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Original Research Article

# Efficacy of flupirtine maleate as pre-emptive analgesic

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## Abstract

**Introduction and Aim:** Post-surgical pain treated with NSAIDs and opioids is associated with many adverse effects and poor patient satisfaction. Our aim was to study the effect of oral Flupirtine (200mg), as a pre-emptive analgesic in maxillo-facial surgeries.

**Materials and Methods:** A total of 60 patients between 18-60 years, ASA I and II, scheduled for maxillo-facial surgeries were randomised to receive orally Flupirtine maleate capsule (200mg) or Vitamin B complex capsule 2 hrs prior to surgery under general anaesthesia. The severity grading of post operative pain and time taken for first analgesic dose requirement in the post operative period was measured using Visual Analogue Score (VAS) as the primary outcome. Sedation and adverse effects of Flupirtine, if any were studied as the secondary outcome.

**Results:** Significant delay in demand for first postoperative analgesic dose was observed in the Flupirtine group. After the first four hours of postoperative period, we did not observe any difference in the analgesic demand between the two study groups. There was no significant sedation or adverse effects in the Flupirtine group. In addition, it was observed that hemodynamic response to intubation was significantly attenuated in the Flupirtine group.

**Conclusion:** Oral Flupirtine maleate is a good pre-emptive analgesic devoid of any side-effects in maxillo-facial surgeries with significant attenuation of intubation response.

## Introduction

Post operative pain following maxillo-facial fracture surgeries/injuries is very distressing to the patient and a major concern. Management of this pain with opioids and NSAIDs in post operative period has many adverse effects such as respiratory depression, sedation and gastropathy, hence leading to suboptimal dosing, higher post operative pain, poor patient satisfaction, delayed recovery and prolonged hospitalisation. Flupirtine, a centrally acting drug has been used as an anxiolytic and preemptive analgesic in some studies. We hypothesised that Flupirtine would reduce postoperative pain of facio –maxillary surgeries and hence analgesic requirement.

## Materials and Methods

We conducted a prospective study on adult patients of 20-60 years, ASA I and II class with body mass index (BMI) range of 20-30 kg/m², posted for elective surgeries for maxillo-facial injuries. Prior approval from the ethics committee of our institute and written consent from all the patients were obtained. During the period of our study, all the patients posted for surgery were male, hence only male patients were enrolled and randomly allocated to two groups. This maybe because males were more frequently involved in two wheeler road traffic accidents.

Excluded from the study are patients with history of psychiatry disorder or on anti-psychotic drugs, on oral anticoagulants, anti epileptics drugs or opioids; those with alcohol abuse; smoking habit; chronic pain and drug allergies.

After a routine Pre anaesthetic evaluation the day before surgery, all patients were randomised to two groups- Control group to receive placebo oral premedication with capsules of Vitamin B complex and Flupirtine group to receive Flupirtine Maleate capsule 200 mg, 2 hrs before planned surgery. The capsules were given to the patients by the anaesthesia postgraduate who was not part of the study. As neither the patient nor the observer (junior resident) were aware of the contents of capsule given, the study was double blinded. Haemodynamic parameters were monitored using multichannel monitor. Peripheral IV access was secured with 18 G cannula. Fentanyl 2mcg/kg was given for analgesia intraoperatively. Other premedication was avoided. All patients in both groups were given General Anaesthesia with oral endotracheal intubation using Propofol (2mg/kg) and 0.1 mg/kg Vecuronium. Isoflurane (1 MAC) based inhalational anaesthesia with Oxygen-Nitrous oxide was given for maintenance along with top-ups of Vecuronium (0.02mg/kg) if necessary. At the end of procedure, after ensuring good muscle power following

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reversal, all patients could be extubated. In the postoperative recovery room, parameters assessed were postoperative pain, request for analgesics and degree of sedation. Side effects like postoperative nausea and vomiting (PONV) and others, if any were recorded. The observations were recorded at 0,1,2,4,6,12,24 hours. Patients complaining of post-operative pain were assessed by Visual Analogue Scale score (11 point VAS) where 0 implied pain free status and 10 implied worst imaginable pain. The first analgesic was administered when the VAS score was more than 4 and the time was noted. IV Tramadol 50 mg was given, followed by repetitions every 6 hrs if required. Ramsay Sedation Score (RSS) (Table 1) was used for assessing sedation. Post-operative nausea and vomiting were assessed by Apfel's four- point scale[1] (Table 2). Ondansetron (0.1 mg/kg) was used as anti- emetic.

Other adverse effects such as respiratory depression, hypotension and allergic reactions were monitored.

Observations made with VAS score for pain assessment before the study required minimum 26 patients in each group. We included 30 patients to compensate for drop-outs. Statistical methods applied were descriptive statistics (mean, standard deviation, percentage) and inferential statistics. Comparison between two groups was done with Independent samples T test and ANOVA used for analysing groups of related dependent variables that represent different measurements of the same attribute (within-subject factors). p value less than 0.05 was considered statistically significant.

## Results

All the patients enrolled completed the study with no drop-outs. There was no statistical difference in the age, ASA status, BMI, duration of surgery (Table 3) among the patients.

Flupirtine had significant effects on the intra operative hemodynamic parameters immediately post intubation. Heart rate, SBP and MAP were significantly lower in the Flupirtine group compared to the control group (p value-0.000) (Fig. 1,2,4) indicating a good attenuation to intubation response. However, there was not much change in DBP (Fig. 3).

In the first four hours of the post operative period, lower VAS scores (<4) were observed in the Flupirtine group compared to the Control group (p value-0.000) (Fig. 5). Hence, time for first analgesic requirement in the post operative period in the Flupirtine group was delayed. No significant postoperative sedation (assessed by RSS Score) was seen in both the groups.

**Table 1:** Ramsay sedation score

| Score | Signs and symptoms |
|---|---|
| 1 | Patient anxious, agitated or restless or both |
| 2 | Patient cooperative, 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. |

**Table 2:** Four point scale: Severity of post-operative nausea and vomiting

| Point | Symptoms |
|---|---|
| 1 | No PONV (absence of nausea or emesis) |
| 2 | Mild PONV (Mild nausea or one emetic episode lasting less than 10 min, no requirement of antiemetic |
| 3 | Moderate PONV (1-2 episodes of emesis, antiemetic required) |
| 4 | Severe PONV (> 2 episodes of emesis, > 1 antiemetic required) |

**Table 3**

| S. No. | Data | Control group | Flupirtine group | P value |
|---|---|---|---|---|
| 1 | Age (Yrs) | 38.8 | 36.56 | .424 |
| 2 | BMI (Kg/M2) | 23.89 | 23.36 | .284 |
| 3 | ASA I and II Status (No.) | 30 | 30 | -(Constant) |
| 4 | Total Intraop Fentanyl used (MCG) | 130 | 122.41 | .030 |
| 5 | Duration of Anaesthesia (Hrs) | 99.21 | 99.20 | .182 |
| 6 | Time to first rescue analgesic dose (Hrs) | 2.26 | 5.79 | .000 |

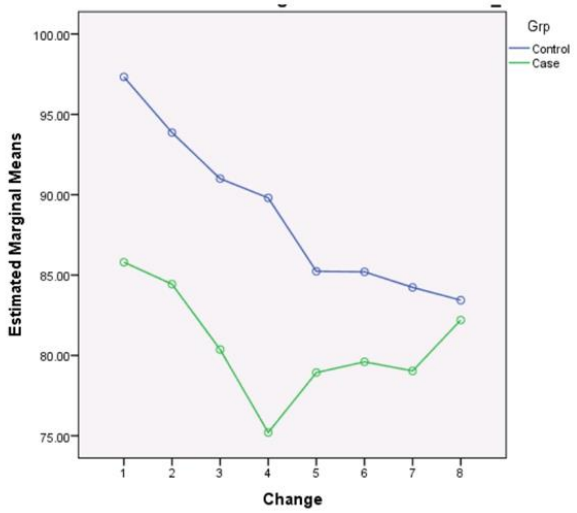


**Fig. 1:** IOP HR

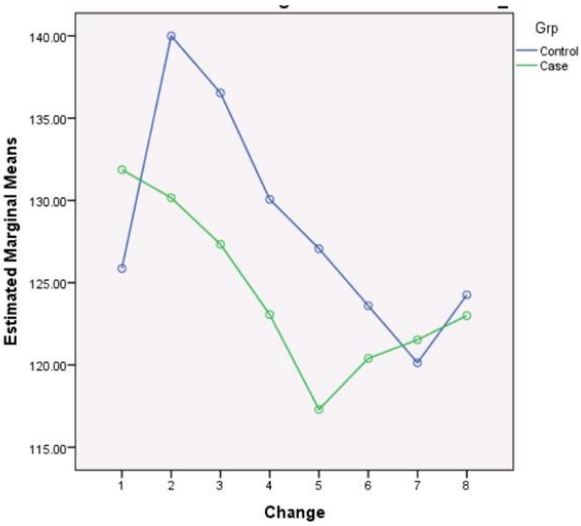


**Fig. 2:** IOP SBP

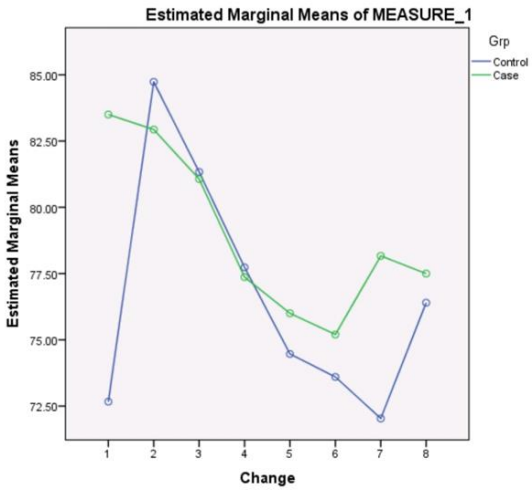


**Fig. 3:** IOP DBP

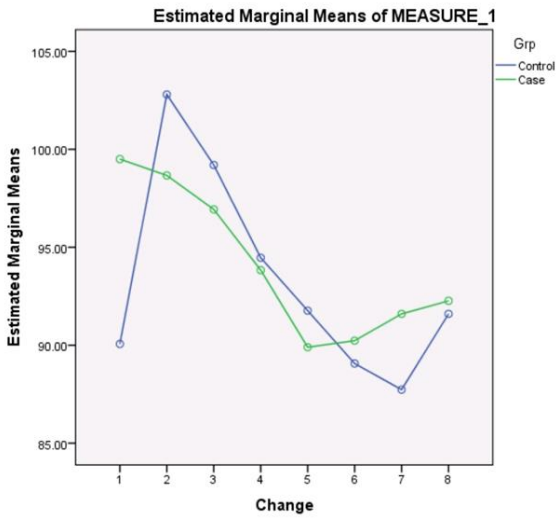


**Fig. 4:** IOP MAP

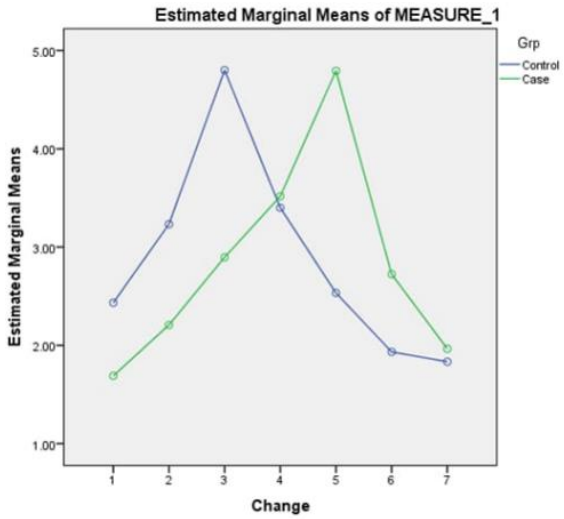


**Fig. 5:** Visual analogue scale (VAS)

## Discussion

Pre operatively administered Flupirtine has shown a significant effect in reducing the intensity and post operative analgesic requirement following facio-maxillary surgeries in our study. Lower VAS scores in patients who received Flupirtine prove the analgesic sparing effect of Flupirtine. The intra operative analgesia was adequate and did not require further supplementation in patients receiving Flupirtine. The hemodynamic response to intubation was also found to be attenuated in the group that received Flupirtine. No other study on Flupirtine as pre-emptive analgesic has documented this additional advantage. There were no major hemodynamic changes in the Flupirtine group intraoperatively. No significant postoperative sedation and adverse effects were observed.

The noxious painful stimuli (from the surgical site) are conducted to the dorsal horn of the spinal cord by the myelinated A∂ nociceptors in the peripheral free nerve

endings triggering a rapid first pain response. Unmyelinated C nociceptors result in a latent burning pain response, second pain.[2] Peripheral tissue damage also releases substances such as prostaglandins, histamine, serotonin, substance P and bradykinins from peripheral nerve endings and extraneural sources. They cause amplification of central nociception which may outlast the initial stimuli and thus become a 'pain memory'. This central sensitization can be prevented by Pre-emptive analgesia which may be more effective than a similar analgesic treatment started in the post operative period.[3,4] Several opioids and NSAID s have been tried for their possible pre-emptive analgesic effects.[5-8]

Flupirtine maleate, is a centrally acting analgesic due to selective opening of neuronal potassium channels and is also an anxiolytic.[9,10] It inhibits pain pathways by its action as an indirect antagonist at N- methyl- D-aspartate (NMDA) receptor and by inhibiting the opening of NMDA channel resulting in hyperpolarization of the neuronal membrane and reduction of its excitability. It is hydrophilic, has oral bio-availability of 90%, attaining peak plasma levels in 1.6-2 hrs, metabolised in liver and most of it is excreted in urine. Adverse effects seen commonly with opioids and NSAIDs usage[5-8] are not seen with Flupirtine maleate.

Several studies have used 100 mg Flupirtine as a single dose[11-13] and multiple doses[14] also. Whereas Yadav G et al[15] have used single dose of 200 mg of Flupirtine for studying the pre-emptive effects in laparoscopic cholecystectomy patients. Hence, our patients were given the single dose of 200 mg, 2hrs before surgery. Common side effects of continued use of Flupirtine such as nausea, vomiting, headache, disorientation and hallucinations were not seen in our patients since only a single dose was administered to them.

## Limitations

The sample size of our study was limited and only male patients of ASA I and II status were enrolled for the study, hence, interpolation of our observations to the general population requires further controlled studies. Further studies are required to study the effect of oral Flupirtine on ASA III patients.

This study involved single oral dose of Flupirtine, demonstration of optimal analgesic dose and adverse effects may require multiple dose studies.

Comprehending the VAS score was difficult in a few subjects due to illiteracy and may have resulted in approximate scoring in them.

## Conclusion

Oral Pre-operative Flupirtine 200 mg has shown to be a good Pre-emptive analgesic by reducing the intensity of pain and delaying the requirement of analgesia in the post operative period.

With Flupirtine, attenuation of intubation response was significant in the patients resulting in stable hemodynamics.

**Conflict of Interest:** None.

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