Clinical Investigation

Comparison of analgesic efficacy of flupirtine maleate and ibuprofen in gynaecological ambulatory surgeries: A randomized controlled trial

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ABSTRACT

Background and Aims: Flupirtine maleate is a centrally acting, non-opioid analgesic with unique muscle relaxant properties as compared to common analgesics. The aim of this study was to compare post-operative analgesic efficacy of flupirtine maleate and ibuprofen in patients undergoing gynaecological ambulatory surgeries. **Methods:** This prospective, randomised controlled study was conducted in 60 women of American Society of Anesthesiologists physical status I/II, 18–70 years of age and scheduled to undergo gynaecological ambulatory surgeries. The participants were randomised to receive either 100 mg oral flupirtine maleate (group flupirtine, $n = 30$) or 800 mg oral ibuprofen (group ibuprofen, $n = 30$), 1 h prior to surgery and then every 8 h for 48 h. Verbal Numerical Rating Scale (VNRS) on movement was assessed at 0, 2, 4, 6 and 8 h following surgery. Following discharge from hospital, the patients were interviewed telephonically at 12, 24 and 48 h post-operatively. VNRS was statistically analysed using Mann–Whitney test. **Results:** VNRS on movement was statistically reduced at 2 h after surgery ($P = 0.04$) in group flupirtine as compared to group ibuprofen. The analgesic efficacy was similar in both the groups at 4, 6, 8, 12, 24 and 48 h after surgery. The satisfaction scores at 24 and 48 h post-operatively were superior in group flupirtine as compared to group ibuprofen ($P < 0.001$). **Conclusion:** Analgesic efficacy of flupirtine maleate was comparable with ibuprofen in patients in ambulatory gynaecological patients up to 48 h postoperatively with superior satisfaction scores.

Key words: Ambulatory surgical procedures, flupirtine, ibuprofen

INTRODUCTION

Ambulatory surgeries are on a rise in developing countries with multidimensional benefits both for patient, hospital and national economy.[1] Gynaecological patients have the highest unplanned admission rate (35.82%). Poorly controlled pain, post-operative nausea and vomiting (PONV) and acute urinary retention are causes resulting in delay in discharge of patients after ambulatory surgeries.[2,3]

Management of post-operative pain following gynaecological ambulatory surgeries includes extensive reliance on opioid medication, which is associated with drowsiness, sedation, PONV, pruritus, urinary retention, ileus, constipation, and respiratory depression.[4] The benefits of non-steroidal anti-inflammatory drugs (NSAIDs) in controlling post-operative pain includes peripheral as well as central analgesic effect, opioid-sparing effect and reduction in PONV.[4] Ibuprofen, a 2-propionic acid derivative has potent anti-inflammatory action with 1.7 (1.4–2.3) number needed to treat (NNT) with 800 mg dose.[5] Ibuprofen suppresses pituitary beta-endorphin release and produces superior analgesia as compared to other NSAIDs.[6] However, it lacks muscle relaxant activity.

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Flupirtine maleate displays properties that are different to common analgesics and is the first representative of an entirely different class of analgesics which are 'selective neuronal potassium channel openers (SNEPCO). These facilitate the opening of neuronal Kv7 potassium channels, which inhibits exaggerated neuronal action potential generation and controls neuronal excitability.[7] Flupirtine is a centrally acting (both spinal and supraspinal), non-opioid analgesic, an indirect N-methyl d aspartate (NMDA) receptor antagonist. The unique pharmacological properties of flupirtine contribute to its therapeutic benefits, without worrisome adverse effects such as respiratory depression, tolerance and dependence that are typical of opioids, or the gastrointestinal and renal problems associated with non steroidal anti-inflammatory drugs (NSAIDs). It has good efficacy for pain relief in post-operative period with incidence of undesirable drug reactions of <1%.[7]

No published clinical study has compared the analgesic efficacy of flupirtine maleate with ibuprofen in gynaecological ambulatory surgeries for acute post-operative pain relief. The primary outcome of the present study was to observe reduction of Verbal Numerical Rating Pain Scale (VNRS) on movement and secondary outcome measures included the need for rescue analgesics, patient satisfaction score and occurrence of any other adverse effects.

METHODS

This prospective, randomised double-blind controlled study was conducted during January 2013 to August 2013 after approval of the Institutional Ethics Committee and written informed consent from patients. The inclusion criteria were women of 18–70 years belonging to American Society of Anesthesiolgists physical status I/II and body mass index of 20–30 kg/m^2 scheduled for gynaecological ambulatory surgeries under general anaesthesia. Women with history of intake of any analgesics in past 3 days, known hypersensitivity to study drugs, gastritis, coagulopathy, and previous cerebrovascular accident history were excluded from the study. After enrolment, 60 participants were randomised to one of the two groups, using computer generated random number table to receive either 100 mg oral flupirtine maleate (n = 30) (Katadol®, Lupin Pharmaceuticals, Mumbai, Maharashtra, India) or 800 mg oral ibuprofen (n = 30). The patients received drugs 1 h prior to surgery and then every 8 h for 48 h post-operatively as per group allocation.

The study drugs were provided to the patients in similar looking brown envelopes. The patients and the nurse assessing the VNRS were blinded to the study protocol. Anaesthesia protocol was uniform in both the groups. All the patients were premedicated with oral ranitidine 150 mg and alprazolam 0.25 mg the night before and 90 min before surgery. In the operating room patients were monitored for heart rate, non-invasive blood pressure, pulse oximetry and end tidal carbon dioxide till completion of surgery. Normal saline 500 ml was infused through 20 gauge intravenous (IV) cannula. Anaesthesia was induced with IV fentanyl 2 μg/kg, propofol 2–2.5 mg/kg and was maintained with oxygen 33% in nitrous oxide, isoflurane on spontaneous respiration with facemask or laryngeal mask airway as required. At the end of the surgery patients received 100% oxygen till recovery (approximately 2–3 min). Patients also received oral ondansetron 8 mg and ranitidine 150 mg twice daily for 48 h. Tramadol 100 mg IV was administered as rescue analgesic in 100 ml normal saline over 30 min if the VNRS on movement was >3 during the study period. On arrival in the post-anaesthesia care unit, pain scoring was assessed using four-point VNRS on movement,[8] 0 = none, 1–3 = mild, 4–7 = moderate, 7–10 = severe pain. VNRS on movement was assessed at 0, 2, 4, 6 and 8 h following surgery by a nurse blinded to the study protocol. Following discharge from hospital, the patients were interviewed telephonically at 12, 24 and 48 h post-operatively. Sedation was assessed using a five-point sedation scale,[9] 0 = none, patient alert, 1 = mild sedation: Occasionally drowsy; easily aroused, 2 = moderate sedation: Frequently drowsy; easily aroused, 3 = severe sedation: Somnolent; difficult to arouse, 5 = none: Normal sleep; easily aroused. Patient satisfaction score[10] was measured with a five-pointe numerical scale; 1 = very satisfied, 2 = satisfied, 3 = undecided, 4 = dissatisfied and 5 = very dissatisfied. Adverse effects assessed for included nausea, vomiting, constipation, drowsiness, respiratory depression, hypotension, and allergic reactions. Secondary outcome measures included tramadol consumption, haemodynamics, patient sedation score, and adverse effects at 0, 2, 4, 6, 8, and 12 h post–operatively. Following discharge from hospital sedation scores were obtained over telephone at 24 and 48 h. Patient satisfaction score at 24 and 48 h after surgery was also obtained by telephonic interview.

With alternate hypothesis that difference exists on comparing flupirtine maleate versus ibuprofen for post-operative pain relief in patients following

gynaecological ambulatory surgeries, the sample size was calculated based on an earlier study considering a mean difference of 1.5[11] and a standard deviation of 2.0 on pain scale between the two groups.A size of 24 patients per group was required at a power of 80% and a type I error of 0.05. Considering loss to follow-up, as this was ambulatory surgery, the sample size was calculated to be 30 patients per group. The statistical analysis was carried out using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA version 15.0 for Windows). The data were calculated as mean and median for all quantitative variables and measures of dispersion. For normally distributed data, mean was compared using independent sample *t*-test. For skewed data, Mann–Whitney test and 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 $P < 0.05$ was considered statistically significant.

RESULTS

Sixty-five patients were enrolled for the study and out of these, five patients were excluded due to non-fulfilment of the inclusion criteria. Hence, 60 patients were randomised into the two study groups, and all patients completed the study [Figure 1]. There were no differences regarding demographics, and types of surgery in both the groups [Table 1]. The type and number of surgeries were similar in both the groups. The type of surgeries were dilatation and curettage, hysteroscopy, polypectomy, cervical biopsy, and re-suturing

Patients in group flupirtine exhibited lower VNRS on movement as compared to ibuprofen group at 2 h post-operatively ($P = 0.04$) [Table 2]. During intragroup analysis, in flupirtine group, VNRS on movement with baseline (0 h) was statistically significant at 2 and 4 h post-operatively ($P = 0.01$, $P = 003$ respectively). One patient in group flupirtine took rescue analgesia at 4 h and in group ibuprofen five patients took rescue analgesia (one patient at 0 h, two patients each at 2 h and 4 h post-operatively), which was statistically not significant. The requirement for rescue analgesia was reduced in flupirtine group as compared to group ibuprofen, but failed to reach statistical significance. The satisfaction scores at 24 and 48 h post-operatively were better in group flupirtine as compared to group ibuprofen ($P < 0.001$) [Table 3]. There were no significant differences in haemodynamics, sedation scores and adverse effects between the two groups.

DISCUSSION

No randomised controlled trial has compared the analgesic efficacy of flupirtine with ibuprofen in ambulatory gynaecological surgeries. Analgesic efficacy of flupirtine maleate was comparable with ibuprofen in patients with ambulatory gynaecological patients up to 48 h with superior satisfaction score in the present study. However, in the early post-operative period flupirtine exhibited reduced VNRS as compared to ibuprofen. This was probably due to the difference in 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.[7] Ibuprofen, a prototype of NSAIDs is known to produce analgesic and antipyretic effects with no muscle relaxant effect. The usual dose is 400–800 mg 3 times a day. It is rapidly bio-transformed

Table 1: Patient characteristics

Characteristics	Group flupirtine (*n*=30)	Group ibuprofen (*n*=30)
Age (years)	41.60±13.15	41.67±10.49
Weight (kg)	59.46±9.37	56.96±8.71
Height (cm)	155.23±3.79	153.36±3.38
Duration of surgery <30 (min)	30 (100)	30 (100)

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

VNRS	Group flupirtine (*n*=30)	Group ibuprofen (*n*=30)	*P*
0 h	0.17±0.59	0.20±0.55	0.69
2 h	0.20±0.62	1.03±2.90	0.04*
4 h	0.35±0.99	0.50±1.00	0.38
6 h	0.44±0.90	0.46±1.02	0.91
8 h	0.51±0.92	0.59±1.18	0.81
12 h	0.64±1.00	0.26±0.93	0.07
24 h	0.18±0.45	0.06±0.25	0.40
48 h	0.00±0.00	0.00±0.00	1.00

Data described as Mean±SD, **P*<0.05 considered statistically significant.
SD – Standard deviation; VNRS – Verbal Numerical Rating Scale

Table 3: Patient satisfaction scale after surgery

Time of assessment	Group flupirtine (*n*=30)	Group ibuprofen (*n*=30)	*P*
24 h	1.23±0.43	1.83±0.46	0.00*
48 h	1.17±0.37	1.80±0.48	0.00*

Data described as Mean±SD, **P*<0.05 considered statistically significant.
SD – Standard deviation

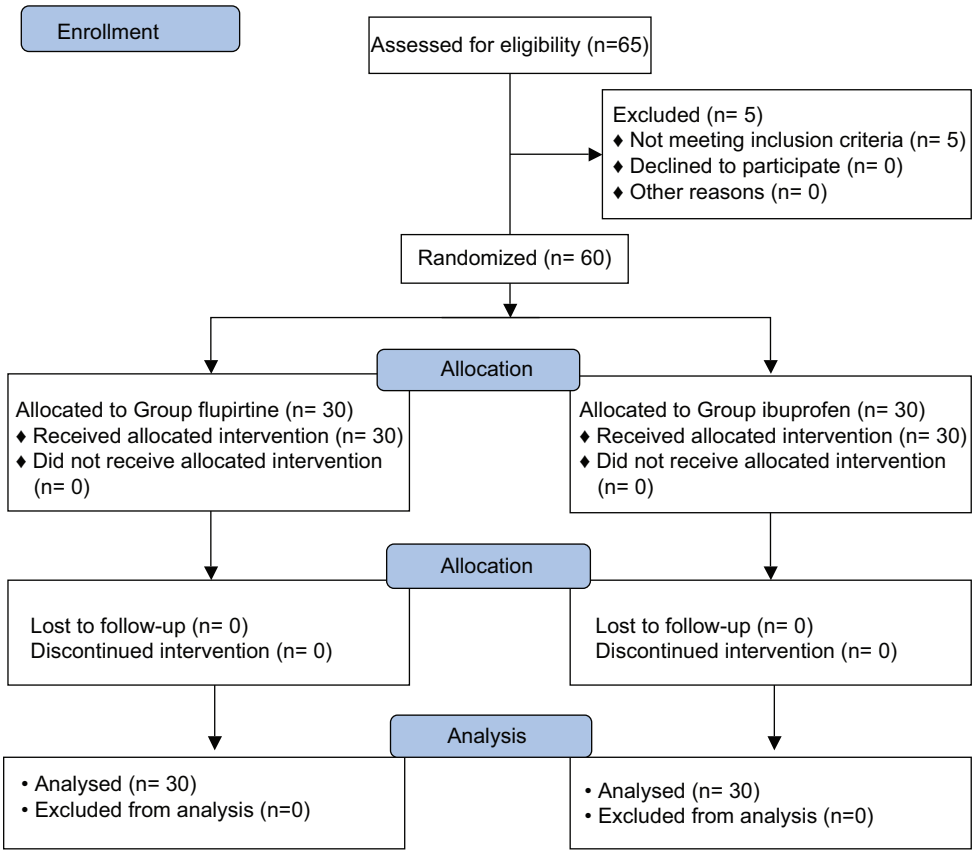

Figure 1: Consort diagram

with a serum half-life of 1.8–2 h and is completely eliminated in 24 h after the last dose. Old age has no significant effects on the elimination of ibuprofen. Renal impairment also has no effect on the kinetics of the drugs and rapid elimination still occurs as a consequence of metabolism. Ibuprofen is mainly used in the treatment of mild to moderate pain related to dysmenorrhoea, headache, migraine, post-operative dental pain, management of spondylitis, osteoarthritis, rheumatoid arthritis and soft tissue disorders.[12] No statistically significant difference was found in VNRS at other time intervals in both the groups as the patients underwent short duration ambulatory surgeries, which were of mild to moderate pain severity. Ibuprofen is a potent analgesic and has good efficacy for pain relief in post-operative period with undesirable drug reactions in <1%.[5] The satisfaction score was superior in group flupirtine as compared to group ibuprofen, but since this was a secondary outcome, further trials are required in this regard.

Studies show equal analgesic efficacy of flupirtine versus diclofenac for post-operative pain relief in patients undergoing gynaecological, orthopaedic and craniotomy surgeries.[12,13] 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.[7] When diclofenac 50 mg was compared with ibuprofen 400 mg following surgical extraction of impacted third molar, increased supplementary medication was required in diclofenac group during the first 2 post-operative days.[14]

Pre-emptive use of NSAIDs before surgery has been shown to be more beneficial in dental pain model. However, there is no clear consensus with respect to major surgeries.[7,12-14] Ibuprofen as compared to diclofenac is superior due to its reduced gastrointestinal complications and better cardiovascular safety.[15,16] Oxford League table for analgesics in acute pain described NNT of 2 or less as effective analgesic. NNT of diclofenac 100 mg is 1.9 (1.6–2.2) as compared to NNT of ibuprofen 800 mg 1.6 (1.3–2.2).[17] Ambulatory gynaecological surgical patients not only require adequate pain relief, but also early discharge from

hospital. The analgesic and the additional muscle relaxant properties of flupirtine benefited the patients in the present study.

Flupirtine has advantages over NSAIDs due to superior tolerability and represents an excellent alternative 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.[12]

Flupirtine has similar analgesic efficacy to the opiate analgesics, codeine, dihydrocodeine, and pentazocine, with superior tolerability when compared with tramadol and pentazocine.[7] Flupirtine can be useful as an alternate analgesic in patients non-tolerant to adverse effects of opioids such as respiratory depression, tolerance and dependence. The most worrisome adverse effect of flupirtine was hepatic dysfunction. However, in the present study no serious adverse effects were observed following short-term oral administration of flupirtine 100 mg, thrice daily.[7]

The present study proves that flupirtine could be used as an alternative analgesic to ibuprofen in patients following ambulatory gynaecological surgeries with better satisfaction score. This was probably due to muscle relaxant effect of flupirtine in addition to its analgesic effect. No adverse events were observed in the present study, and there were no readmissions.

There are some limitations to the present study. It was targeted to a specific population of ambulatory surgeries and NNT for flupirtine was not calculated, as placebo was not used in the study. Further multicentre randomised controlled trials may validate the results of the present study.

CONCLUSION

Analgesic efficacy of flupirtine maleate was comparable to ibuprofen with better satisfaction score in patients following ambulatory gynaecological surgeries for up to 48 h. Flupirtine with additional muscle relaxant effect is an effective alternative in these patients where ibuprofen is either contraindicated or not desired.

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Conflicts of interest

There are no conflicts of interest.

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