Original Article

Effect of preoperative flupirtine on postoperative morphine sparing in patients undergoing total abdominal hysterectomy

ABSTRACT

Background: Flupirtine is a unique non-opioid, centrally acting analgesic with muscle relaxant properties. So far no study has evaluated, use of preoperative flupirtine on postoperative morphine sparing effect in patients undergoing total abdominal hysterectomy (TAH).

Materials and Methods: We performed a prospective, controlled, and randomized study in 50 female patients of American Society of Anesthesiologists physical status I–II, aged between 30 and 60 years scheduled for TAH under general anesthesia (GA). Patients were randomized to receive either single dose flupirtine 100 mg or placebo 1 h prior to surgery. A standard anesthetic and analgesic protocol was followed in both the groups. Postoperatively, a titrated loading dose of intravenous morphine 0.1 mg/kg was followed with patient-controlled analgesia with morphine (bolus of 0.01 mg/kg with a lockout time of 7 min). The primary outcome was cumulative morphine consumption at 48 h postoperatively. Secondary outcomes included hemodynamics, visual analog scale (VAS) at rest, VAS on cough, and any adverse effects.

Results: All enrolled 50 patients completed the follow-up. The cumulative mean morphine consumption (standard deviation [SD]) at 48 h (40.4 [6.0] vs. 47 [6.6] mg, $P = 0.001$) was reduced in-group flupirtine as compared with placebo. The cumulative mean VAS at rest (SD) (3 [0.7] vs. 3.7 [0.7], $P = 0.001$) and on cough (3 [0.9] vs. 3.8 [0.5], $P = 0.002$) were reduced in-group flupirtine as compared with placebo at 48 h postoperatively.

Conclusion: Preoperative use of flupirtine exhibited morphine sparing effect in patients following TAH under GA at 48 h.

Key words: Abdominal hysterectomy; acute pain; analgesia

Introduction

Postoperative pain, acute postoperative pain, when managed sub-optimally, leads to unfavorable outcomes like reduced organ function and increased the length of stay in hospital. During surgical insult, the production of hyperalgesia around the wound amplifies the noxious stimulus and postoperative pain leading to a state of persistent postoperative pain.[1]

Major surgical procedures like total abdominal hysterectomy (TAH) involve significant postoperative pain and morbidity, demanding a multimodal approach for postoperative pain relief for guaranteeing high-quality analgesia with minimal side-effects.[2]

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Thapa D, Ahuja V, Dass C, Gombar S, Huria A[1]

Departments of Anesthesia and Intensive Care and [1]Obstetrics and Gynecology, Government Medical College and Hospital, Chandigarh, India

Address for correspondence: Dr. Vanita Ahuja, Department of Anesthesia and Intensive Care, Government Medical College and Hospital, Sector 32, Chandigarh, India. E-mail: painmanagementgmch@gmail.com

The most effective modality remains a patient-controlled epidural analgesia (PCEA) system[3] but had been discredited with some serious complications. PCEA is usually withheld in patients with raised intracranial tension, coagulopathy, restlessness, and severe hypovolemic.[4] Use of systemic drugs, opioids versus tramadol patient-controlled analgesia (PCA) following TAH for postoperative period pain relief have been found to be equivalent.[2,5] Recently, preoperative use of analgesics have shown to modulate nociception process in the intra- and postoperative periods and resulted in reduced postoperative analgesics.[6] The existing methods for management of postoperative pain relief after TAH target noxious pain stimulus rather than pain occurring due to hyperalgesia.

Flupirtine, a triaminopyridine derivative[7] facilitates gamma amino butyric acid-A receptors, and voltage-gated potassium (K_V7) channels are responsible for the non-opioid analgesic action of the drug.[8] There is limited data regarding the preoperative role of flupirtine in the prevention of analgesics consumption in the postoperative period. Hence, the present study was aimed at evaluating the effect of preoperative single dose oral flupirtine on morphine sparing effect and postoperative pain relief in patients following TAH.

Materials and Methods

We undertook a prospective, randomized, double-blind, and placebo-controlled clinical trial. The primary objective was to evaluate the effect of preoperative single dose oral flupirtine on morphine sparing effect and postoperative pain relief in patients following TAH. The study was conceived in accordance with the Declaration of Helsinki and its amendments. The study protocol was approved by the hospital Institutional Ethics Committee (GMC/TA – I (19D)/2013/05428) and registered with Clinical trials registry India (CTRI/2013/12/004226). Written informed consent was obtained from all subjects recruited during February 2013 to June 2014. The design and conduct of our trial adhered to the CONSORT statement. All female patients of American Society of Anesthesiologists (ASA) physical status I and II, aged between 30 and 60 years, having weight between 50 and 80 kg, and scheduled for TAH were eligible for the study. Patients having ASA status > II, body mass index >30 kg/m^2, history of substance abuse, inability to use PCA pump, allergy to study drug morphine, flupirtine, known significant abnormalities of renal or hepatic functions and patients on warfarin were excluded from the study.

Randomization and blinding

All routine investigations were done preoperatively and any other investigation, whenever necessary, was also advised. All study patients were instructed about the use of PCA pump a day prior to surgery, before shifting to the operation theater and also in post-anesthesia care unit (PACU). Patients were explained about the visual analog scale (VAS) for pain where "0" being "no pain" and "10" being "worst imaginable pain."[5] Categorical scoring system (CSS) of nausea and vomiting was used, where "0" being "no nausea/vomiting," "1" for "slight nausea resolving without treatment," "2" for "slight nausea and or vomiting resolves on treatment" and "3" for "nausea and or vomiting not resolving on treatment."[2] Any patient who failed to understand the functioning of PCA pump or VAS or CSS was excluded from the study design. Patients were kept fasting after midnight and premedicated with alprazolam 0.25 mg and ranitidine 150 mg orally the night before surgery and 2 h before surgery. Computer generated random numbers were used to randomize patients to either Group flupirtine (n = 25) received study drug flupirtine 100 mg per oral (PO) 60 min prior to surgery and underwent surgery under general anesthesia (GA) followed by PCA morphine for postoperative analgesia. Group placebo (n = 25) patients received an identical looking placebo PO 60 min prior to surgery and underwent surgery under GA followed by PCA morphine for postoperative analgesia. Concealment was done with opaque colored envelopes. The drug was given by an anesthesiologist who was not part of the study and was also not involved in the subsequent evaluation of the patients. Both the anesthesiologist giving the drug and the patient were blinded to the drug. All the patients after enrolment were allocated to either group flupirtine or group placebo.

An intravenous (i.v.) access was established and patients received PO flupirtine 100 mg or identical looking empty gelatin capsule oral placebo 60 min before surgery. In the operating room, the patients were monitored for baseline hemodynamic parameters using multichannel monitors (Aestiva 5™ 7900, GE healthcare, Datex-Ohmeda division, Helsinki, Finland). A standard technique GA technique was maintained in all the patients. Glycopyrrolate 0.2 mg was given i.v. to all patients just before induction of anesthesia. After preoxygenation with 100% oxygen for 3 min; anesthesia was induced with i.v. fentanyl 1.5 μg/kg and thiopentone sodium 5-7 mg/kg. Vecuronium bromide 0.1 mg/kg i.v. was used to facilitate tracheal intubation. Fentanyl doses were further adjusted to hemodynamic drifts and signs of pain. Anesthesia was maintained with 66% nitrous oxide in oxygen supplemented with isoflurane (1-2%). At the end of surgery, the residual neuromuscular blockade was reversed with i.v. neostigmine 50 μg/kg and glycopyrrolate 10 μg/kg. In both the groups, 20 min before the completion of surgery, i.v. ondansetron 0.1 mg/kg was administered.

A standard protocol for postoperative care was followed for patients in both the groups. All the patients received a titrated loading dose of i.v. morphine 0.1 mg/kg, during a 15 min period on arrival in the PACU followed with a continuous background infusion of morphine at 0.01 mg/kg/h from PCA pump (Master PCA pump, Fresenius Kabi Company, Bad Homburg, Germany). The PCA pump was set to deliver background infusion of morphine at 0.01 mg/kg/h plus a bolus of 0.01 mg/kg (by the patient in case VAS >4) with a lockout time of 7 min,[9] and a 24-h maximum dose of 40 mg. Both the groups received i.v. ondansetron 4 mg 3 times a day till 48 h. Patient in both the groups received rectal diclofenac 100 mg every 12 h till 48 h. All patients were monitored in PACU and later in ward for morphine consumption, hemodynamic parameters, VAS at rest and on coughing, nausea or vomiting, sedation at 2, 4, 6, 8, 12, 24, and 48 h interval.

Statistical analysis

Sample size was calculated based on the mean morphine requirement of 55 mg during 48 h in a previous study.[2] To detect a change of 30% in morphine consumption in first 48 h, with standard deviation (SD) of 17 mg,[2] the calculated sample size was 22 patients per group with a β value of 90% and an α value of 0.05. For compensating possible dropouts and loss to follow-up, 25 patients per group were required. The results were analyzed using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA, version 15.0 for Windows). Mean and medians were calculated for all quantitative and for measures of dispersion were calculated. For normally distributed data, the mean was compared using independent sample *t*-test. For skewed data, Mann–Whitney test was applied. For time related variables repeated measure Analysis of variance was applied. Qualitative or categorical variables were described as frequencies and proportions. Proportions were compared using Chi-square or Fisher's exact test whichever was applicable. All statistical tests were two-sided and performed at a significance level of $\alpha = 0.05$.

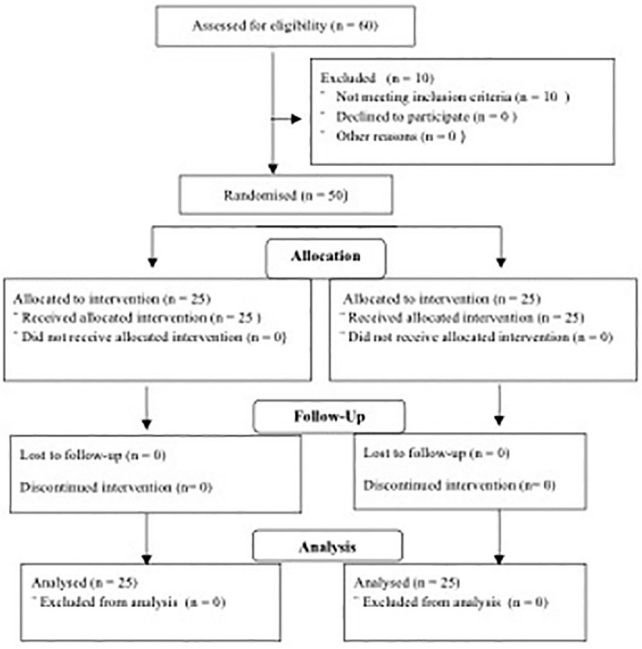

Figure 1: CONSORT diagram of patient distribution

Results

During February 2013 to June 2014, 60 patients were enrolled and out of these 10 patients did not meet the inclusion criteria. Hence, 50 patients were randomized to either of the two groups. All the patients completed the study [Figure 1]. Patient and clinical characteristics for each group showed no significant differences between the groups in Table 1. The calculated post-study power had also been higher at 93%. The cumulative mean morphine consumption (SD) at 48 h was 40.4 (6.0) mg in-group flupirtine when compared to 47.0 (6.6) mg in-group placebo ($P = 0.001$). The cumulative morphine consumption at 2, 4, 6, 8, 12, 24, and 48 h was reduced in patients of group flupirtine as compared to group placebo in Table 2. Similarly, the mean cumulative VAS at rest (SD) was at 48 h was 3.0 (0.7) in-group flupirtine as compared to 3.7 (0.7) in-group placebo ($P = 0.001$) [Figure 2]. The mean VAS

Table 1: Baseline demographic characteristic of patients

Patient characteristics	Flupirtine (n = 25)	Placebo (n = 25)
Age (years)	43.8 (6.4)	44.2 (5.1)
Weight (kg)	60.7 (6.8)	60.8 (7.5)
Height (cm)	157.3 (5.6)	157.3 (5.7)
BMI (kg/m^2)	24.6 (2.2)	24.5 (2.7)
ASA physical status		
I	18	16
II	7	9

Data expressed as mean with SD in parentheses unless otherwise stated. No significant differences between groups. SD: Standard deviation; BMI: Body mass index; ASA: American society of anesthesiologists

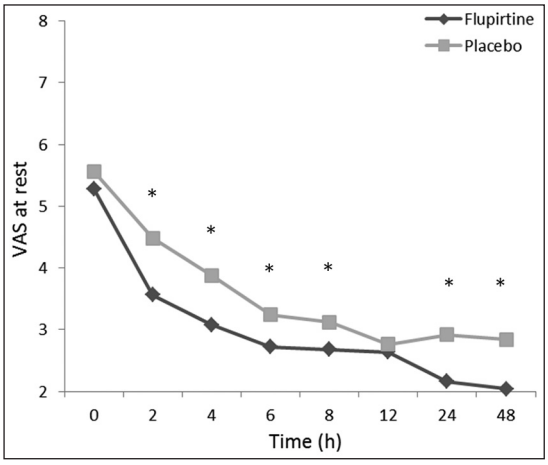

Figure 2: Visual analog scale pain scores at rest in postoperative period following total abdominal hysterectomy in flupirtine and placebo group: *$P < 0.01$

Table 2: Postoperative morphine consumption (mg) in patients undergoing total abdominal hysterectomy in flupirtine and placebo group

Time (h)	Flupirtine (n = 25)	Placebo (n = 25)	P
0	4.9 (1.0)	5.3 (1.3)	0.29
2	6.9 (1.3)	8.1 (1.7)	0.009*
4	8.1 (1.7)	10.5 (2.2)	0.004*
6	10.6 (2.2)	13.0 (3.0)	0.002*
8	12.3 (2.7)	15.2 (3.5)	0.002*
12	15.6 (3.3)	19.2 (4.1)	0.001*
24	23.6 (6.3)	29.0 (5.0)	0.002*
48	40.4 (6.0)	47.0 (6.6)	0.001*

*P < 0.01. Values expressed as mean and SD. SD: Standard deviation

on cough (SD) at 48 h was 3.0 (0.9) in-group flupirtine when compared to 3.8 (0.5) in-group placebo (P = 0.002), [Figure 3].

The hemodynamic parameters in both the groups were within the normal physiological limits. The mean cumulative CSS for nausea (SD) at the end of 24 h was 0.1 (0.4) in-group flupirtine and 0.8 (0.5) in-group placebo (P = 0.001). The mean cumulative CSS for nausea (SD) at the end of 48 h was 0.2 (0.5) in-group flupirtine when compared to 0.8 (0.5) in-group placebo (P = 0.001). Patients in both the groups received injection ondansetron according to protocol and few patients required injection metoclopramide, which was statistically non-significant. None of the patients in either group complained of shivering. There were 7 patients of group placebo who had pruritus at 24 and 48 h as compared to none in-group flupirtine (P = 0.004). The sedation score was higher in the early postoperative period (up to 4 h, P = 0.02) in the patients of group flupirtine. However, the patients in both the groups were arousal at all-time intervals.

Discussion

The major finding of this randomized controlled trial was morphine sparing effect of preoperative flupirtine on postoperative pain relief in patients following TAH under GA. The potential anti-hyperalgesic effect of flupirtine (action on Kv 7 channels) offered the rationale behind the preoperative use of flupirtine for postoperative pain relief in the present study.[2,6,8] Significant reduction in cumulative morphine consumption was observed in patients of group flupirtine with simultaneous records of lower mean cumulative VAS score at rest and on cough at 48 h. The results of our study are in contrast to an earlier study in the human surrogate model of neurogenic hyperalgesia, where flupirtine 100 mg could not show anti-hyperalgesic effect to pinpricks after intradermal capsaicin.[9] It appeared that the level of capsaicin-induced hyperalgesia was superficial and insufficient to unmask the anti-hyperalgesic effects of flupirtine. On the contrary, patients following TAH underwent deeper tissue

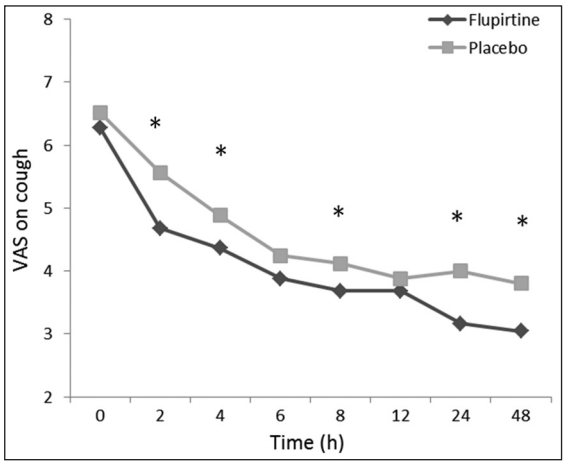

Figure 3: Visual analog scale pain scores on cough in postoperative period following total abdominal hysterectomy in flupirtine and placebo group: *P < 0.01

dissection, which could initiate significant hyperalgesia and can be a proper model for appreciating the anti-hyperalgesic effect of flupirtine.[10]

The use of morphine boluses with background infusion is in line with White *et al*.[10] in which the patients operated for colorectal carcinoma were benefited with a similar administration technique of morphine background infusion and PCA. In the present study, we used PCA morphine boluses with background infusion, which resulted in lower mean cumulative VAS in patients both the groups. In an earlier study, the mean cumulative numeric Rating Scale score (SD) in bolus plus infusion regime was 3.4 (1.9) as compared to 5.7 (1.2) in bolus only regimen.[10] Morphine sparing effect has also been observed in patients after TAH surgery when transverses abdominal block with ropivacaine was compared to saline.[2]

The analgesic efficacy and safety of flupirtine has been described in scientific literature. The safety and efficacy of flupirtine 100 mg, when administered on 2nd postoperative day was comparable to that of diclofenac 50 mg in patients with moderate to severe post-craniotomy pain.[11] The speed, duration, and intensity of the analgesic effect of flupirtine had been found to be superior to diclofenac for relieving postoperative pain relief in orthopedic patients by Mastronardi *et al*.[12] Flupirtine has been found similar in efficacy as compared to tramadol for relieving the post-operative pain with lesser side effects.[13] Analgesic effects of flupirtine have also been found comparable to pentazocine and tramadol when used for post-hip surgery pain and low back pain, respectively.[14,15]

Sedation was however significantly higher in-group flupirtine for up to 4 h after the surgery probably due to combined

sedative effect of flupirtine as well as the residual effect of anesthetic agents in early postoperative period. This corresponds to the half-life of flupirtine 100 mg on oral administration, which is 6.5 h.[16] In spite of sedation, all patients were arousable and the mean sedation scores remained between quietly awake or drowsy. In a supporting evidence by Cepeda *et al*., mild sedation was observed in 85.3% of the patients in the morphine group in 24 h period.[17] Another study by Yadav *et al*. failed to show the significant difference in Ramsay sedation score between flupirtine and diclofenac, when these analgesics were administered on 2nd postoperative day onwards.[11]

The sedation in patients of ASA I and II status in flupirtine group was well tolerated by in the present study, however further study may be required to demonstrate the effect of sedation in patients with higher ASA grading.

The mean cumulative nausea/vomiting scores at 24 and 48 h were significantly higher in the group placebo which could be related to the significantly higher consumption of morphine in this group. It should be noted that the scores were significantly higher in the initial 8 h in the group placebo which decreased as the rescue antiemetics were given. The mean nausea/vomiting scores in-group placebo were comparatively higher to that in-group flupirtine because in patients receiving both flupirtine exhibited morphine sparing effect and reduced nausea/vomiting scores. In a study by Hong *et al*., nausea was observed in 68% of the patients 8 h postoperatively who received PCA morphine after lower abdominal or pelvic gynecological surgery.[18] Dierking *et al*. reported that 35% of the patients had nausea, and 47% had vomiting when morphine PCA was used for postoperative pain relief after abdominal hysterectomy when observed up to 24 h postoperatively.[19] Morphine PCA is undoubtedly associated with postoperative nausea/vomiting. The use of preoperative flupirtine in-group flupirtine patients of our study was responsible for the decrease in the overall morphine consumption and indirectly led to decreased nausea/vomiting.

None of the patients had postoperative shivering because adequate precautions for maintaining patients' body temperature were taken by using warm fluids and warming blankets. We observed pruritus in seven patients of group placebo at 24 h and 48 h. This could be related to increased morphine consumption by patients in this group. Cepeda *et al*. reported mild pruritus in 10% of the patients who received morphine PCA for postoperative pain relief after TAH.[17] In the present study, few patients required rescue antiemetic metoclopramide for nausea/vomiting. However, the cumulative metoclopramide consumption at the end of 24 h and 48 h was significantly higher in the group placebo due to higher nausea/vomiting scores in-group placebo and could be related to higher consumption of morphine in this group of patients.

The limitations of the present study were that only ASA grade I and II patients were included. The effect of preoperative flupirtine in ASA III and a higher grade of patients would require further studies. We used a single oral dose of flupirtine 100 mg preoperatively, which may not have been sufficient to produce a large difference in morphine consumption between the two groups. In order to see a large difference in morphine consumption further studies would be required.

Conclusion

Our study demonstrated that preoperative use of flupirtine was safe, effective, and had morphine sparing affect in patients undergoing TAH surgery under GA.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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