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RESEARCH ARTICLE

ROLE OF FLUPIRTINE AS A PROPHYLACTIC ANALGESIC IN PATIENTS HAVING LAPAROSCOPIC CHOLECYSTECTOMY

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BACKGROUND: The International Association for the Study of Pain (IASP) describes pain as an unpleasant emotional and sensory experience connected to tissue damage that has occurred or may occur. The early mobilization and overall health of the surgical patient are significantly impacted by the prevention and treatment of postoperative pain, which remains a significant problem in postoperative care. Untreated post-operative pain has a negative impact on cost, length of hospital stay, and morbidity. It is also a serious health concern. Dorsal horn neurons become more sensitive after surgical activation, and this is linked to an increase in pain. Regional anesthesia, opioids, non-steroidal anti-inflammatory drugs, and local anesthetics remain the mainstays for post-operative analgesia treatment; however, their effects may be transient and they are invariably linked to the risk of respiratory depression, emesis, itching, and urine retention. Since postoperative pain is the most common complaint following laparoscopic cholecystectomy and can cause delays in the healing process, we conducted a prospective randomized trial to examine the potential benefits of flupirtine as a preventive analgesic for postoperative pain management in patients having the aforementioned procedure.

AIM: To evaluate the efficacy of oral flupirtine in reducing acute postoperative pain after laparoscopic cholecystectomy and to observe whether the drug has sedative or any other adverse effects.

MATERIAL AND METHOD: Eighty patients between the ages of 18 and 60 who were scheduled for a laparoscopic cholecystectomy under general anesthesia and who fit into ASA physical status I or II participated in the randomized, double-blind, prospective trial. A comprehensive pre-anesthetic examination was performed on each patient 48 hours before surgery. The Ramsay Sedation Score (RSS) and Visual Analogue Scale (VAS) were explained to them. Other crucial investigations and essential laboratory work were completed. Prior to the day of operation, written informed permission was obtained from each patient. Using computer-generated random numbers, participants in the trial were divided into two groups (A and B) of forty patients each.

RESULTS: Eighty adult patients participated in the study. They were split into two groups at random and given either a placebo or 200 mg of flupirtine orally two hours before general anesthesia was induced. It was discovered that there was no statistically significant difference between group A and group B's demographic profiles, including age, sex, and weight. Regarding demographics, length of anesthesia, total fentanyl intraoperative dose, total rescue analgesic demand (tramadol), and paracetamol required on the first postoperative day, there were no statistically significant differences. The length of surgery and the ASA physical status of groups A and B were determined to be non-statistically significant.

CONCLUSION: Giving 200 mg of flupirtine orally Painkillers that are administered two hours before a laparoscopic cholecystectomy work better than placebos in terms of reducing pain in the early postoperative phase. Without changing intraoperative hemodynamics, flupirtine can be utilized as a preventive analgesic with effective prolonging of analgesia in the early postoperative phase during laparoscopic procedures.

KEYWORDS: Flupirtine, Laparoscopic Cholecystectomy and Postoperative Analgesia

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INTRODUCTION:

Depending on the length of the treatment, acute postoperative discomfort might increase the risk of problems after surgery. It is a serious health concern.[1] There is mounting evidence that the central or peripheral sensitization of receptors caused by acute postoperative pain also plays a role in the development of chronic pain.[2] The preemptive analgesia research has been spurred by these observations. By repeatedly activating nociceptors, it is a prophylactic measure against the hypersensitization brought on by incision and inflammatory lesions.[3] Many drugs have been investigated for potential preemptive analgesic effects, including as opioids and nonsteroidal anti-inflammatory drugs either orally or systemically.[4,5]

One type of acute pain linked to surgical trauma and an inflammatory response is post-operative pain. Endocrine, autonomic, physiological, metabolic, and behavioral reactions are typically linked to this unpleasant sensory and emotional experience.[6] After abdominal surgery, acute postoperative discomfort is a significant issue that, depending on how extensive the procedure was, may make postoperative issues worse.[7] Through the peripheral or central sensitization of receptors, acute postoperative pain may potentially have an impact on the development of chronic pain. Even though postoperative pain from laparoscopic surgery is typically less severe than that from open procedures, it can nevertheless contribute to a delayed recovery, a delayed discharge, and higher healthcare costs. Following laparoscopic surgery, pain is felt at the trocar insertion locations as well as the incision. Additionally, diaphragmatic irritation and peritoneal strain brought on by carbon dioxide insufflation may cause generalized pain in the abdomen and shoulders.[8]

The concepts of multimodal pharmacology and balanced analgesia are the result of an ongoing effort to broaden our understanding of pain treatment. Acupuncture, psychotherapy, massage, thermal treatment, aromatherapy, meditation, and deep breathing are a few non-pharmacological pain management techniques. Postoperative pain has been treated with a variety of pharmacological techniques administered via the oral, sublingual, parenteral, intrathecal, epidural, and intraperitoneal routes. These include non-steroidal anti-inflammatory drugs (NSAIDs) like paracetamol, local anesthetics for wound infiltration, continuous peripheral nerve blockade, continuous epidural infusion, opioids like morphine, fentanyl, pethidine, tramadol, and transdermal analgesic patches like fentanyl and lidocaine.[4]

Flupirtine is a centrally acting analgesic that does not function as an opiate or NSAID and has antagonistic effects on the N-methyl-D-aspartate (NMDA) receptor. The maintenance of respiratory functions and an improved stomach tolerability profile are its relative benefits. In general, people respond well to short-term administration of flupirtine. As the medication is prolonged, common side effects include headache, drowsiness, nausea, disorientation, and hallucinations. Since flupirtine doesn't interfere with anesthetics or cause negative side effects like respiratory depression or increased bleeding after surgery, it can be used as a preventative analgesic. Promising outcomes have been observed in a clinical investigation aimed at determining the efficacy of flupirtine as a preventive analgesic in supplying sufficient analgesia in the immediate postoperative phase following laparoscopic cholecystectomy surgery.[9] Numerous research works have examined its ability to relieve both acute and chronic pain. But in none of the trials, its effectiveness as a preventative analgesic has been the main focus. Both acute surgical pain and chronic pain have been treated with it.[10] Thus, the purpose of this study was to assess if flupirtine can prevent acute postoperative discomfort following laparoscopic cholecystectomy surgery.

MATERIAL AND METHODS

The randomized, double-blind, prospective study was carried out on 80 patients between the age of 18-60 years, belonging to ASA physical status I and II, scheduled for laparoscopic cholecystectomy under general anesthesia. A comprehensive pre-anesthetic examination was performed on each patient 48 hours before surgery. The Ramsay Sedation Score (RSS) and Visual Analogue Scale (VAS) were explained to them. Other crucial investigations and essential laboratory work were completed. Prior to the day of operation, written informed permission was obtained from each patient. Using computer-generated random numbers, participants in the trial were divided into two groups (A and B) of forty patients each. Patients in Group A were given a 150 mg tablet of Pregabalin orally one hour before surgery, and patients in Group B were given a 200 mg capsule of Flupirtine orally two hours before surgery along with a drink of water by a staff nurse who was not participating in the study. Each set of two consecutive patients has two

distinct numbers designating which group the patient will be assigned to.

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 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.

Methods

All the patients were premedicated with glycopyrrolate 0.004mg/kg and fentanyl 1.5µg/kg intravenously. After preoxygenation for 3 minutes, general anesthesia (GA) was induced by propofol 2mg/kg body weight followed by suxamethonium 1.5 mg/kg body weight intravenously. A properly sized, well-lubricated portex cuffed endotracheal tube was used for endotracheal intubation. In order to maintain an appropriate depth of anesthesia, nitrous oxide-oxygen (65%:35%) and isoflurane (0.6 to 1%) were used. An intravenous dose of 0.1 mg/kg of vecuronium bromide was used initially, and then 0.025 mg/kg to induce muscle relaxation. The end-tidal CO was maintained between 30 and 40 mmHg by adjusting the ventilation.

Continuous electrocardiogram (ECG), pulse oximetry, noninvasive blood pressure, and end-tidal carbon dioxide concentration (ETCO) monitoring were used to monitor patients throughout surgery. After the procedure, patients were extubated and the remaining effects of two vecuronium were reversed with a mixture of glycopyrrolate and neostigmine (0.008 mg/kg and 0.05 mg/kg, respectively). Patients were evaluated for vital signs, pain, sedation (VAS and RSS, respectively), and any further adverse effects in the post-anesthesia care unit (PACU). This received a score of 0. VAS and RSS were then measured 1, 2, 4, 6, 12, and 24 hours after surgery. As a rescue analgesic, 1 gm of paracetamol IV was infused intravenously during a 15-minute period for every pain complaint (VAS >3). This procedure was repeated if necessary, but not before every 4 hours. Additionally, the intensity of postoperative nausea and vomiting (PONV) over the course of a day was evaluated.

All patients were extubated and moved to the post-anesthesia care unit (PACU) after reversal and sufficient recovery. Patients in the PACU had their levels of pain, sedation, and other consequences evaluated. On the first postoperative day, an IV dose of 1 g Paracetamol was administered for any pain complaints (VAS > 3), with a minimum of 4 hours passing between doses. A two-minute injection of 50 mg of diluted Tramadol dissolved in normal saline was given to patients who complained of discomfort between Paracetamol doses as rescue analgesia.

STATISTICAL ANALYSIS

Data entry was done using MS Excel 2007 computer software. Numerical variables were presented as mean ± SD (Standard Deviation), median ± IQR (Interquartile Range), and scores were compared with the Man Whitney U test. Chi x2 was used to compare categorical variables. The package SPSS 16.0 (SPSS Inc, Chicago, IL) and Graph Pad instate were used for statistical analysis.

RESULT: -

After being randomly assigned to two groups using computer-generated random numbers, out of the 80 patients who were initially chosen for the trial, two patients were removed from group A (pregabalin group) and three patients were removed from group B (flupirtine group). which led to the analysis of 40 patients from group A and 40 patients from group B.

Table 1: Age, Sex, and Weight Distribution of the Patients.

Age Distribution				
Age Group	**Group A (n=40)**		**Group B (n=40)**	
	No	%	No	%
Up to 30	7	17.5	11	27.5
31-40	11	27.5	10	25
41-50	20	50	15	37.5
51-60	2	5	4	10

	38.09±6.32		37.42±6.24	
Gender Distribution				
Gender	**Group A (n=40)**		**Group B (n=40)**	
	No	%	No	%
Female	28	70	25	62.5
Male	12	30	15	37.5
Weight Distribution				
	No. of patients	**Min. (in Kg)**	**Max. (in Kg)**	**Median**
Group A	40	53	100	49.50
Group B	40	43	94	60.00
Total	80	43	100	600.00

The difference between demographic profiles like age, sex, and weight, between group A and group B were found to be not statistically significant.

Table 2: Comparison of treatment characteristics among the groups.

Parameters	Control group (n=40)	Flupirtine group (n=40)
Duration of anesthesia (min)	31.77±12.24	31.60±11.20
Intraoperative fentanyl requirement (mg)	108.50±15.12	102.40±13.53
No. of paracetamol injections (POD1)	2.21±0.64	2.12±0.58
Total rescue analgesic requirement (mg)	13.56±6.63	11.82±5.41
ASA physical status(I/II)	34/12	35/13
Duration of surgery inminutes	47.43±521	46.5±6.20

Regarding demographics, length of anesthesia, total fentanyl intraoperative dose, total rescue analgesic demand (tramadol), and paracetamol required on the first postoperative day, there were no statistically significant differences. The length of surgery and the ASA physical status of groups A and B were determined to be non-statistically significant. The VAS (median ± interquartile range), was significantly lower in **the** B group for the first 4 postoperative hours. **The time** to **the** first analgesic requirement was significantly longer in **the** B group **Side effects** did not vary significantly between the groups except for sedation, which was greater in **the** B group.

DISCUSSION

Flupirtine maleate is a water-soluble substance that is quickly absorbed in the stomach and has a 90% bioavailability when taken orally. In roughly 1.62 hours, it reaches a peak plasma concentration of 0.82 mg/L.[11] **Hummel et al.1991**[12] in their study observed the dose-related analgesic effect of flupirtine and concluded that it has a dose-dependent analgesic effect. It did not work in a linear fashion for the 100–400 mg therapeutic effect range. The therapeutic dose of 200 mg of the medication used in this trial had the greatest analgesic benefit while having little sedation-related adverse effects.

The goal of the current study was to ascertain whether flupirtine, used as a preventive analgesic, could reduce post-operative pain and the need for rescue analgesics in patients having laparoscopic procedures done while under general anesthesia. It is a chemical that dissolves in water and absorbs quickly in the stomach. Peak plasma concentration is reached after oral dosing in roughly two hours.[13]

In the study conducted by **Yadav et al., 2015**[14] Flupirtine provided adequate pain relief during the immediate postoperative period. The single dosage of flupirtine had no effect on the total 24-hour analgesic requirement because of its 6–8-hour duration of action. The first 24 hours also saw the occurrence of adverse effects, including sedation, sleepiness, dizziness, muscle tremor, itching, dry mouth, nausea, and vomiting, but none of these were statistically significant in either group.

In a comparative study done by **Mishra R et al.2016**[15] 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 the early postoperative period, however, the sedation score was never more than four. **Singh TH et al.2014**[16] compared two different doses of Pregabalin (150 and 300 mg) with placebo for post-cholecystectomy pain relief and observed higher sedation in the 300 mg Pregabalin group when compared to the 150 mg Pregabalin and placebo group. In a study done by **Ali A et al.2012**[17] comparing the preoperative dose of Pregabalin with Celecoxib for attenuation of postoperative pain after open cholecystectomy, it was observed that the frequency and severity of sedation were higher in the Pregabalin group in the initial 12 hours but later no significant differences were observed between the groups.

Flupirtine differs from other popular analgesics in that it functions as an oxidizing agent at the redox site of NMDA 9 receptors and a selective opener at potassium channels.[18] **Moore et al.1983**[19] compared flupirtine with dihydrocodeine in patients undergoing hysterectomy and found equal postoperative pain 10 relief and patient satisfaction.

This study found that giving patients having laparoscopic cholecystectomy 200 mg of flupirtine orally two hours before to surgery has a preventive analgesic effect. This study also demonstrates that giving analgesics before to surgery will guarantee proper drug distribution and absorption at the surgical site by the time the patient awakens from general anesthesia. This is supported by the finding that, in contrast to group P's greater VAS scores in the early postoperative period, patients who received flupirtine before to the surgical stimulus had lower VAS scores throughout the first four hours of the postoperative period. Flupirtine's superior preemptive analgesic efficacy was further supported by group F's lower need for rescue analgesics in comparison to group P.

S.M Abrams et al.1988[20] stated that flupirtine when given orally, attained peak plasma concentration at 1.5 to 2 hours and the analgesic effects lasted for 6.5 to 8 hours. Therefore, it is likely that flupirtine reached its highest plasma concentration in our trial during the intraoperative phase and offered sufficient analgesia at that time. Stable vitals that were recorded up until the early postoperative phase were indicative of this. However, in the late postoperative phase, there was little statistically meaningful change observed. Patients in group B required a longer period of time to receive rescue analgesia. It was comparable to studies done by **Vanitha Ahuja 2015**[21] and **Ambarish sharma2015**[22]. **Vanitha Ahuja et al.2015**[21] conducted a study to compare the pre-emptive analgesic effect of 100 mg of flupirtine with ibuprofen in gynecological ambulatory surgeries. Their study showed VNRS score was lower in 2nd hour of the postoperative period in flupirtine groups. **Ambrish Sharma et al.2015**[22] conducted a study to compare the analgesic effect of flupirtine with piroxicam in low backache patients. Their study revealed flupirtine has an analgesic effect similar to piroxicam with better tolerability.

CONCLUSION:

Giving 200 mg of flupirtine orally Painkillers that are administered two hours before a laparoscopic cholecystectomy work better than placebos in terms of reducing pain in the early postoperative phase. Because flupirtine doesn't have the negative consequences of repeated administration, its analgesic impact from a single dose is more tolerable. Without changing intraoperative hemodynamics, flupirtine can be utilized as a preventive analgesic with effective prolonging of analgesia in the early postoperative phase during laparoscopic procedures. A pleasant patient who complies with instructions in the post-operative phase is made possible by the medication's little sedative impact. Apart from a rare but statistically insignificant frequency of nausea and vomiting, there were no notable side effects associated with this medication.

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