine in reducing acute postoperative pain after laparoscopic cholecystectomy as compared to Ibuprofen when administered by oral route prior to surgery and to observe and compare side effect profile of oral Flupirtine maleate and Ibuprofen. ***Method:*** This study was conducted in 60 patients of ASA1/2,21 to 70 years of age who were randomly divided into two groups to receive either 200mg oral flupirtine maleate or 800 mg oral Ibuprofen 2 hrs prior to the procedure. Post operatively patient was observed for vas score, RSS, rescue analgesia requirement and post-operative nausea and vomiting. ***Result:*** Patients from flupirtine group had lower VAS score than that of ibuprofen group in first 6 hours. RSS score was satisfactory in first 4 hours in flupirtine group than ibuprofen group. Rescue analgesia requirement was more in ibuprofen group than flupirtine group also post-operative nausea and vomiting was seen more in ibuprofen group than flupirtine group. ***Conclusion:*** This study concluded that, patients undergoing laparoscopic cholecystectomy, pre-emptive use of oral flupirtine 200 mg is more effective compared to oral ibuprofen 800 mg and flupirtine provides better pain relief with additional muscle relaxation and mild sedation in early post-operative period.

Keywords: Laparoscopic Cholecystectomy; Flupirtine; Ibuprofen; Pre-emptive Analgesia.

Introduction

Post-operative pain is considered as a form of acute pain due to surgical trauma with an inflammatory reaction. It's an unpleasant sensory, emotional and mental experience which usually is associated with autonomic, endocrine, metabolic, physiological and behavioral response.[1] Acute postoperative pain is a major problem following abdominal surgery which may aggravate postoperative complications depending on extent of the procedure.[2] Acute postoperative pain also influences development of chronic pain through central or peripheral sensitization of receptors.[3] Though severity of pain is less following laparoscopic surgery compared to open procedure, postoperative pain may still

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be a factor which may lead to delayed recovery, delayed hospital discharge and increase the cost of patient care. Pain after laparoscopic surgery is at the incision and at the trocar insertion sites. There may also be diffuse abdominal and shoulder pain due to peritoneal stretching and diaphragmatic irritation by carbon dioxide insufflation. With evolution of multimodal analgesia, a wide range of pharmacological methods have been used for treatment of postoperative pain.

These include Opioids like morphine, fentanyl, pethidine, tramadol, Transdermal analgesic patches like fentanyl, lidocaine, Non-steroidal anti-inflammatory drugs (NSAIDs) like paracetamol, ibuprofen, Local anesthetic drugs for wound infiltration, peripheral nerve blockade, epidural analgesia, N-methyl-D-aspartate (NMDA) receptor antagonist like ketamine. Flupirtine is a non-opioid analgesic without antipyretic or antiphlogistic properties. This N-methyl D-aspartate (NMDA) receptor antagonist and selective neuronal potassium channel opener (SNEPCO) is one of the most preferred analgesics for the treatment of musculoskeletal pain. Flupirtine is a derivative of triaminopyridine. The actual site of action of this drug is in the central nervous system, at spinal as well as supra spinal level.

The drug is available in 50 and 100 mg capsules for oral use and 75 and 150 mg suppository for rectal use.[4] Ibuprofen is most used NSAID for pain relief. It is a 2 propionic acid derivative, non-selective inhibitor of cyclooxygenase- 1 (COX-1) and Cyclooxygenase-2 (COX2).[5] Ibuprofen is supplied as tablets with a potency of 200 to 800 mg. Ibuprofen suppresses pituitary beta endorphin release and produces superior analgesia as compared to other NSAIDs.

Method and Material

After obtaining approval from the ethical committee, 60 patients of either sex belonging to American Society of Anaesthesiologists (ASA) grade I and II aged 21 to 70 years posted for laparoscopic cholecystectomy using computer generated random number table in each group 30 patients included. Written informed valid consent was obtained from all the patients. Preanesthetic evaluation done one day prior to the surgery. On day of surgery all investigations and NBM status was confirmed. Patients were randomly divided into two groups with 30 in each group. Group F received cap. Flupirtine 200mg orally in preoperative room 2 hours with sip of water prior to induction of anaesthesia. Group I received Tab. Ibuprofen 800 mg orally in preoperative room 2 hours with sip of water prior to induction of anaesthesia. Patients were educated about visual analogue scale and RSS and its use for post-operative pain. After taking patient to operation theatre, all ASA monitor such as pulse oximeter, non-invasive blood pressure (NIBP), ECG, $EtCO_2$ were attached. Intravenous access secured and IV fluids were started. Both groups were premedicated with inj. Ondensatron 0.08mg/kg, inj. Glycopyrrolate 0.004mg/kg, inj. Midazolam 0.2 mg/kg, inj. Fentanyl 2mcg/kg. Anaesthesia induced by inj. Propofol 2mg/kg and inj. Vecuronium bromide 0.1mg/kg. Patient was intubated with endotracheal tube of appropriate size using direct laryngoscopy.

Anaesthesia was maintained with 1.0 MAC of sevoflurane in mixture of 50% O_2 and air. Patients were ventilated on pressure control mode with tidal volume 8 to 10 ml/kg and expiratory rate depending upon end tidal CO_2. At the end of the surgery patient was reversed with neostigmine 0.05 mg/kg body weight and glycopyrrolate 0.008 mg/kg body weight IV and extubated after adequate recovery and then shifted to anaesthesia recovery room. In the post anaesthesia care unit (PACU), patients were assessed for vital parameters, pain, sedation (VAS and RSS respectively).

This was taken as 0 time. Subsequently, VAS and RSS was recorded at 1, 2, 4, 6, 12 and 24 hours post-operatively. For any pain complaint (VAS > 3), 1gm paracetamol IV was given as rescue analgesic by intravenous infusion over 15 mins and was repeated if required, at not earlier than 4 hours interval. The severity of postoperative nausea and vomiting (PONV) during 24 hours was also assessed.

Statistical Analysis

Data was collected and compiled using Microsoft Excel 2013 and then analyzed using SPSS 23.0 version and Open Epi Software Version 2.3 by calculating frequency, percentage and cross-tabulations between various parameters. The means and standard deviations (SD) were 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. Parentage, odds ratio and 95% confidence interval were estimated, wherever necessary. For comparison between the two means of quantitative data, student's t-test applied.

Result

Total 60 patients were enrolled in this study which were randomized in group F and group I. The groups were not statistically significant in age, gender, ASA grade and weight hence comparable in these factors. Vital parameters like heart rate, systolic and diastolic blood pressures and room air oxygen saturation (SPO_2) were noted post-operatively. There was no statistically significant difference between the groups with regard to these parameters.

In group F, who received Flupirtine preoperatively were comfortable with a mean VAS score of 2.20±0.407. However, in group I, who received ibuprofen complained of pain with VAS score of 3.80±0.961. This difference in VAS score between two groups was statistically significant. VAS score was statistically significantly higher in group I till 6 hrs. time interval. The mean VAS score at 6 hrs. in group F was 2.80±0.407 and 2.90±0.305 in group I, with P value of <0.05. There was statistically significant difference between VAS Score in both groups in first 6 hours. VAS score was later comparable in both the groups up to 24 hours.

The mean RSS score at 1hr, in group F was 2.20±0.407 and in I group was 1.17±0.592 with p value <0.05.Similarly at 2 hrs mean RSS score in group F was 2.10±0.305 and in group I was 1.30±0.466 with p value 0.05.At 4 hrs, mean RSS score in group F was 2.03±0.183 and in group I was 1.40±0.498 with p value <0.05. This showed that, patients receiving Flupirtine were comfortable and mildly sedated whereas those who received Ibuprofen were anxious and restless. RSS score was later comparable in both the groups up to 24 hours.

Requirement of rescue analgesia was present in both groups in which 18 patients required rescue analgesia in group I which was more than in group

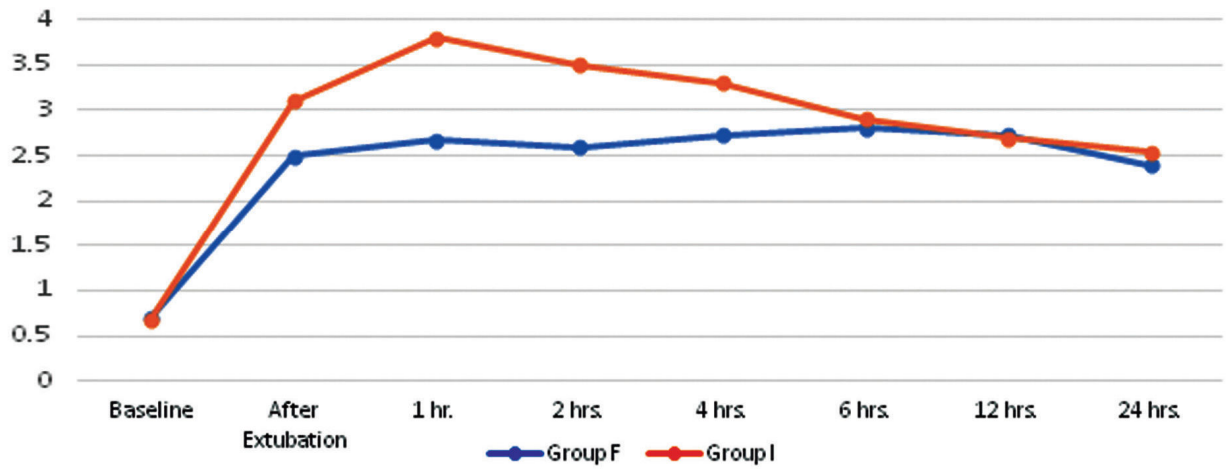

Fig. 1: Comparison between the groups according to VAS Score.

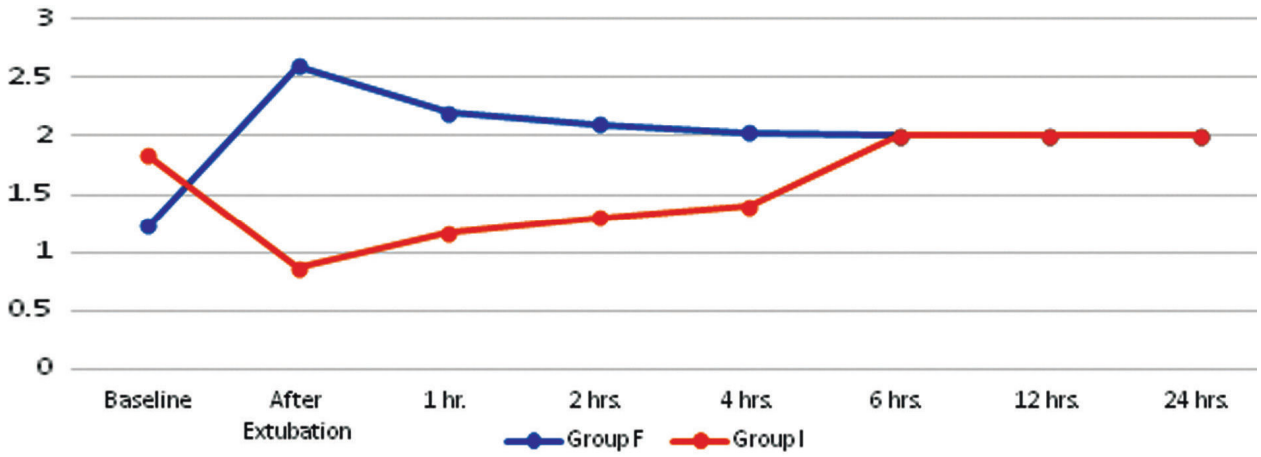

Fig. 2: Comparison between the groups according to RSS score.

F (7) this difference was statistically significant. (P value <0.05). Similarly, postoperative nausea vomiting was seen in both groups in which 12 patients showed PONV in group I which was more than in group F(4) this difference was statistically significant. (P value <0.05).

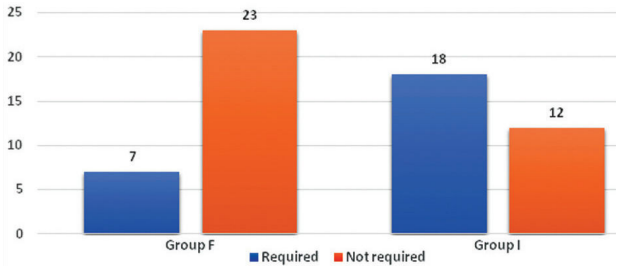

Fig. 3: Comparison between the groups according to Rescue Analgesia.

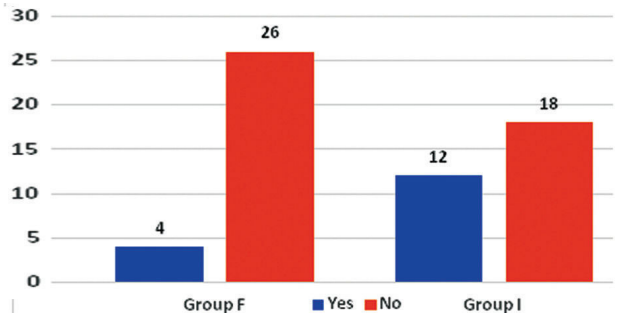

Fig. 4: Comparison between the groups according to PONV.

Discussion

Flupirtine is a water-soluble compound. It is completely absorbed from gastrointestinal tract with a bioavailability of 90% by oral route and 70% by rectal route. It appears in plasma within 15 to 30 min and achieves peak plasma concentration of 0.8mg/L at 1.6 to 2 hours following an oral 100 mg dose. Its elimination half-life ranges from 6.5 to 9.6 hours after oral route. Ibuprofen is well absorbed orally; peak plasma concentrations are achieved in 1 to 2 hours after oral administration. It is rapidly bio-transformed with a serum half-life of 1.8 to 2 hours. The drug is eliminated in 24 hours after the last dose and eliminated through metabolism. In our study we compared these two drugs for analgesic efficacy in laparoscopic cholecystectomy.

This prospective, randomized controlled study was conducted in tertiary care hospital. In the early post-operative period flupirtine exhibited reduced VAS score as compared to ibuprofen. This was probably due to the difference in mechanism of action of both the drugs. Oral flupirtine is known to produce analgesic as well as muscle relaxant effects that occur due to inhibition of spinal polysynaptic flexor reflex and is mediated by NMDA receptors.[6] In this study mean age was 34.2 yrs. with age range between 21 to 65 yrs. and maximum number of patients were in age group 20 to 30 yrs. and male patients were more than female patients in both the groups. Both the groups were comparable in terms of age, gender, ASA grade and weight as difference in groups was not statistically significant. Vanita Ahuja[7]et al in their study mentioned similar findings.

Ghanshyam Yadav[8] observed that there were no significant differences regarding demographics, duration of anesthesia, total intra-operative dose of fentanyl. In this study comparison of VAS score between the groups, group F throughout the interval VAS was between 0.70 to 2.80 and in group I VAS score 0.67 to 3.80. The difference of VAS score between two was statistically significant with p value of 0.01 at 1, 2, 4 and 6 hrs. Ghanshyam Yadav[8] mentioned that 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.

Vanita Ahuja[7] mentioned in their study that analgesic efficacy of flupirtine maleate was comparable with ibuprofen in patients with ambulatory gynecological patients up to 48 h with superior satisfaction score and in the early post-operative period flupirtine exhibited reduced VNRS as compared to ibuprofen. Moore et al[9] showed equivalent postoperative pain relief when flupirtine (100 mg) was compared with dihydrocodeine (60 mg) in patients undergoing hysterectomy. Li C et al.[10] Flupirtine showed an overall pain-relieving efficacy comparable to tramadol. Singal et al.[11] mentioned that Flupirtine is as effective as opioids to settle the pain in post-surgical cases, cancer related, neuropathic and myofascial in origin. The clinical use of flupirtine will be more acceptable as it lacks the typical side effects of the opioid drugs.

Requirement of rescue analgesia was present in both groups in which 18 patients required rescue analgesia in group I which was more than in group F in which 7 patients required rescue analgesia this difference was statistically significant. (P value <0.05). Similarly, Yadav et al[8] observed that 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. Godara et al.[12] also mentioned that in post inguinal hernia surgery flupirtine can result in significant decrease in pain within a short time and is well tolerated

by most patients and flupirtine could be a better alternative to opioids and NSAIDs in postoperative pain relief.

We observed that in group F4 patients had PONV and in group I 12 patients had PONV. Godara et al.[12] also mentioned that heartburn was more in diclofenac group than flupirtine group in patients undergoing inguinal hernia surgery.

Conclusion

Laparoscopic cholecystectomy offers several advantages over the open abdominal surgeries such as less stress response, less post-operative pain, less post-operative surgical site infection and less bleeding. Preemptive analgesia is an analgesic intervention before noxious stimulus arises in order to block central and peripheral sensitization. In our study we compared two different drugs, cap Flupirtine 200mg and tab ibuprofen 800mg for prevention of post-operative pain in laparoscopic cholecystectomy patients and we concluded that,

- Preemptive use of oral flupirtine 200mg, 2 hours prior to the laparoscopic cholecystectomy and oral ibuprofen 800mg, 2 hours prior to the laparoscopic cholecystectomy were effective in controlling post-operative pain.
- Flupirtine stands effective compared to ibuprofen, as in patients who received Flupirtine had less VAS score, less rescue analgesic requirement and were comfortable post operatively.
- Flupirtine showed less side effects as compared to the ibuprofen where patients who received flupirtine had less post-operative nausea and vomiting than those who received ibuprofen which was statistically significant.

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