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FLUPIRTINE REDUCES MORPHINE REQUIREMENTS AFTER CARCINOMA BREAST SURGERY: A RANDOMIZED DOUBLE BLIND CONTROLLED TRIAL.

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ABSTRACT

Background. Multimodal analgesia is indicated for perioperative pain management to reduce opioid use and its associated adverse effects. NMDA receptor plays an important role in pain mechanism. Activation of K+ channel blocks the NMDA receptor mediated glutamate induced rise in intracellular Ca++ ion. Activation of K+ channel may increase inhibition of nociceptive input and improve pain relief. flupirtine, a selective K+ opener, has demonstrated efficacy in chronic pain conditions such as painful diabetic neuropathy and post-herpetic neuralgia. The objective of the study was to evaluate the efficacy of flupirtine in reducing morphine requirements in patients after carcinoma breast surgery.

Methods. Fifty patients received either two doses of oral flupirtine 100 mg (2 h before surgery and on first postoperative day) or placebo. All patients received patient-controlled analgesia with morphine for 48 h after operation. Pain and adverse effects were assessed at 0.5, 1, 2, 6, 12, 24, and 48 hrs after surgery on an 11-point numeric rating scale.

Results. Twenty-three patients in the flupirtine group and 24 patients in the placebo group completed the study. Morphine requirements during the 48 h after surgery were significantly lower in the flupirtine group [19.5 mg, standard deviation (SD) 14.5 mg] compared with the placebo group (30.3 mg, SD 18.1 mg) (P¼0.017). There were no statistically significant differences between the groups in pain scores (at rest and on movement) or in adverse effects.

Conclusions. Perioperative administration of flupirtine reduced postoperative morphine requirements during the first 48 hrs after carcinoma breast surgery, without significant adverse effects.

KEYWORDS: **analgesia, postoperative; analgesics non-opioid; pain, acute**

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INTRODUCTION

Multimodal analgesia utilizes a combination of opioids and non-opioids to target various sites in the central and peripheral nervous system to manage postoperative pain.[1] The objective is to minimize opioid use and, therefore, opioid-related adverse effects or opioid-induced hyperalgesia. Tissue trauma resulting from surgery can also sensitize peripheral nociceptors leading to central neuronal sensitization. [2] Therefore, the use of adjuvants such as ketamine, gabapentinoids (gabapentin and pregabalin), and clonidine has been shown to be useful in perioperative pain management.[3] Appropriate management of postoperative pain is also important as the intensity of acute postoperative pain has been shown to increase the risk of chronic post-surgical pain.[4,5] Although multiple types of voltage-gated ion channels are associated with neuronal hyperexcitability, voltage-gated K^+ channels (Kv) are one of the important physiological regulators of membrane potentials in excitable tissues, including nociceptive sensory neurons. Since the opening of K^+ channels leads to hyperpolarization of cell membrane and a consequent decrease in cell excitability, several Kv channels have been proposed as potential target candidates for pain therapy. flupirtine elective k_+ channel opener, has been shown to be effective in treating chronic pain.[6,7,8] The primary aim of our study was to investigate the efficacy of flupirtine in reducing morphine requirements after carcinoma breast surgery. Secondary aims include reduction in postoperative pain scores, adverse effects, and the incidence of chronic postoperative pain at 3 and 6 months after surgery.

METHODS

The study was approved by our hospital Institutional ethical committee . Written informed consent was obtained from all subjects. The primary objective was to evaluate the efficacy of two doses of oral flupirtine 100 mg in reducing morphine requirements in patients undergoing elective carcinoma breast surgery at L.N. Medical college and associated J.K. Hospital. Patients between the ages of 18 and 70 yr and of ASA physical status I–III were eligible for the study. Patients were recruited from the Department of Surgery between December 2009 and January 2011. The exclusion Criteria were: illiterate patients, patients with psychiatric illness, a known allergy to flupirtine or morphine, pre-existing pain syndrome and/or analgesic treatment [excluding acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and Cox-2 inhibitors], a history of drug or alcohol abuse, and abnormal renal and liver function tests. Oral analgesics were discontinued 24 h before surgery. Standard monitoring include electrocardiography, noninvasive arterial pressure measurement, pulse oximetry, and capnography . Anaesthesia was induced with i.v. propofol 2 mg/ kg2 and fentanyl 1–2 mcg/ kg2 and endotracheal intubation was facilitated by iv vecuronium 0.1 mg/kg with an appropriate size of endotracheal tube. Anaesthesia was maintained with isoflurane with nitrous oxide-oxygen mixture in the ratio of 40:60 and patient was kept on mechanical ventilation on IPPV mode throughout the procedure. During surgery, titrated doses of morphine up to a total of 0.1 mg/ kg2 was administered by the anaesthetist in accordance with standard practice to maintain the patient's heart rate and arterial pressure within 20% of preoperative baseline. The same two surgeons performed the mastectomy using the same techniques in all the patients. After surgery, pain treatment consisted of patient controlled analgesia (PCA) with i.v. morphine. The settings were 1 mg bolus, 5 min lockout time, and a maximum hourly limit of 8 mg. All patients were also given acetaminophen 1 g 6 hourly. NSAIDs were prohibited for the purpose of this study. The study was a parallel group, double-blind, randomized, placebo-controlled trial [9,10]. Patients received either oral flupirtine 100 mg or identical matching placebo capsules 2 hrs before surgery and on the morning of the first postoperative day. Study medication was marked with consecutive numbers according

to a computer-generated table of random numbers. Patients were assigned consecutively to their group according to their number. Randomization and allocation were only revealed for data analysis when the study was completed and the required number of subjects had been recruited. The patients did not receive any premedication. A blinded observer who was not part of the anaesthesia team or study team followed up with the patients. The primary outcome measure was total morphine requirements at 48 h after surgery. The secondary outcome measures were pain scores at rest and on movement (i.e. mobilization during physiotherapy) and the presence or absence of adverse effects such as headache, nausea, vomiting, constipation, blurred vision, dizziness, and somnolence. Pain scores were recorded at 0.5, 1, 2, 6, 12, 24, and 48 h after surgery on an 11-point numeric rating scale (NRS) (with '0' being 'no pain' and '10' being the 'worst possible pain'). Before discharge from the hospital, all patients were prescribed with acetaminophen 1 g 6 hourly, etoricoxib 120 mg daily and tramadol 50 mg 8 hourly for 2 weeks. They were instructed to note the amount of pain they had at home and their analgesic needs. We defined chronic pain as the presence of pain 3 months after surgery, independent of its intensity or analgesic requirements. Three and 6 months after surgery, patients were interviewed via telephone, by an anaesthetist blinded to their treatment group, regarding any pain, abnormal sensation (allodynia, hyperalgesia, dysaesthesia, or hypoaesthesia), or both at the surgical site. The presence of pain ('yes' vs 'no' pain), the pain intensity (NRS; 0–10), and the analgesic requirements at home, if any, were recorded. Initial sample size estimation was based upon morphine consumption in a retrospective sample of 50 patients who received carcinoma breast surgery in our department. Approximately 24 patients in each group were required for a power of 0.80 at an a level of 0.05 for detecting a 50% difference in morphine consumption between groups at 48 h post-surgery. SPSS 17 software was used for statistical analysis (SPSS Inc., Chicago, IL, USA). A value of P,0.05 was considered significant. Patient characteristics, duration of surgery, and anaesthesia were compared between groups with two-tailed unpaired t-test. To assess for normality on the data set, the Shapiro–Wilk test was performed. Data were presented as median (with inter-quartile range) or mean [with standard deviation (SD)] as appropriate. Assumption of normality was rejected for most data, and consequently, the nonparametric Mann–Whitney U-test for independent samples was used for comparison. Significant Mann–Whitney U values were Bonferroni corrected for the various time points investigated. Rates of adverse effects and the number of patients in each group who required analgesics for chronic pain 3 and 6 months after surgery were compared using x2 test or Fisher's exact test.

RESULTS

From december, 2009 to january, 2011, 58 consecutive patients who fulfilled inclusion criteria were eligible for the study . Seven patients refused to participate and one patient had newly diagnosed impaired liver function. Therefore, 50 patients were randomized and included in the study. However, three patients were subsequently excluded, resulting in data from 47 patients in the final analyses. Patient and clinical characteristics for each group (Table 1) showed no significant differences between the groups. The morphine requirement at 24 h was 12.9 mg (SD 10.4 mg) in the flupirtine group and 19.8 mg (SD 13.7 mg) in the placebo group (P¼0.039). At 48 hrs, total morphine requirement was significantly lower in the flupirtine group (19.5 mg, SD 14.5 mg)

Table 1

Patient characteristics. Data expressed as mean with standard deviation in parentheses unless otherwise stated. No significant differences between groups.

	Placebo	Flupirtine
No. Of patients (n)	24	23
Age (yr) range	65.7 (51-79)	65.2 (50-80)
Height (cm)	154 (10)	156 (8)
Weight (kg)	65.2 (12.0)	70.2 (12.2)
ASA physical status		
I	2	1
II	19	18
III	3	4
Duration of surgery (min)	72 (18)	78 (21)
Duration of anaesthesia (min)	96 (17)	100 (31)

Table 2

Pain scores (NRS) at rest and on movement at 0.5, 1, 2, 6,12, and 24 h after surgery in the placebo and Flupiritine groups. There were no statistically significant differences between groups. Values expressed as median with inter-quartile range in parentheses

Time (h)	Placebo		Flupirtine	
	Rest	Movement	Rest	Movement
0	0(0-1.25)	0(0-125)	0(0-2)	0(0-3)
0.5	0(0-2)	0(0-2)	0(0-2)	0(0-2.5)
1	0(0-2)	0.5(0-2)	0(0-2.5)	0(0-3.5)
2	1(0-2)	2(0-3)	1(1-3)	2(1-4)
6	1(0-3.25)	2.5(1-4.25)	1(0-3)	2(0.5-3)
12	2(1-3)	2(1-4.25)	1(0.5-3)	3(1-5)
24	1(0-3.25)	5(1-6.25)	1(0-3)	2(1.5-5)
48	0(0-1)	4(1-6)	0(0-0)	1(1-2)

Table 3

Adverse effects

Adverse effect	Placebo (n=24)	Flupirtine(n=23)
Pruritis	1	0
Somnolence	3	0
Headache	0	1
Dizziness	3	2
Nausea and vomiting	5	3

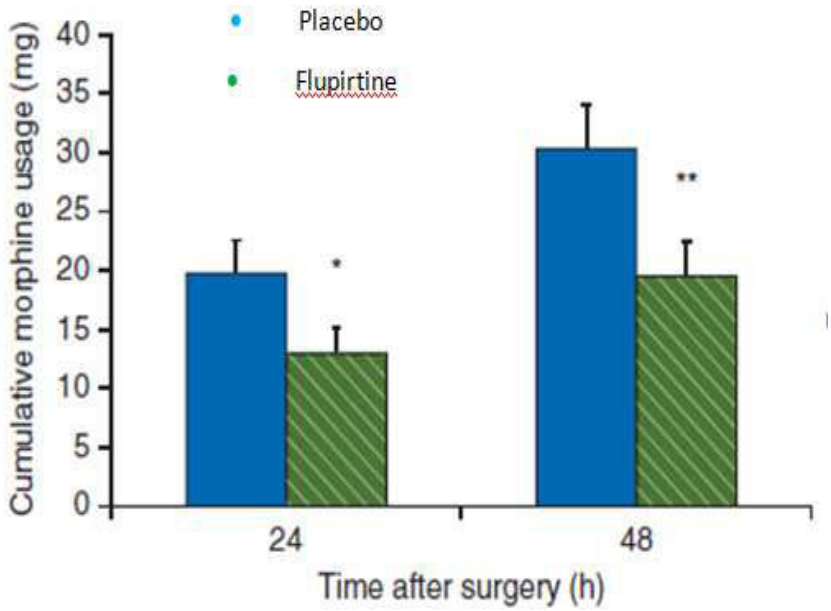
Table 4

Adverse effects

Follow-up	Placebo (n=22)	Flupirtine(n=21)
3 months		
Abnormal sensation	10	4
Pain	6	2
6 Month		
Abnormal sensation	9	4
Pain	5	2

Figure 1

Morphine requirements at 24 and 48 h after surgery in the placebo and duloxetine groups. *P¼0.039 compared with placebo. **P¼0.017 compared with placebo.



compared with the placebo group (30.3 mg, SD 18.1 mg) (P¼0.017) (Fig. 1). There were no statistically significant differences in pain scores at rest and on movement at all time points between the placebo and flupirtine groups (Table 2). The most common adverse effect experienced by subjects in the study was dry mouth and constipation (Table 3). No statistically significant differences were noted between groups. At the third and sixth month after surgery, two patients in the placebo group and one in the flupirtine group could not be contacted. In addition, one patient in the flupirtine group died from myocardial infarction 6 months after surgery. Twenty-two patients in the placebo group and 21 patients in the flupirtine group were contacted (Table 4). At the 3 month follow-up, the presence of abnormal sensation at the surgical site was reported in 10 patients in the placebo group and four patients in the flupirtine group (P¼0.065). Six patients in the placebo group reported residual pain at 3 months post-surgery (mean NRS-pain intensity 3/10). Pain resolved in only one of these patients in the placebo group after 6 months. In comparison, residual pain was reported in two patients at 3 and 6 months in the flupirtine group (mean NRS-pain intensity 2/10) (P¼0.41). No statistically significant difference was noted.

DISCUSSION

Perioperative oral administration of two doses of flupirtine 100 mg resulted in reduction in morphine requirements at 24 and 48 hrs after breast surgery. However, pain scores at rest and on movement were not significantly different statistically between groups at all time points. No significant difference in adverse effects or residual pain after 3 months from the surgery was observed between flupirtine and placebo in this study. Surgical tissue injury results in both peripheral and central sensitization. Such neuroplastic changes can manifest as hyperalgesia or allodynia in patients after surgery.[11,24,25]. As such, 'antihyperalgesic' drugs have been used as adjuvants as an integral part of multimodal analgesia.[12,13] Gabapentin and pregabalin bind the a-2-d-subunit of voltage-dependent calcium ion channels to block the development of hyperalgesia and central sensitization. Both drugs have well established roles in the treatment of neuropathic pain. The perioperative administration of gabapentin or pregabalin has been shown in clinical trials and meta-analyses to be effective in reducing pain scores, opioid requirements, and opioid-related adverse effects after surgery.[12–16]

flupirtine is a k+ channel opener that is efficacious in chronic pain conditions such as painful diabetic neuropathy and fibromyalgia.[6, 7, 17]. According to previous study evaluating the role of flupirtine in acute postoperative pain, we chose flupertin100 mg dose in this study[18,22,23]. The possible mechanism of action of flupirtine in our study could be explained by the pain inhibitory action secondary to k+ channel opening. Mean NRS-pain scores in both groups were 5 throughout the entire study period. Patients had access to i.v. PCA morphine and were instructed to use it to administer morphine as and when they experienced pain. Therefore, we believe that morphine requirement is an appropriate surrogate indicator of the intensity of postoperative pain in our study. It was also noted that pain scores appeared to be slightly higher in the first few hours after surgery in the flupirtine group compared with the placebo group. However, this was not statistically significant and also unlikely to be clinically important as pain scores remained , 3 in both groups. Nevertheless, this might be related to the fact that peak plasma concentration of flupirtine is only achieved about 2 to 3 hours after oral administration. Our study showed that the incidence of adverse effects such as sedation and dizziness were similar between the flupertin and placebo groups. Previous studies of gabapentin or pregabalin with placebo have demonstrated an increased incidence of sedation or dizziness with such adjuvants. [14 19–21] Our finding may suggest that flupirtine can be an useful alternative to the gabapentinoids as it does not increase drug-related adverse effects. However, our study was not powered to detect any real difference in adverse effects between the two groups. There is a limitations to our study, that the detection of chronic pain or abnormal sensitization 3 and 6 months after surgery was carried out via a phone interview. Patients did not return to the hospital to be examined objectively and this might give an inaccurate representation of the true nature of pain or abnormal sensitization over the operated breast. In conclusion, our study showed that perioperative administration of two doses of flupertine mg was efficacious in reducing morphine requirements in the 48 hrs after carcinoma breast surgery. fluprtine can be a useful adjuvant when used with opioids, non-opioids, and regional analgesic techniques as part of a multimodal approach in postoperative pain management. Data from our study are only preliminary in nature. Further work should explore larger patient samples and a longer duration of flupertine administration. The use of flupirtine in surgery associated with greater postoperative pain or surgery that has a higher risk of chronic pain development (e.g. thoracotomy, amputation, and inguinal herniorrhapy, etc.) should also be investigated.

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