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ORAL FLUPIRTINE FOR POSTOPERATIVE ANALGESIA IN LAPAROSCOPIC CHOLESYSTECTOMY: A RANDOMIZED PROSPECTIVE STUDY

Anesthesiology

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ABSTRACT

Aim- To evaluate the efficacy of oralflupirtine in reducing acute postoperative pain after laparoscopic cholecystectomy and toobserve whether the drug has sedative orany other adverse effects.

Materials and Methods- The study was conducted on 60 adult patients who were randomly divided in to two groups, who received flupirtine 200mg or placebo orally 2 hours prior to induction of general anaesthesia.Visual Analogue Scale (VAS), Ramsay Sedation Score (RSS), time to first rescue analgesic requirement,incidence of Post-Operative Nausea and Vomiting (PONV)or any other side effects, if any were noted.

Results- Patients who received flupirtine had lower VAS scores during first four hours postoperatively.Rescue analgesic requirement was less in flupirtine group when compared to placebo. There were no significant side effects except for sedation in flupirtinegroup as compared with placebo.

Conclusion- This study showed that pre-emptive analgesia with oral flupirtine 200mg 2 hours prior to laparoscopic cholecystaectomyis effective compared to placebo and provided adequate pain relief and sedation during the immediate postoperative period.

KEYWORDS

Flupirtine, Laparoscopic cholecystectomy, postoperative analgesia

INTRODUCTION

Post-operative pain is considered as a form of acute pain due to surgical trauma with an inflammatory reaction. It is an unpleasant sensoryand emotional experience which isgenerally associated with endocrine,autonomic, physiological, metabolic 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 may also influence the development of chronic pain throughperipheral or central sensitization of receptors.[3] Though severity of pain is less following laparoscopic surgery compared to open procedure, postoperative pain may still be a factor which may lead to delayed recovery, delayed 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 diaphragmatic irritation andperitoneal stretching by carbon dioxide insufflation.[4]

A pursuing increase in the knowledge base of pain management have led to the idea of multimodal pharmacology and balanced analgesia. Various non-pharmacological methods of pain management include acupuncture, psychotherapy, meditation, massage, heat therapy, aromatherapy and deep breathing. A wide range of pharmacological methods have been used to treat postoperative pain like oral, sublingual, parenteral, intrathecal, epidural and intraperitoneal routes. These include opioids like morphine, fentanyl, pethidine, tramadol and transdermal analgesic patches like fentanyl and lidocaine, non-steroidal anti-inflammatory drugs (NSAIDs) like paracetamol, local anaesthetic drugs for wound infiltration, continues peripheral nerve blockade, continues epidural infusion, N-methyl-D-aspartate (*NMDA*) receptor antagonist like ketamine.[5]

Flupirtine is a non-opioid analgesic without antiphlogisticor antipyretic properties and is a derivative of triaminopyridine. The actual site of action of this drug is unknown but most probably it acts in the central nervous system, at spinal as well assupra spinal levels. The drug is available in 50 and 100 mg capsules for oral use and 75 and 150 mg suppository for rectal use.[6]

MATERIALS AND METHODS

After approval of the medical ethics committee of the institute, a prospective randomized comparative study was conducted on 60 patients of either sex aged 21 to 70 years. Randomization done using computer generated random number table. All the patients were subjected to thorough pre-anaesthetic evaluation 48 hours prior to surgery. They were explained about the Visual Analogue scale (VAS) and Ramsay sedation score (RSS.) Relevant laboratory and other essential investigations were done. Written and informed consent was obtained from all the patients. Patients who were on opioidsor other psychotropic medications, pregnant patients, lactating mothers, those with chronic pain, drug allergies, hepatic or renal disease were excluded from the study.

60 patients were divided into two groups- Group F – flupirtine group. In this group capsule flupirtine 200mg was given orally with a sip of water in preoperative room 2 hours prior to induction of anaesthesia.Group P – placebo group. In this group capsule Vitamin B complex was given orally with a sip of water in preoperative room 2 hours prior to induction of anaesthesia.

All the patientswere premedicated with glycopyrrolate 0.004mg/kg and fentanyl 1.5µg/kg intravenously. After preoxygenation for 3 minutes, general anaesthesia (GA) was induced by propofol 2mg/kg body weight followed by suxamethonium 1.5 mg/kg body weight intravenously.Endotracheal intubation was done using and a well lubricated portex cuffed endotracheal tube of appropriate size.Anaesthesia was maintained with nitrous oxide-oxygen combination (65%:35%) and isoflurane (0.6 to 1%) to maintain adequate depth of anaesthesia. Muscle relaxation was achieved using initial dose or vecuronium bromide 0.1mg/kg and subsequently 0.025mg/kg intravenously. Ventilation was adjusted to keep the end tidal CO_2between 30-40 mmHg.

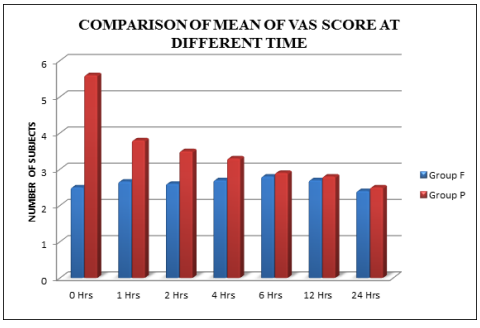
Intraoperatively patientswere monitored with continuous ECG, pulse oximetry, noninvasive blood pressure and end tidal carbon dioxide concentration ($ETCO_2$).At the end of surgeryresidual effect of vecuronium was reversed with glycopyrrolate-neostigmine combination (0.008mg/kg and 0.05mg/kg respectively) and patients were extubated.In the post anaesthesia care unit (PACU), patients were assessed for vital parameters, pain, sedation (VAS and RSS respectively), and any other side effects. This was taken as 0 time. Subsequently, VAS and RSS was recorded at 1, 2, 4, 6, 12 and 24 hours postoperatively.For any pain complaint (VAS>3), 1gm paracetamol IV was given as rescue analgesic by intravenous infusion over 15 min. 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.

RESULT

Both the groups (Group F and Group P) of 60 each were comparable with respect to their age, sex, body weight and American Society of Anaesthesiologist's physical status (ASA PS)with no statistically significant difference between the two groups (P>0.05). Vital parameters like heart rate, systolicand diastolic blood pressures and room air oxygen saturation (SPO_2) were noted preoperatively. There was no clinically or statistically significant difference between the groups with regard to these parameters. Blood loss was negligible during surgery and urine output was adequate. Mean duration of surgery was 1.1±0.32 in group F and 1.1±0.56 in group P with no statistically significant difference between the two groups (P>0.05).

Figure1 depicts VAS (Visual analogue scale) score at various time intervals inboth the groups. After shifting the patient to the PACU, it was observed that patients of group F, who received Flupirtine pre-operatively were comfortable with a mean VAS score of 2.5±1.04. However, in group P, who received placebo complained of moderate to severe pain with VAS score of 5.6±2.34. This difference in VAS score between two groups was statistically highly significant. VAS score was statistically significantly higher in group P till 4 hrs. time interval. The mean VAS score at 4 hrs. in group F was 2.7±0.52 and 3.3±0.46 in group P, with P value of <0.05. There was statistically significant difference between VAS Score in both groups in first 4 hours. VAS score was later on comparable in both the groups up to 24 hours.



The meanRSS score at 2 hours in group F was 2.10±0.30 and 1.3±0.46 in group P, with P value of<0.05 indicating that most of the patients in group F,flupiritne group were comfortable and responding to commands while majority of patients in group P, placebo group were restless and anxious. RSS score was later on comparable in both the groups up to 24 hours.

Total number of patients who required rescue analgesic was 3 (10%) in groupF, flupirtine group and 23 (76.66%) in group P, placebo group. Less rescue analgesic requirement for patients ofgroup F, flupirtine group shows that patients were pain free compared to group P, placebo group. The difference between both the groups was statisticallysignificant.In Group F, 3 (10%) patients had PONV,while in Group P, placebo group, it was 5 (16.66%). Side effects observed in Group F and Group P were not statistically significant. No other side effects were observed in the study.

DISCUSSION

Flupirtine maleate is a water-soluble compound and undergoes rapid gastric absorption with a bioavailability of 90% after oral administration. It attains a peak plasma concentration of approximately 0.82mg/L,in about 1.62h.[7] Hummel et alin their study observed the dose related analgesic effect of flupirtine and concluded that it has dose dependent analgesic effect. It was not in linear fashion for range of therapeutic effects(100-400mg). Dose of drug chosen for this study was 200mg, which is therapeutic dose of flupirtine with maximum analgesia, but insignificant sedation related side-effects.[8]

Flupirtine shows properties that are different from other common analgesics being a selective opener at potassium channelsand also by acting as an oxidizing agent at the redox site of the NMDA receptors.[9]Moore et alcomparedflupirtine with dihydrocodeinein patients undergoing hysterectomy and found equal postoperative pain relief and patient satisfaction. [10]

In this study it was observed that 200mg flupirtine giving orally 2 hours before surgery has preemptive analgesic effect in patient undergoing laparoscopic cholecystectomy. This study also supports that administration of analgesic drugs before the operation will ensure adequate drug absorption & distribution to the effect site by the time the patient wakes up from general anaesthesia.This is proved by the observation that patients who received flupirtine before the surgical stimulus had lower VAS during the first 4 hours of postoperative period in contrast to the higher VAS scores in group P during the early postoperative period. Lesser rescue analgesic requirement in group F when compared to group P also indicatedthe better preemptive analgesic effect of flupirtine.

Common side effects of flupiritinewith long term administration include sedation, gastrointestinal upset, headache, disorientation, and hallucinations.[11] In this study we used flupirtine as a preemptive analgesic with no repeated doses and we found no significant side effects except for sedation as compared with the placebo group.

CONCLUSION

Administration of oral flupirtine 200mg 2 hours prior to laparoscopic cholecystectomyis more effective as compared to placebo to provide pain relief during the early postoperative period.The analgesic effect of flupirtine by single dose is more acceptable as it lacks the side effects of repeated administration.Minimal sedative effect of the drug is an added advantage in the post-operative period with a comfortable patient responding to commands.There were no significant side effects for this drug apart from low incidence of nausea and vomiting which was statistically not significant.

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