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A Prospective Randomised Controlled Study of Pre-Emptive Oral Flupirtine on Postoperative Analgesia in Patients Undergoing Abdominal Surgeries Under General Anesthesia

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Abstract

Introduction: Flupirtine is non-opioid, non-NSAID, centrally acting indirect NMDA receptor antagonist. It's analgesic effect is equivalent to NSAIDs and opioids with devoid of their side effects. Abdominal surgeries are the most painful surgeries amongst the surgical procedures. *Aim:* To evaluate the pre-emptive analgesic effect of flupirtine for postoperative pain relief in patients undergoing abdominal surgeries. *Methods:* 60 patients of either sex posted for elective abdominal surgeries were included in this study. These patients were aged between 18 and 60 years with ASA physical status I and II. They were randomly divided into two groups, named group A and group B. Patients in group A received 2 oral placebo capsules and group B patients received 2 flupirtine 100 mg capsules orally. Both drugs were administered two hours before the surgery. All patients underwent abdominal surgeries under general anesthesia. In the postoperative period patients were assessed for the intensity of pain using Numerical rating scale, Time to first rescue analgesia, Ramsay sedation score and side effects in the first 24 hours postoperative period. If NRS score ≥ 4, rescue analgesic tramadol 50 mg iv was given at 6 hours interval. *Results:* The mean NRS score was significantly decreased (p = 0.00) in group B patients for the first 3 hours. The time to first rescue analgesia was significantly high (p = 0.00) in group B patients. 60% of patients in group A received rescue analgesia in the first hour of the postoperative period. The mean RSS score was high in group B patients in the first 3 to 5 hours. The side effects were less in both groups. *Conclusion:* This study concludes that pre-emptive administration of oral flupirtine 200 mg provides effective analgesia in the first 2 to 3 hours of the postoperative period in patients undergoing abdominal surgeries with mild to moderate sedation.

Keywords: Pre-emptive analgesia; Flupirtine; Abdominal surgeries.

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Introduction

Pain from surgery occurs as a result of tissue trauma and results in physical and psychological discomfort to the patients. There is a relationship between perioperative tissue damage and postoperative pain.[1] Acute and sustained release of chemical mediators during perioperative period leads to central sensitization. This causes acute pain to become chronic pain. Avoiding the central sensitisation will help in decreasing the intensity of acute pain and in preventing this acute pain from becoming chronic.[2] Pre-emptive analgesia is a treatment strategy that starts before the surgery

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to prevent the establishment of central sensitization due to incisional and inflammatory injuries. The concept of pre-emptive analgesia was practiced by George Washington Crile in the early 1900s. He stated that trauma caused by surgery produced a "shock and exhaustion" to the central nervous system. Washington Crile advocated pre-incisional local anaesthetic infiltrations combined with general anesthesia. By this way noxious stimuli were prevented from reaching the brain.[3]

A wide range of medications have been examined for their possible pre-emptive 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 non-opioid, non-NSAID, 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 pre-emptive analgesic has not been the primary stand point in any trial.[6]

Abdominal surgeries are the most painful procedures amongst surgical procedures.[7] Pain is a uniquely individual experience and subjective. Patients who undergo abdominal surgeries will have hypoventilation, due to pain from the surgical incision. This hypoventilation in turn will lead to postoperative hypoxia and result in increased morbidity.

Aim

To Study the Efficacy of Pre-Emptive Oral Flupirtine on Postoperative Analgesia in Patients Undergoing Abdominal Surgeries under General Anesthesia

Materials and Methods

This Prospective randomized controlled study was conducted between June 2015 and May 2016 in the Department of Anaesthesiology, in a medical college in South India. The study was approved by the institutional ethical committee. Sixty patients scheduled for abdominal surgeries were included in this study. After getting departmental approval and informed written consent from study patients, this study was started.

Inclusion criteria

1. Patients aged between 18–60 years of either sex with weight 50 to 90 kg
2. American Society of Anaesthesiologist physical status I and II
3. Patient scheduled for elective abdominal surgeries

Exclusion criteria

1. Consent not given
2. History of drug allergy
3. Chronic alcoholism
4. History of psychiatric disorder
5. History of analgesic or opioid usage within one month
6. Pregnancy
7. Liver and renal dysfunction

All patients were nil per oral for 8 hours before the procedure. Aspiration prophylaxis was followed with Injection ranitidine 50 mg iv plus Injection metoclopramide 10 mg IM in all patients. 60 patients posted for abdominal surgeries under general anaesthesia were divided into two groups, 30 patients in each group. When patients arrived in the pre-anaesthetic room all patients were explained about the interpretation of the numerical rating scale (NRS) to assess the postoperative pain intensity. 18 gauge venflon was started. A maintenance fluid Ringer Lactate/ Normal Saline at 100 ml /hr. was given. In the pre-anesthetic room, baseline pulse rate, blood pressure and oxygen saturation were recorded. Then patients in Group A received 2 placebo capsules resembling flupirtine 2 hours before surgery. Patients in Group B received 2 capsules of 100 mg flupirtine 2 hours before surgery. Both groups of patients were monitored with pulse oximetry for pulse rate and oxygen saturation at 15 minutes interval for 2 hours, until being shifted to the operating room. Injection Glycopyrrolate 5 mcg/ kg, injection Midazolam 0.03 mg/kg and injection Fentanyl 2 mcg/kg were given intravenously as premedication. Patients were preoxygenated with 6 l/min of 100% O2 through facemask for 5 mins. Patients were induced with injection Propofol 2 mg/kg IV. Intubation was facilitated with injection Vecuronium 0.1 mg/kg iv, then using direct laryngoscopy endotracheal intubation was done. Anaesthesia was maintained with oxygen and nitrous oxide in a concentration of 66%:33% ratio and sevoflurane at 1%. Injection vecuronium 0.02 mgkg/iv was repeated as the patient recovered from

relaxant effect. Injection Fentanyl 25 mcg iv was given if baseline blood pressure increased above 20%. After the procedure was completed, residual paralysis was reversed with injection Neostigmine 0.05 mg/kg and injection Glycopyrrolate 0.01 mg/kg iv. After achieving adequate recovery, the patient was extubated and shifted to the post anaesthesia care unit (PACU). In PACU, patients were monitored for postoperative pain using NRS score and sedation was assessed by using Ramsay sedation score. The data were analyzed using SPSS (Statistical Package for Social Science) software Version 16.01. The data collected were scored and analyzed, Continuous variables were presented as means with Standard deviation (sd). Categorical variables were presented as frequency and percentages. Student t-test was used for testing the significance of all the variables mean and standard deviation in groups. Chi-square test was used to compare proportions. All the Statistical results were considered significant at p value ≤ 0.05.

Results

Group A and Group B were comparable with respect to gender distribution. Males and females were equally distributed in both groups and statistically insignificant (p=0.61) (Table 1).

Maximum age in both groups was between 31 -40 years of age. Age was comparable in both groups with a p value of 0.86. In respect to weight group A and group B were comparable with each other (p=0.15). With respect to American society of anaesthesiologist physical status both groups were comparable. In both groups a maximum number of ASA 1 patients were included in this study. (Table 2).

The types of surgery performed in both groups were equally distributed in group A and group B. The most common surgery performed in both groups was incisional hernia repair under general anesthesia (Table 3).

Table 1: Gender Distribution

Gender	Group A		Group B		Total	
	Number of patients	%	Number of patients	%	N	%
Male	17	56.67%	15	50.00%	32	53.33%
Female	13	43.33%	15	50.00%	28	46.67%
Total	30	100%	30	100%	60	100%

Table 2: Age Distribution

Age (in years)	Group A		Group B	
	N	%	N	%
≤ 19	2	6.67%	2	6.67%
20–30	3	10.00%	6	20.00%
30–40	8	26.66%	11	36.67%
40–50	17	56.67%	6	20.00%
50–60	0	0%	5	16.67%
Total	30	100%	30	100%

Table 3: Type of Surgery

Surgery	Group A		Group B	
	N	%	N	%
Incisional Hernia	20	66.67%	19	63.34%
Para Umbilical Hernia	5	16.67%	6	20.00%
Appendectomy	4	13.33%	4	13.33%
Open Cholecystectomy	1	3.33%	1	3.33%
Total	30	100%	30	100%

Pulse rate and oxygen saturation were not significantly changed after giving the study drugs. The mean value of pulse rate after drug administration was graphed in a line diagram. No significant change in the pulse rate was observed after drug administration. There were no significant changes in pulse rate, systolic blood pressure and diastolic blood pressures in group B during the surgery and postoperative period. (Fig. 1).

Both groups were comparable in the duration of surgery. It was statistically not significant (p=0.71). The mean duration of surgery in group A and group B was 123.67 minutes and 121.17 minutes respectively (Fig. 2).

The mean numerical rating scale scores were initially lower in Group B patients than Group A for first 3 hours. Of these, the first 2 hours of postoperative analgesia were statistically significant. The mean value of NRS score in group B was initially less than three for the first 3 hours. Higher values were noted between the 4-6th hour of the postoperative period (Fig. 3).

Sixty percent of the patients in group A asked rescue analgesia in the first hour of the postoperative period. But only 3.3% of patients in group B asked rescue analgesia in the first hour. 81% (13% in the 2nd hour, 46% in a 3rd hour) of patients in group B required rescue analgesia after 3rd hour of the postoperative period. This difference was significant (Fig. 4).

There was a statistically significant change noted in Ramsay sedation score (RSS) for the first 5 hours of the postoperative period. The patients in the flupirtine group exhibited more sedation, but remained responsive to commands (Fig. 5).

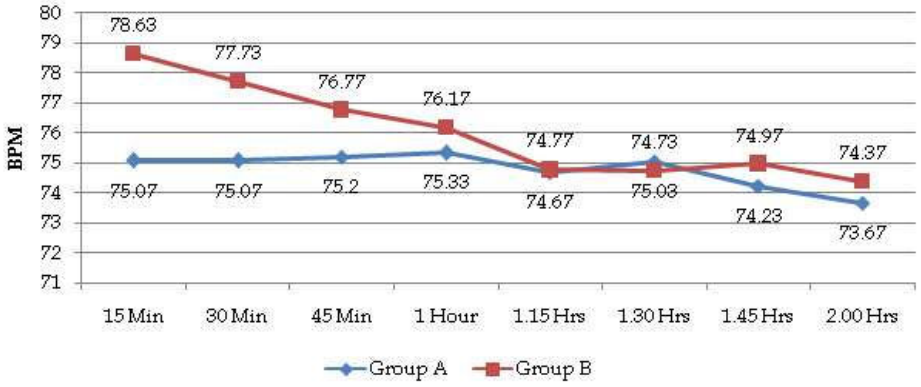

Fig. 1: Pulse Rate after Drug (Placebo/Flupirtine) Administration

Fig. 2: Duration of Surgery (in Minutes)

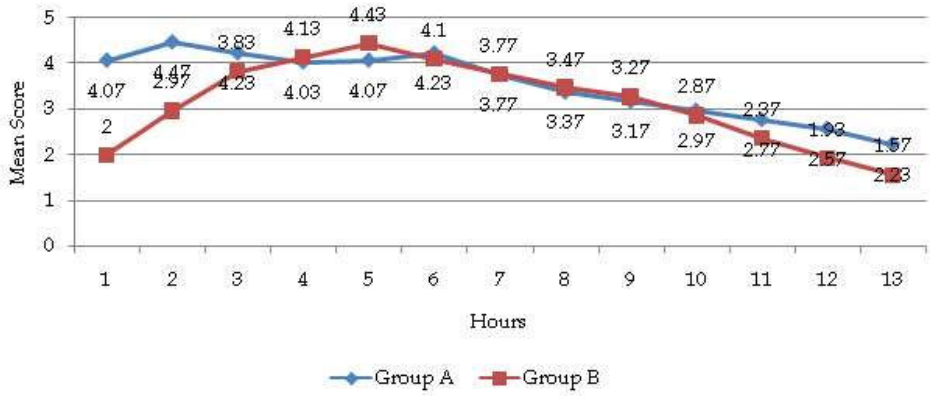

Fig. 3: Numerical Rating Scale

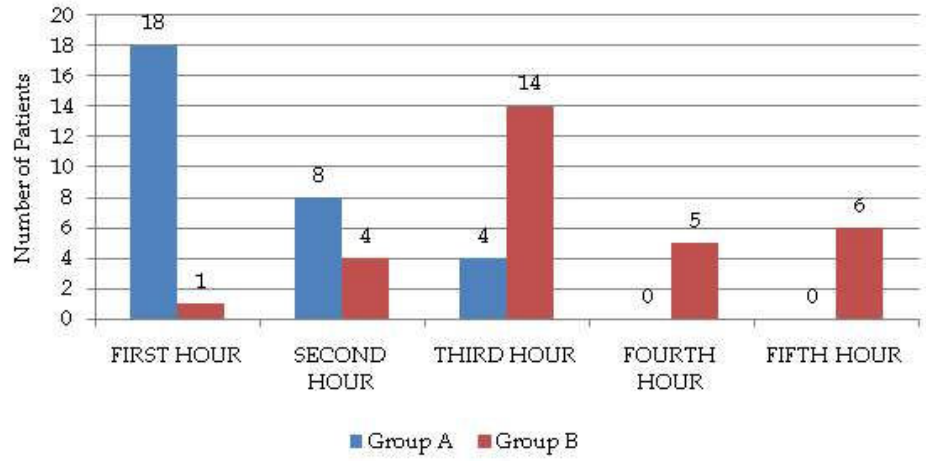

Fig. 4: Time to Rescue Analgesia

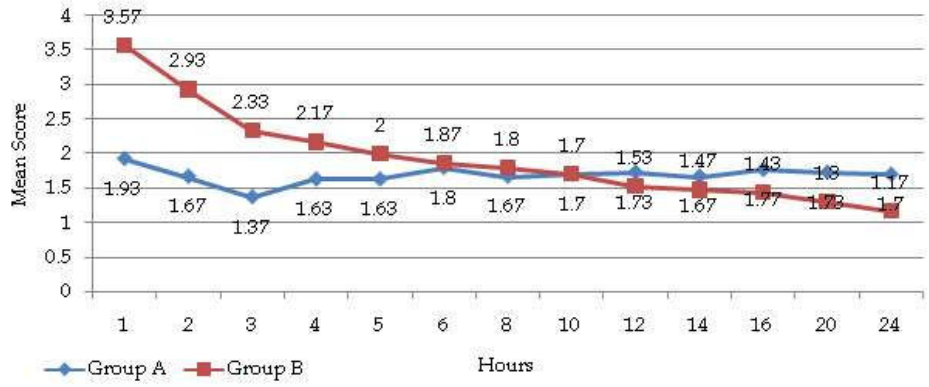

Fig. 5: Ramsay Sedation Scale

Table 4: Side Effects

Side Effects	Group A		Group B	
	No	%	No	%
Nil	29	96.67%	23	76.67%
Bradycardia	0	0%	1	3.33%
Retrosternal Discomfort	0	0%	1	3.33%
Nausea	0	0%	2	6.67%
Vomiting	1	3.33%	1	3.33%
Giddiness	0	0%	2	6.67%
Total	30	100%	30	100%

Seven patients in group B experienced side effects like bradycardia, retrosternal chest discomfort, nausea, vomiting and giddiness. Only one patient in group A experienced vomiting (Table 5).

Discussion

Pre-emptive analgesic modalities can be used as single or in combination. Many studies have been done to evaluate the pre-emptive analgesic effect of opioids and NSAIDs. Ong CK-S *et al.*[8] performed a meta-analysis and demonstrated that the ability of pre-emptive analgesic interventions to decrease the postoperative pain scores, prolong the time to first rescue analgesia and decrease postoperative opioid requirement. Using these measures pre-emptive analgesia showed a beneficial effect after epidural analgesia, local infiltration, and NSAIDs drug administration. Pre-incisional analgesic drug administration showed more effectiveness in decreasing the postoperative pain by protecting the CNS from noxious stimuli induced delirious effect, and which may lead to increased pain and hyperalgesia.

Flupirtine, an indirect acting NMDA receptor antagonist, has a beneficial effect in controlling acute and chronic pain like trauma, migraine, cancer pain and low backache. Its muscle relaxant and the neuroprotective effects are additionally beneficial.

In this study group A and group B patients were comparable with respect to gender distribution, age, weight, height, ASA physical status, types of surgery performed and duration of surgery. Flupirtine attained the peak plasma concentration in about 1.6 to 2 hours when given through oral route. Many studies showed that flupirtine analgesic effect was dose-dependent. Previous studies done with 200 mg flupirtine revealed effective analgesia in controlling postoperative pain in their studies. Further increase of flupirtine dose may lead to side effects like sedation, giddiness, drowsiness in the postoperative period so we choose 200 mg of oral flupirtine to achieve effective analgesia with fewer side effects.

In this study pre-emptively given oral flupirtine 200 mg provides effective analgesia for the first 2 to 3 hours of the postoperative period. Of these first 2 hours of postoperative analgesia were statistically significant (p<0.001, p<0.001). Thereafter a patient experienced only mild pain for the entire postoperative period. This is most convincingly shown by the numerical rating scale score as it was initially low in the first 3 hours of the postoperative period. After that the numerical rating scale score, has shown lower values in the study group than the control group for the remaining postoperative period. Patients were followed up for 24 hours postoperatively. S.M. Abrams *et al.*[9] stated that, flupirtine when given orally, it attained peak plasma concentration at 1.5 to 2 hours and the analgesic effects lasted for 6.5 to 8 hours. Hence it is assumed that, in our study flupirtine attained peak plasma concentration during the intraoperative period and provided adequate analgesia during that period. This was indicated by stable vitals which were noted, till the early postoperative period. But there was not much statistically significant difference noted in the late postoperative period. The time to first rescue analgesia was longer in duration in group B patients (p=0.00). It was comparable to studies done by Vanitha Ahuja and Ambarish Sharma. Ahuja V *et al.*[10] conducted a study to compare the pre-emptive analgesic effect of 100 mg of flupirtine with ibuprofen in gynaecological ambulatory surgeries. Their study showed VNRS score was lower in the 2nd hour of the postoperative period in flupirtine groups. Ambrish Sharma *et al.*[11] 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 the piroxicam with better tolerability.

In this study Ramsay sedation score was statistically significant in the first 5 hours of postoperative period (p=0.00, p=0.00, p=0.00, p=0.01 and p=0.04). The mean value of RSS for the first five hours in group B patients were 3.57, 2.93, 2.33,2.17 and 2.0 respectively. The mean value of RSS in group A patients were 1.93, 1.67, 1.37, 1.63 and 1.63 respectively. Patients in group B experienced mild to moderate sedation in the first 3 hours of the postoperative period. Yadav G *et al.*[12] conducted a study to assess the pre-emptive analgesic effect of flupirtine in patients undergoing laparoscopic cholecystectomy. They showed that flupirtine effectively controlled postoperative pain in the first 4 hours of postoperative period,

with higher sedation in flupirtine groups. Yadav G *et al.*[12] done a study in post-craniotomy patients to compare the analgesic effect of flupirtine with diclofenac sodium. Their study showed flupirtine provided analgesia which is equivalent to that of diclofenac sodium, with moderate sedation. But in our study, patients in the study group experienced mild to moderate sedation in the first 3 hours of the postoperative period. In the entire study period, all patients in group A and group B maintained oxygen saturation above 96%. There was no incidence of hypoxia noted in the study period.

Even though the side effects were not statistically significant in this study, 23.3% of group B patients experienced few side effects which include nausea, giddiness, vomiting, retrosternal discomfort and bradycardia. Of this nausea and giddiness were frequently experienced. In contrast, only one patient had vomited in the control group.

Conclusion

This study concludes that pre-emptive administration of oral flupirtine 200 mg provides effective analgesia in the first 2 to 3 hours of the postoperative period in patients undergoing abdominal surgeries with mild to moderate sedation effects. Thereby it prevents pulmonary complications also.

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