

A Comparative Study of the Post Operative Analgesic Efficacy of Flupirtine maleate and Ibuprofen in Patients Undergoing Diagnostic Laparoscopy for Gynaecological Surgeries under General Anaesthesia

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Abstract

Background and aim: Effective control of pain postoperatively is essential in providing enhanced patient care and a cost-effective hospital stay. The aim of this study was to compare the post-operative analgesic efficacy of flupirtine maleate and ibuprofen in patients undergoing diagnostic laparoscopy for gynaecological surgeries under general anesthesia as primary outcome variable. Secondary outcome measures included diclofenac consumption, haemodynamic parameters and adverse effects in post-operative period.

Methods: This prospective, randomized, double blinded study was conducted in 106 women of American Society of Anesthesiologists physical status I/II, 16-60 years of age, undergoing diagnostic laparoscopy for gynaecological surgeries under general anesthesia. The patients were randomised to receive either 100 mg oral flupirtine maleate (group flupirtine, n = 53) or 800 mg oral ibuprofen (group ibuprofen, n = 53), 1 h prior to surgery and then every 8 h for 24 h. Assessment of Verbal Numerical Rating Scale (VNRS) on movement was done at 0, 1, 2, 4 and 6 h following surgery. After discharge from hospital, the patients were interviewed telephonically at 12 and 24 h post-operatively. VNRS was statistically analysed using Mann-Whitney test.

Results: VNRS on movement was significantly reduced at 1h and 2 h after surgery (P 0.011 & 0.012) in group flupirtine as compared to group ibuprofen. The analgesic efficacy was similar in both the groups at 0, 4 and 6 h after surgery. The satisfaction scores at 12 and 24 h post-operatively were superior in group flupirtine as compared to group ibuprofen (P < 0.001).

Conclusion: Analgesic efficacy of flupirtine maleate was comparable to ibuprofen for providing post operative pain relief with better satisfaction score in patients undergoing diagnostic laparoscopy for gynecological surgeries for up to 24 h.

Keywords: Diagnostic laparoscopy, flupirtine, gynaecological surgeries, ibuprofen

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I. Introduction

Ambulatory surgeries are on a rise in developing countries with multidimensional benefits both for patient, hospital and national economy.^[1] Poorly controlled postoperative pain is a major concern as it enhances postoperative complications and hospital stay.

A wide range of medications are being used for management of post-operative pain following gynaecological surgeries including opioids, and non-steroidal anti-inflammatory drugs (NSAIDs), through systemic or oral route.

Ibuprofen, a 2-propionic acid derivative has potent anti-inflammatory action. It suppresses pituitary beta-endorphin release and produces superior analgesia as compared to other NSAIDs.^[2] Ibuprofen is associated with various side effects, like gastrointestinal haemorrhage, renal and liver dysfunction thereby limiting its use in many patients.

Flupirtine is a centrally acting, nonopioid, non NSAIDs analgesic and is the first representative of selective neuronal potassium channel openers (SNEPCO), which interacts with N-methyl-D-aspartate (NMDA) receptors.^{[3],[4]} It is a potent analgesic and muscle relaxant and also has anticonvulsant and antioxidant properties, without any major adverse effects.^{[5],[6],[7]}

Therefore, we undertook this study to compare the analgesic efficacy and adverse effects of oral flupirtine maleate and oral ibuprofen in patients undergoing diagnostic laparoscopy for gynaecological surgeries under general anaesthesia.

II. Material & Methods

This hospital based prospective, randomized, double blinded comparative study was conducted during May 2016 to December 2016 after obtaining approval of the Institutional Ethics Committee and written informed consent from patients. Women of 16–60 years of age, of American Society of Anesthesiologists physical status I/II, scheduled for diagnostic laparoscopy for gynaecological surgeries under general anaesthesia were included in the study. Exclusion criteria included women with history of intake of any analgesics in past 2 days, known allergy to study drugs, coagulopathies and with history of cerebrovascular accident. 106 chosen participants were randomized into two groups, using chit in box method to receive either 100 mg oral flupirtine maleate ($n = 53$) or 800 mg oral ibuprofen ($n = 53$). All patients received drugs 1 h prior to surgery and then every 8 h for 24 h post-operatively as per group assigned.

The study drugs were given in similar brown envelopes to the patients. The patients and the anaesthetist involved in assessing the VNRS were blinded to the study protocol. On arrival in the operation theatre, fasting status, written informed consent and PAC were checked. Baseline parameters were recorded, thereafter monitoring for heart rate, non-invasive blood pressure, pulse oximetry and end tidal carbon dioxide were continued till completion of surgery. IV line was secured with 20G intravenous cannula and infusion of Ringer lactate 500 ml was started. Patients were preoxygenated and premedicated with inj. ranitidine 1mg/kg, inj. metoclopramide 0.2 mg/kg, inj midazolam 0.02mg/kg and inj glycopyrrolate 5mcg /kg.

Induction of anaesthesia was done with inj. fentanyl 2mcg/kg and inj. propofol 1.5 to 2 mg/kg & intubation of trachea was facilitated with inj succinylcholine 2 mg/kg body wt.

Anaesthesia was maintained with N_2O/O_2 (60/40%) and isoflurane. Further neuromuscular block was maintained with intermittent bolus dose of atracurium. At the completion of surgery, reversal was done with neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg) and patient was extubated.

In post operative period, patients were assessed for pain using four-point VNRS score ^[8] (0 = none, 1–3 = mild, 4–7 = moderate, 7–10 = severe pain) on movement at 0, 1, 2, 4, 6 h (Zero hour is considered at 10 minutes after extubation). Patients were given inj. diclofenac 75 mg iv as rescue analgesia on VNRS on movement of more than 3, in addition to it on demand rescue analgesia was also offered.

Patient satisfaction score was assessed using a five-point numerical scale; (1-very satisfied, 2-satisfied, 3-undecided, 4-dissatisfied and 5-very dissatisfied). Following discharge from hospital, the patients were interviewed telephonically at 12 and 24 h post-operatively to obtain patient satisfaction score.

Adverse effects such as nausea, vomiting, constipation, drowsiness, respiratory depression, hypotension, and allergic reactions were noted.

The sample size of 53 patients was calculated at 95 % confidence interval and 80 % power to verify the expected difference of 0.83 (± 1.5) in pain score (VNRS) on movement at 2 hrs in both groups.

Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA version 15.0 for Windows). The qualitative data was presented as proportion & percentage and the quantitative data was presented as mean \pm SD. The difference in the mean was analyzed using student t-test and difference in the proportion was analyzed using chi square test. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

III. Observations & Tables

One hundred and six patients were chosen for the study and randomized into the two study groups. All the patients were comparable regarding demographics data and duration of surgery in both the groups. (Table1)

Patients in group flupirtine exhibited lower VNRS on movement as compared to ibuprofen group at 1 and 2 hrs post-operatively (p value 0.011 & 0.012 respectively). No statistically significant difference was found in VNRS at other time intervals in both the groups. (Table2) Analgesic efficacy of flupirtine and ibuprofen were comparable up to 24 h but patients in flupirtine group had superior satisfaction scores. In group flupirtine, two patients were given rescue analgesia within 6 hr and in group ibuprofen five patients were given rescue analgesia within 2 hr, but it was not significant statistically. The requirement for rescue analgesia was less in flupirtine group as compared to group ibuprofen but difference was not significant statistically.

The satisfaction scores at 12 and 24 h post-operatively were significantly better in group flupirtine as compared to group ibuprofen ($P < 0.001$) (Table 3)

There were no significant difference was found in haemodynamic variables between two groups. Adverse effects like heartburn and impaired taste sensation was observed more in ibuprofen group. ($P < 0.05$)

Table 1: Demographic profile of patients in both groups

Parameter	Flupirtine (n=53) (mean±SD)	Ibuprofen (n=53) (mean±SD)	P value*
Age (yr)	34.96±6.427	35.28±4.143	0.761
Weight (kg)	53.47±9.451	52.75±5.381	0.632
Height (cm)	155.23±7.74	152.25±8.36	0.600
ASA Grade (I/II)	45/8	46/7	1

Table 2: VNRS on movement at different time intervals post-operatively

VNRS	Flupirtine(n=53) (mean±SD)	Ibuprofen(n=53) (mean±SD)	P value*
0 hour	0.184±0.419	0.202±0.473	0.887 (NS)
1 hour	0.27±0.446	1.02±1.483	0.011 (S)
2 hour	0.246±0.498	1.114±1.657	0.012 (S)
4 hour	0.386±0.837	0.534±0.865	0.534 (NS)
6 hour	0.438±0.932	0.477±0.842	0.598 (NS)

* P value calculated using Mann Whitney rank sum test, SD- Standard deviation

Table 3: Patient satisfaction score after surgery

Time of assessment	Flupirtine (n=53) (mean±SD)	Ibuprofen (n=53) (mean±SD)	P value*
12 hour	1.245±0.4344	1.887±0.4666	<0.001
24 hour	1.208±0.4094	1.849±0.5334	<0.001

* P value calculated using Mann Whitney rank sum test
P<0.05 considered statistically significant, SD- Standard deviation

IV. Discussion

In present study ,we observed that analgesic efficacy of flupirtine maleate was comparable with ibuprofen in patients undergoing diagnostic laparoscopy for gynaecological surgeries under general anaesthesia up to 24 h with added advantage of superior satisfaction score.

In the early post-operative period at 1 and 2h, less VNRS were observed with flupirtine as compared to ibuprofen. This difference may be attributed to the different mechanism of action of both the drugs. Oral flupirtine is known to produce analgesic as well as muscle relaxant effects that occur due to inhibition of spinal polysynaptic flexor reflex and is mediated by NMDA receptors. [5] While ibuprofen, produce analgesic and antipyretic action without any muscle relaxant effect. No statistically significant difference was found in VNRS at other time intervals in both the groups.

Our observations are in accordance to various studies [9], [10], which showed equal analgesic efficacy of flupirtine versus diclofenac for post-operative pain relief in patients undergoing gynecological, orthopedic and craniotomy surgeries. Earlier studies used flupirtine in oral doses of 100 mg and 300 mg, with a maximum daily dose of 600 mg in patients after episiotomy, surgical or dental procedures with clinical benefit. [5]

Pre-emptive use of NSAIDs before surgery has been shown to be beneficial but there is no clear consensus with respect to major surgeries [5], [9], [10] Patients undergoing diagnostic laparoscopy requires adequate pain relief as well as early discharge from hospital. The analgesic and the additional muscle relaxant action of flupirtine benefited the patients in the present study.

Flupirtine has advantages over NSAIDs due to superior tolerability and works as an excellent alternative analgesic in patients at risk of NSAID-associated gastropathy. Oral flupirtine 100 mg 3 times daily is significantly better tolerated with fewer adverse effects than are usually associated with opioids, such as nausea, vomiting, dizziness and sedation. The doses of test drugs were based on established literature. [9]

Flupirtine has been used as pre-emptive analgesic to provide adequate pain relief postoperatively in a study conducted by Yadav et al [11] and Thapa et al. [12] They concluded that pre-emptive use of flupirtine provided immediate postoperative pain relief. Hence, administering this drug pre-emptively followed by postoperative dosing may be a better modality for postoperative analgesia in short gynaecological surgeries.

Similar results were reported by other studies [13], [14], [16] on comparing analgesic efficacy of oral flupirtine 100 mg with diclofenac sodium 50 mg in patients undergoing various surgeries. They observed no significant reduction in pain scores with both the drug in first 2 hrs but the second dose administration produced, significant reduction in pain scores in both the groups. Perioperative administration of two doses of 100 mg flupirtine was found to be effective in reducing morphine requirements in 48 h postoperative period after carcinoma breast surgery. [15] So the results of the present study are similar to the above studies.

The present study revealed that incidence of heartburn, impaired taste sensation and dizziness was significantly high in ibuprofen group than in flupirtine group. Rest of the adverse effects like nausea, vomiting, headache, dry mouth and body rashes were comparable in both the groups. Mueller- Schwefe^[17] and Ringe^[18] also observed same results. Other studies^{[19], [20]} also showed that use of flupirtine causes efficacious pain relief with lower incidence of adverse effects as that of opioids and other drugs.

Flupirtine is known to cause hepatic dysfunction. However, in the present study no serious adverse effects were observed following short-term oral administration of flupirtine 100 mg, thrice daily.^[5]

The present study proves that flupirtine could be used as an alternative analgesic to ibuprofen in patients undergoing diagnostic laparoscopic gynecological surgeries with better satisfaction score.

V. Conclusion

Hence, we conclude that analgesic efficacy of flupirtine maleate is comparable to ibuprofen for providing post operative pain relief with better satisfaction score in patients undergoing diagnostic laparoscopic gynecological surgeries for up to 24 h. Flupirtine with additional muscle relaxant effect can be used in patients having contraindications to use of NSAIDs.

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