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Preemptive Flupirtine in Patients Undergoing Laparoscopic Cholecystectomy for Postoperative Pain Management.

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ABSTRACT

Background: Postoperative pain after laparoscopic surgery limits the function and mobility of patients in postoperative period. Aim: The aim of present study is to study Flupirtine regarding its efficacy as preemptive analgesic in elective laparoscopic surgeries. **Methods:** In this randomized prospective study 100 patients were divided into two groups. Group-F received two capsules of Oral Flupirtine 100 mg each and group- P received two multivitamin capsules(placebo) with sip of water 2 hour before the expected time of induction of anaesthesia. Time for requirement of first dose of rescue analgesic post operatively, VAS score and dose of rescue analgesic used in first 24 hours post operatively were assessed. **Results:** Group F had lower visual analogue score(VAS) score in comparison to P group. Time for requirement of first dose of rescue analgesic in P group was less compared to F group. Consumption of rescue analgesic was less in F group in comparison to P group. **Conclusion:** Flupirtine as preemptive analgesic produced prolonged postoperative analgesia compared to placebo.

Keywords: Cholelithiasis, Flupirtine, Laparoscopic Cholecystectomy.

INTRODUCTION

Pain is defined by International Association for Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage.[1] Prevention and treatment of postoperative pain continues to be a major challenge in postoperative care and plays an important role in the early mobilization and well being of the surgical patient.Untreated post operative pain is a major health issue and has deleterious effect on morbidity, increased hospital stay and cost.Surgical stimulation leads to sensitization of dorsal horn neurons, which are associated with augmentation of pain.[2] The basic remedies for post operative analgesia are still confined to regional anaesthesia, opioids, non steroidal anti-inflammatory drugs(NSAIDS) and local anaesthetics, but they are inevitably associated with risk of respiratory depression, emesis, itching, retention of urine and their actions may be short lived.[3]

Preemptive analgesia is an antinociceptive treatment that prevents establishment of altered central processing of different input which amplifies post operative pain and is thereby thought to consequently decrease the incidence of hyperalgesia and allodynia after surgery and is also effective in reducing chronic postoperative pain.[4]Different drugs has been tried as preemptive analgesia such as Diclofenac, Ketorolac, Ibuprofen, Fentanyl, Morphine, Pregabaline, Gabapentine through systemic or oral route.[5] Flupirtine is a non-opiate, non NSAID, centrally acting analgesic and is unique as first in class of selective neuronal potassium channel opener that also has NMDA receptor antagonist properties.[6-7] It has been tried for chronic pain as well as acute postoperative pain.[8-11] Flupirtine may be a useful pre-emptive analgesic, as it does not have interaction with anaesthetic agents and side effects like respiratory depression & increased postoperative bleeding. Therefore, we undertook this study to evaluate the pre-emptive efficacy of Flupirtine in laparoscopic surgeries.

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MATERIALS AND METHODS

This prospective, randomized, double blind, placebo-controlled study, was carried out over a period of 2 years, from October 2014 to September 2016, after getting approvesd by institutional ethical committee. Total 100 patients, aged 18-60 years, of ASA physical status I&II, who were posted for elective laparoscopic surgery of anticipated duration

of one hour, were included in the study. Patients having history of liver, heart & kidney endocrinological, neurological & psychiatric diseases, pregnant patients and patients with anticipated difficult airway were excluded from study. In the preoperative chekup all patients were instructed about interpreting the visual analogue scale (VAS) for assessing pain. All patients were randomly assigned to Flupirtine group (F group) or the placebo group (P group) to receive either 2 Capsules of Flupirtine 100mg or physically similar 2 Capsules of Vitamin B complex, respectively. An anaesthesiologist, who was not the part of the study, administered two capsule to all the patients with sips of water 2 hour before surgery. Neither patients nor the observer was aware of the type of medications.The following parameters like Heart Rate, SPO2,Systolic, Diastolic blood pressure were recorded. A 18 G IV cannula was inserted and Inj glycopyrrolate 0.004 mg/kg body wt and inj midazolam 0.04mg/kg and inj fentanyl 2 mcg/kg was given. Preoxygenation with 100% oxygen for 3 minutes was done. Induction was done with inj propofol (2mg/kg iv). Intubation was facilitated by using inj vecuronium 0.1 mg/kg and appropriate sized cuffed endotracheal tube was used. Anaesthesia was maintained with 66%N2O in oxygen plus isofurane 1-2%.Depth of anaesthesia was monitored with BIS monitor & it was maintained between 40-50. Inj ondansetron 0.08 mg/kg was given approximately 30mins before the end of surgery. At the end of surgery reversal was done with inj neostigmine & inj glycopyrrolate and all the patients were shifted to post operative care unit.

On arrival in PACU patient were observed every hourly till 6hours, then 2hourly up to 12 hour, then 6hourly upto 24hour.Pain was assessed using visual analogue scale (VAS) score from 0-10, where 0- no pain, 10-worst imaginable pain.[12] For any pain complaints (VAS score >3), a dose of 1g paracetamol IV was given , with the shortest interval of at least 4 h between each dose. Time of 1st analgesic requirement and number of patient requiring rescue analgesia were noted. Sedation was assessed using the Modified Ramsay sedation score.[13]1 - patient is anxious and agitated or restless, or both,2 - patient is co-operative, 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. Any side effects(nausea,vomiting,dizziness,muscle tremor,pruritus) occurred during 1st postoperative 24hour was noted.Primary outcome was the severity of post operative 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.

After conducting the whole study, the data were tabulated.Data entry was done using MS Excel 2007 computer software.Numerical variable were presented as mean ± SD (Standard Deviation), median ± IQR (Interquartile Range), score were compared with Man Whitney U test. Chi x2 was used to compare categorical variables. The package SPSS 16.0 (SPSS Inc, Chicago, IL) and Graphpad instate was used for statistical analysis. Median± IQR of VAS & sedation score were compared with Man Whitney U test. Chi x2 was used to compare percentage of patient who required rescue analgesia and occurrence of side effects. $P < 0.05$ was considered significant & $p< 0.001$ and less was considered as statistically highly significant.

RESULTS

The difference between demographic profile like age, sex, weight ,ASA physical status and duration of surgery between group P and group F were found to be not statistically significant. [Table 1]

There was no statistically significant difference between heart rates and mean blood pressure at different time intervals during the intraoperative period between the two groups.[Figure 1 & 2]

Table 1: Patient Demography.

	Group F (mean± SD)	Group P (mean± SD)	P Value
Age in years	41.24±9.17	41±7.35	0.9
Sex (Female:Male)	30:20	27:23	0.54
Weight in Kg	50.9±9.52	53.16±8.09	0.20
ASA physical status(I/II)	36/14	35/15	0.82
Duration of surgery in minutes	53.53±6.25	52.5±8.81	0.82

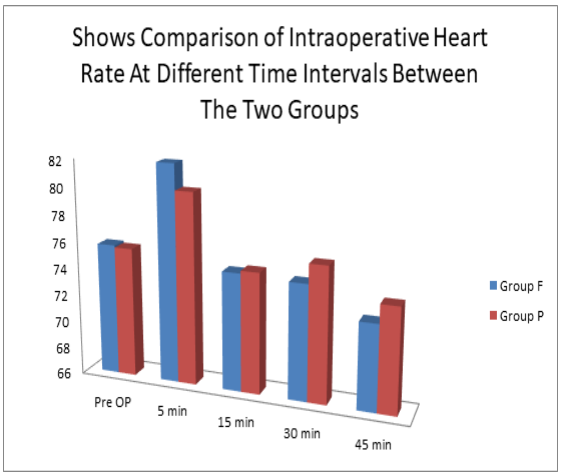

Figure 1: Comparison of Intraoperative Heart Rate at different time intervals between the two groups.

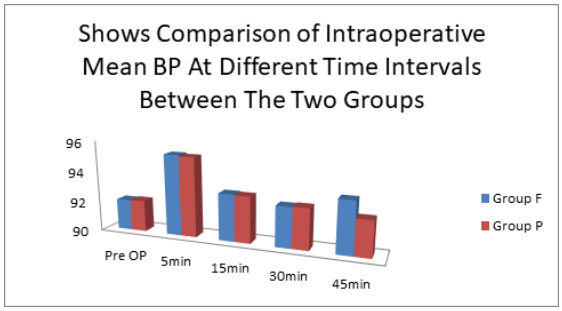

Figure 2: Comparison of Intraoperative BP at different time intervals between the two groups.

There was significant difference between the time of first analgesic requirement between group F and group P(p value <0.05). In group F the mean time of first analgesic requirement was about 123 minutes after surgery, whereas in group P the mean time of first analgesic requirement was about 24 minutes after surgery.[Figure 3]

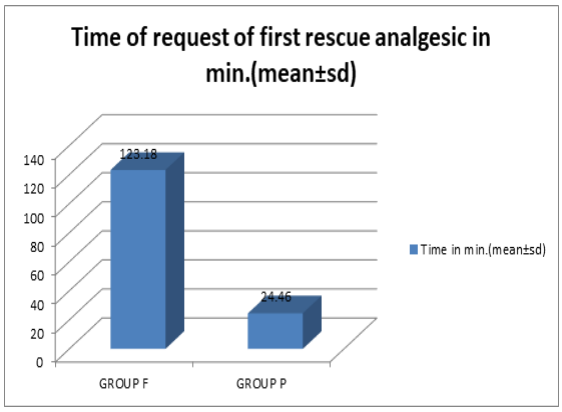

Figure 3: Time of Request of first rescue analgesic in minute.

The VAS on arrival in PACU, at 1st and 2nd hours was significantly low in Flupirtine group when compared to control group (P<0.05) and thereafter there was no statistically significant difference in VAS between the group.[Figure 4]

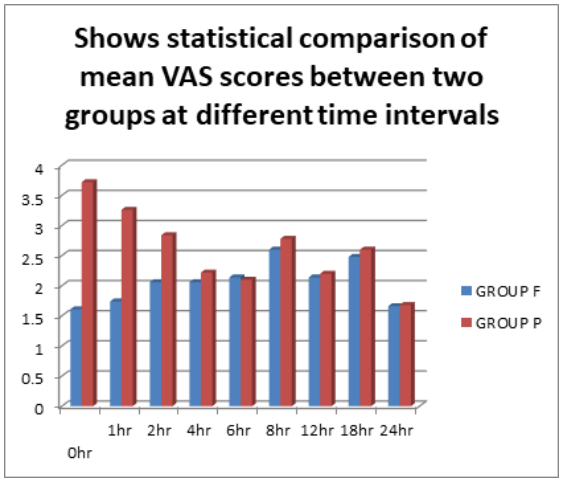

Figure 4: Statistical Comparison of Mean VAS scores between two groups at different time intervals.

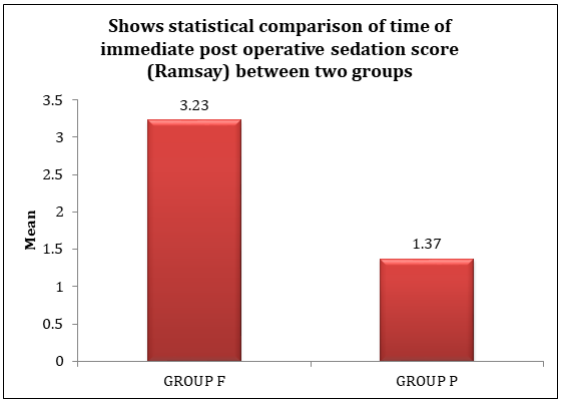

Figure 5: Statistical comparison of time of immediate post operative sedation score between two groups.

Patients of group F were more sedated than patients of group P during the immediate postoperative period. There was statistically significant difference between the two groups [Figure 5].

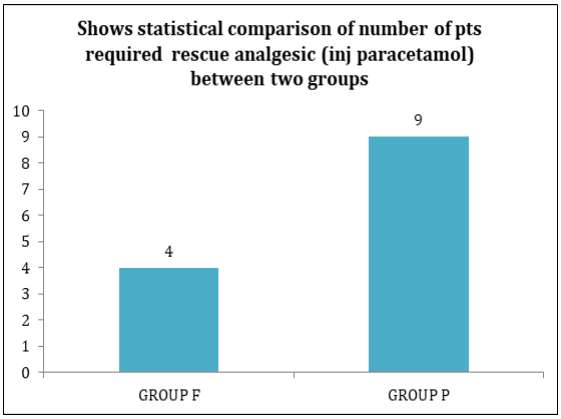

Figure 6: Statistical Comaprison of number of patients required rescue analgesic between two groups.

In the group F, no of rescue analgesic requirement was low compared to Group P which was statistically significant. [Figure 6]

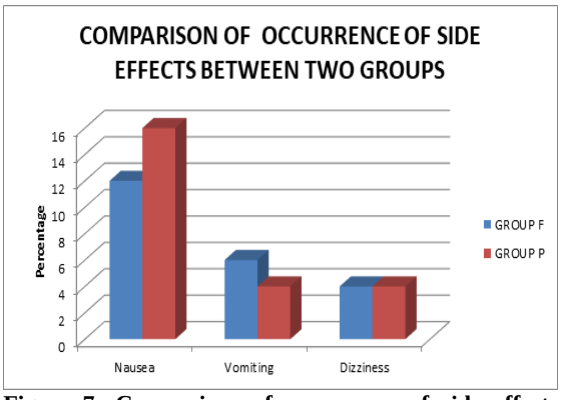

Figure 7: Comparison of occurrence of side effects between two groups.

In both the groups there was no significant difference in the occurrence of side effects (nausea, vomiting, dizziness, muscle tremor and pruritus) [Figure 7].

DISCUSSION

The present study was undertaken to determine the effect of Flupirtine as preemptive analgesic to decrease post operative pain and rescue analgesic requirement in patients undergoing laparoscopic surgeries under general anaesthesia. It is water soluble compound with rapid gastric absorption. After oral administration peak plasma concentration is achieved in about 2 hrs.[14] Previous studies have shown that Flupirtine 200mg had better analgesic properties with insignificant side effects.[15-19] So we have used a therapeutic dose of Flupirtine (200mg) for maximum therapeutic analgesia. Intraoperative mean heart rate and mean arterial pressure was comparable in both the groups. The post operative assessment was done soon after the patient was shifted to the post anaesthesia care unit. VAS scores was recorded in the scale of 0-10 at rest ,at intervals of 1hr,2hr,4 hr,6hr,8hr,12hr, then 6 hourly till 24 hours post operative period. Heart rate and mean arterial pressure (MAP) were also recorded in postoperative period.Mean heart rate and mean MAP values did not show any statistical significant difference between two groups in postoperative period. Pain was recorded in PACU on a visual analogue score (VAS) at rest. During the first two hours there was a significant difference found between the two groups ,with Flupirtine group having significantly less VAS scores ($p<0.05$) on first two hours. After 2 hours there was no significant difference between the two groups. The above result was similar to the study conducted by Yadav et al. There was a significant difference of time of first analgesic requirement between the Flupirtine group and placebo group. In the Flupirtine group the mean time of first analgesic requirement was about 123±28 minutes but in placebo group the mean time of first analgesic requirement was about 24±16 mins.The above result was similar to the study conducted by Malik et al in gynaecological laparoscopic surgeries.[21]

Total rescue analgesic requirement in 1st 24 hour (no of Paracetamol 1gm injection) was similar in both the groups.There was no significant difference between the two groups.The above result was similar to study conducted by Yadav et al.[20] Flupirtine provided adequate pain relief during the immediate postoperative period. As it has duration of action of 6-8 hrs, single dose of Flupirtine did not affect the total 24hour analgesic requirement. The side effects (sedation, drowsiness, dizziness, muscle tremor, pruritus, dry mouth, nausea, vomiting) were also recorded in first 24 hours but it was not significant in either group.

Sedation of the patients was assessed using modified Ramsay sedation scores. Patients of Flupirtine group were found to be significantly more sedated than patient in the placebo group just immediately after surgery.Similar findings was observed in study conducted by Malik et al.[21] In our study patients were more sedated in Flupirtine group as compared to control group, that might be due to synergistic interaction between Flupirtine and opioid (fentanyl) used intra-operatively.[21]

Yadav et al in his study opined that Flupirtin is as effective as diclofenac sodium in post craniotomy pain.[22] Ahuja et al in their study concluded that Flupirtin is as equally potent as ibuprofen.[23] Thapa et al in their study concluded that preoperative Flupirtine reduced the postoperative requirement of morphine in patients undergoing total abdominal hysterectomy.In our study requirement of paracetamol was reduced postoperatively. [24]

The limitation of our study was that we have not measured plasma flupirtine level.

CONCLUSION

Flupirtine can be used as preemptive analgesic with effective prolongation of analgesia in immediate post-operative period in laparoscopic surgeries without altering the intraoperative hemodynamics.

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