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ROLE OF FLUPERTINE AS A PERIOPERATIVE ANALGESIC IN PATIENTS UNDERGOING SPINAL SURGERY: A PROSPECTIVE, RANDOMIZED CONTROLLED STUDY

Anaesthesiology

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ABSTRACT

Background: The present study assessed flupertine's effectiveness as a preemptive analgesic for managing postoperative pain following spine surgery, which could aid in early neurological evaluation. **Methods:** Sixty-four patients of either sex undergoing spine surgery under general anesthesia were randomly divided in to two groups. The patients in group I received flupertine 100 mg orally, 1 hour preoperatively and 12 hours postoperatively and patients in group II received placebo at same time interval with sips of water. Anesthesia technique was identical in both groups. The patients in both the groups were given fentanyl as a postoperative analgesic via a patient-controlled analgesia pump. Primary outcome was postoperative pain assessment at different time intervals by using a visual analogue scale. Secondary outcome was severity of postoperative nausea and vomiting. **Results:** The requirement of fentanyl and visual analogue score in the first 24 hours postoperative period was significantly reduced in the group I ($p<0.05$). The incidence of postoperative nausea and vomiting 0-24 h was significantly reduced in the group I compared to the group II ($p<0.05$). **Conclusion:** Perioperative use of flupertine 100 mg every 12 hr in spine surgery reduces postoperative fentanyl requirement and improves pain score, along with a reduction in postoperative nausea and vomiting in the first 24 hr period.

KEYWORDS

Flupertine, spine surgery, visual analogue score, postoperative nausea and vomiting

INTRODUCTION

Acute postoperative pain is a serious health issue that, depending on the scope of the procedure, might exacerbate postsurgery consequences. [1] Acute postoperative pain may also contribute to the development of chronic pain by sensitizing receptors in the central or peripheral nervous system, according to mounting evidence. The study of preemptive analgesia has been prompted by these findings. [2] Various drugs, such as opioids, pregabalin and nonsteroidal anti-inflammatory drugs (NSAIDS), have been studied for their potential preemptive ananalgesic effects when taken orally or systemically. [3-6] The ideal preemptive analgesic depends upon its pharmacokinetics, efficacy, complications, and cost-effectiveness.

Flupertine is a centrally acting analgesic that is nonopiate and nonNSAID, and it has antagonistic effect on the N-methyl-D-aspartate (NMDA) receptor. [7] Flupertine preserves respiratory functions compared to opioid and better gastric tolerability profile than NSAID. Its analgesic effect on both acute and chronic pain has been the subject of various investigations. Hence the present prospective, randomized, placebo-controlled, double blind study is designed to evaluate the preemptive efficacy of flupirtine in reducing acute postoperative pain after spinal surgery.

MATERIALS AND METHODS

This prospective, randomized study was conducted after approval from the Institutional Ethics Committee and written informed consent from the patients and the legally acceptable relative of the patients. The study was registered at Clinical Trials.gov www.ctri.nic.in (ref: CTRI/2016/04/006889).

A total of 68 patients 20-65 years of age, American Society of Anesthesiologist (ASA) physical status I and II, either sex, and scheduled for elective spine surgery under general anesthesia were included in this study. Patients with a known sensitivity to study drugs, history of preoperative neuromuscular disease, hepatic, renal, endocrinal, hematological disorder or cardiovascular dysfunction, BMI>30 kg/m^2, chronic use of opioids and analgesics were excluded from the study.

The 64 patients were randomly allocated to two groups of 32 each with the help of a computer generated table of random numbers.

Group I (Flupirtine) - Patients were received flupertine 100 mg orally, 1 hour preoperatively and 12 hours postoperatively with sips of water.
Group II (control) - Patients were received a similar looking placebo tablet orally, 1 hour preoperatively and 12 hours postoperatively with sips of water.

In the operating room, preloading was done with 10 ml/kg of normal saline. Routine monitoring of electrocardiography (ECG), pulse oximetry and blood pressure were established before starting study drug.

Anesthesia was induced with inj. midazolam 0.03 mg/kg, inj. fentanyl 1 µg/kg and inj. propofol 10 mg every 5 seconds until the BIS below 60 followed by vecuronium 0.1 mg/kg body weight and intubation completed with appropriate size cuffed endotracheal tube. Anesthesia was maintained with oxygen: nitrous oxide (O_2:N_2O; 40:60), sevoflurane, and propofol infusion. Ventilation was adjusted to maintain an end-tidal carbon dioxide (ETCO2) between 35 and 40 mmHg. After skin closure, all infusion drugs were stopped and neuromuscular blockade was reversed with inj. neostigmine (40 µg/kg) and inj. glycopyrolate (10 µg/kg).

The patients in both the groups were given fentanyl (5 mcg/ml) as a postoperative analgesic via a patient-controlled analgesia (PCA) pump (Smith Medical ASD, Inc., USA). The continuous infusion of 0.4 mcg/kg/h, a demand dose of 0.2 mcg/kg/hr, and a lock-out interval of 20 minutes for 24 hours (total fentanyl dose was limited to 1 mcg/kg/h). In the 24-hour postoperative period, the total fentanyl requirement was recorded (primary outcome).

Postoperative pain was assessed at 0, 2, 4, 6, 12 and 24 h using a visual analogue scale (VAS) (between 0 and 100; where 0 means no pain and 100 means worst imaginable pain). The severity of postoperative nausea and vomiting (PONV) was assessed by four-point scale on which 1 indicated no. PONV: Absence of any emesis or nausea, 2 indicated mild PONV: Patient having only mild nausea, or one emetic episode or nausea lasting for <10 min and where no antiemetic is required, 3 indicated moderate PONV: Patient has 1-2 emetic episodes or moderate to severe nausea and antiemetic therapy is required and 4 indicated severe PONV (secondary outcome).

The sample size calculation was based on self-reported VAS score for pain assessment before the commencement of this study. To detect a

30% difference in the postoperative VAS score among the groups with a standard deviation of 30% estimated from previous studies, with 80% power and 5% alpha error, we need to enroll 27 patients/group. We selected 30 patients/group to compensate for any dropouts in the study.

RESULTS

A total of sixty-eight patients were assessed for eligibility, out of which sixty-four patients were included in the study after randomization and all patients completed the study. Four patients were excluded in this study on account of patient's analgesic consumption.

There was no significant difference between the two groups regarding demographic variables (p>0.05) [Table 1].

Table 1 – Demographic Data

Variables	Group I (n=32)	Group II (n=32)	P value
Mean age (yrs)	45.56 ± 11.93	46.81 ± 7.83	0.622
Sex Male/Female	22/10	18/14	0.439
Weight (kg)	61.03 ± 9.31	63.16 ± 9.91	0.380
Duration of surgery	146.25±33.34	153.28±34.98	0. 413

Data are presented as mean values ± SD

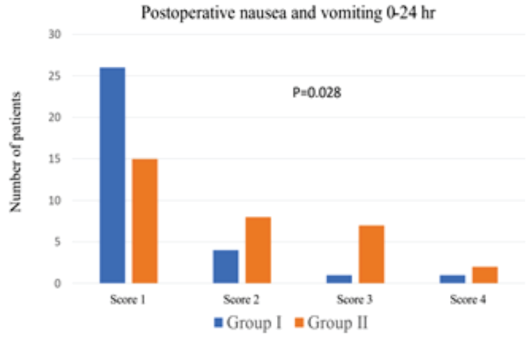
The requirement of fentanyl in the first 24 hours postoperative period was significantly reduced in the group I compared to the group II (641±106.16 mcg vs. 878.81±202.10 mcg) (P<0.0001). Visual analogue score at 0, 2, 4, and 6 hr were significantly lower in the group I compared with that in the group II (p<0.05) [Table 2].

Table 2 – VAS for Each of the Indicated Times

N	Group I 32	Group II 32	P value
VAS 0 hr	3 (2-4)	4 (3-5)	0.014
VAS 2 hr	2 (2-3)	3 (2-4)	0.018
VAS 4 hr	2 (1-3)	2.5 (2-3)	0.042
VAS 6 hr	1.5 (1-2)	2 (1-3)	0.043
VAS 12 hr	1.5 (0-1)	1 (0.75-2)	0.233
VAS 24 hr	0 (0-1)	1 (0-1)	0.071

Data are presented as median (IQR)

The incidence of postoperative nausea and vomiting 0-24 h was significantly reduced in the group I compared to the group II (p<0.05). In group I, 81.3% of patients had absence of any emesis or nausea, while in group II, only 46.9% of patients had no PONV. More patients in group II (28.1%) than in group I (6.2%) had the requirement of rescue antiemetic [Figure 1].



DISCUSSION

Acute postoperative pain is a major health concern, which augments postsurgery complications, depending upon the complexity of the surgery, sometimes it may also provide hinderance in early postoperative neurological examination after completion of spine surgery.

Flupirtine maleate, a hydrophilic compound, undergoes rapid gastric absorption with a bioavailability of 90% by oral administration. In healthy, normal volunteers, 100 mg of oral flupirtine produced a peak plasma concentration of 773 µg/L at 1.6-2 hours. The half-life of flupertine following oral administration is approximately 9.6 hours. So, we have given flupertine dose with 12 hrs intervals. [7]

Attri JP et al [4] used 100 mg flupertine in elective abdominal surgeries after 12 hr postoperative period and confirmed that it was better tolerated by the patients because of its minimal adverse effects. Ahuja V et al [5] also used 100 mg oral flupirtine maleate 1 hr prior to surgery and then every 8 hr for 48 hr and noted that flupertine has superior satisfaction scores in ambulatory gynaecological surgeries. Thapa D et al [9] demonstrated that preoperative use of 100 mg flupirtine1 h prior to surgery was safe, effective, and had morphine sparing affect in patients undergoing TAH surgery under GA. Based on these studies we have administered 100 mg flupertine, first dose 1 hr before surgery and second dose in postoperative period after 12 hr of first dose. The peak analgesic effect of flupertine occurs after 2 hr of administration that matched with intraoperative intense painful stimulus of surgery.

The significant reduction in cumulative fentanyl consumption in first 24 hr postoperative period was observed in patients of flupirtine group with simultaneous records of lower VAS during observation period. In our study, flupertine causes 27% reduction in fentanyl requirement compared to control group. Thapa D et al [8] also used the same dose of flupertine, 1 hr prior to surgery in total abdominal hysterectomy and had morphine sparing affect. Yadav G et al [9] compared flupertine 100 mg and diclofenac 50 mg on 2nd postoperative day for post-craniotomy pain and concluded that flupirtine is safe and as effective as diclofenac in reducing postcraniotomy pain. Flupirtine has been found similar in efficacy as compared to tramadol and NSAID for relieving the postoperative pain with lesser side effects. [10, 11]

Flupirtine is the prototype for the selective neuronal potassium channel openers (SNEPCO) class of medications that activate this channel. By activating K+ channels, flupirtine functions indirectly as an antagonist of the N-methyl-D-aspartate (NMDA) receptor. Flupirtine reduces the glutamate-induced increase in intracellular Ca++ concentration that is mediated by the NMDA receptor in a dose-dependent manner. It attaches itself to G-protein linked inwardly rectifying K+ channels and activates them. This channel's activation causes the neuron's membrane to become hyperpolarized and less excitable, which stabilizes the resting membrane. This is the mechanism responsible for analgesic action of flupertine. [12]

Postoperative nausea and vomiting (PONV) is a common cause of discomfort and dissatisfaction after anesthesia. PONV is sometimes rated by patients as being worse than postoperative pain. Postoperative opioids, nitrous oxide, and volatile anesthetics are among the anesthetic risk factors for PONV. In the first few days after spinal surgery, the severe pain that follows the surgery is often managed with opioids. Opioids may increase the incidence of PONV by prolonging gastric emptying time and stimulation of the chemoreceptor trigger zone. [13] A longer duration of general anesthesia was also linked to a higher incidence of PONV. In our study incidence of moderate to severe PONV in control group was 28% while it was 6% in flupertine group, because fentanyl consumption in 24 hr postoperative period was significantly decreased in flupertine group.

Common adverse effects of using opioids to relieve pain include postoperative nausea and vomiting, constipation, drowsiness, disorientation, pruritis, urinary retention, tolerance, and dependence. [13, 14] These adverse effects did not exhibit with flupertine in our study because of significant reduction of fentanyl amount in flupertine group patients. Hence, flupirtine could be a better adjunctive to opioids for sparing of opioids related adverse effects. Additionally, flupertine is more tolerable than NSAIDS due to the absence of NSAIDS-related side effects, such as heartburn, dyspepsia, and epigastric pain. [15]

There are some limitations to the present study. First, we only included ASA I and II patients who were scheduled for specific spine surgery, not spinal fusion surgery. Second, we used 100 mg of flupertin preoperatively and the next dose 12 hours after the first dose, which may only result in a 27% reduction in fentanyl requirements between the two groups. Further studies with higher doses of flupertine at different time intervals in different types of surgeries and continuing after 24 hours of postoperative period are needed.

CONCLUSION

Our study demonstrated that perioperative use of two doses of 100 mg flupertine every 12 hr in spine surgery reduces postoperative fentanyl requirement and improves pain score, along with a reduction in postoperative nausea and vomiting in the first 24 hr period. So flupertine can be a useful adjuvant when used with fentanyl in spine surgery.

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