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Flupirtine for Pre-Emptive Analgesia Following Laparoscopic Gynaecological Surgeries

KEYWORDS: surgery laparoscopic gynaecological, analgesic flupirtine, analgesia postoperative pre-emptive, side effects minimum

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ABSTRACT *Aim: The aim of this study was to evaluate the efficacy of flupirtine, a NMDA receptor antagonist for postoperative analgesia when administered orally in patients undergoing gynaecological laparoscopic surgeries.Materials and Methods: Sixty adult female patients posted for laparoscopic gynaecological surgeries were randomly divided in to two groups to receive preoperatively either flupirtine or B complex orally as a placebo in a randomized double blind manner. Rest of the anesthetic management was same in both the groups. Pain/sedation scores, clinical parameters and side effects were studied and compared in both groups.The time to first dose of rescue analgesic and number of such rescue doses during first 24 hours postoperatively and patient's satisfaction were noted.*

Results: It was observed that mean time to first dose of rescue analgesic drug was 2 to 2.5 hours postoperatively in patients who received flupirtine preoperatively as compared to patients of placebo group who demanded first dose of analgesic almost immediately after surgery. This difference was statistically significant. Subsequently there was no difference between the two groups as regards pain and sedation scores as well as requirement of analgesia and incidence of side effects.

Conclusions: Pre-emptive use of flupirtine provides adequate analgesia with mild sedation during immediate postoperative period after laparoscopic gynaecological surgeries and its use is devoid of any side effects.

INTRODUCTION

Acute postoperative pain and it's management is a major concern for anaesthesiologists in patients undergoing surgery[1]. Postoperative pain management is the most important component of adequate postsurgical patient's care[2]. Postoperative pain adversely affects patient's operative outcome, wellbeing and satisfaction from medical care. It also causes tachycardia, hyperventilation and decrease in alveolar ventilation, transition to chronic pain, poor wound healing and insomnia [3-5]. It also delays hospital discharge. Postoperative pain management is based on pharmacological and non-pharmacological protocols. Pharmacological protocols make use of different routes of administration like oral, intravenous (IV), intramuscular (IM), subcutaneous (SC), rectal, transdermal, intrathecal and epidural. Among the pharmacological protocols opioids have been routinely used for postoperative pain control but they have some unpleasant side effects like drowsiness, sedation, nausea, vomiting, pruritus, ileus, urinary retention, constipation and ventilator depression. Some other analgesic drugs like non-steroidal anti-inflammatory drugs (NSAIDs), local anesthetic drugs, ketamine, tramadol, pregabalin, acetaminophen etc[6-8]. They are also being used due to their fewer side effects. Though severity of pain is less following laparoscopic surgery compared to laparotomy, it still requires due care by the anaesthesiologist. Laparoscopic surgical pain is at sites of incision, trocar insertion and is also due to peritoneal stretching and diaphragmatic irritation by carbon dioxide insufflation[9].

Flupirtine is N-methyl D-aspartate (NMDA) receptor antagonist. It is a derivative of triaminopyridine. The actual site of action of this drug is unknown but most probably it acts in the central nervous system, at spinal as well as supra spinal level. The drug is available in 50 and 100 mg capsules for oral use and 75/150 mg rectal suppository[10].

There are a very few reports on use of flupirtine for postoperative analgesia in the recent past. On searching the literature on this subject it was found that use of this drug in the perioperative period is quite safe and is devoid of any side effects. Therefore we undertook this study to evaluate analgesic efficacy of this drug following laparoscopic gynaecological surgeries in adult female patients. The primary outcome measured was severity of postoperative pain, time to first analgesic dose requirement and total analgesic dose required in both groups. The secondary outcome measured was incidence of complications in both the groups.

MATERIALS AND METHODS

This prospective randomized double blind placebo controlled study was conducted at our teaching institute from October 2015 to march 2016. Sixty adult female patients between 21 and 45years belonging to American society of anesthesiologists physical status I/II (ASA I/II) were selected for the study after obtaining written informed consent from the patients. Prior approval of institutional ethics committee was also obtained. All patients were posted for elective laparoscopic gynaecological procedures after thorough pre-

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operative evaluation and necessary investigations. Patients already on analgesic and sedative medication for various indications during previous one month and patients who were un co-operative or un able to understand use of visual analogue scale (VAS) were excluded from the study. Patients suffering from chronic hepatic and renal disease were also excluded. All patients were randomly assigned to flupirtine group (F group) or the placebo group (P group) to receive either capsule flupirtine 200 mg or physically similar capsule of vitamin B complex, respectively. Randomization was done by simple lottery method. Sample size was decided using power analysis of the study suiting the non-parametric data comparison by Student's t test. The study was conducted in a double blind manner in which the person not taking part in the study administered the medication. The anesthesiologist directly involved in anesthesia and postoperative care of the patient and the patient himself were an aware of the drug administered. In the preoperative ward, all patients were explained the use of VAS scale: VAS 0 – No pain, 0-3 – Mild pain,3-5 – Moderate pain,>7 – Severe pain and 10 - Worst pain one can imagine. Ramsay sedation score (RSS) was used postoperatively to observe depth of sedation : RRS 1 = patient anxious and agitated or restless, or both, 2 = patient cooperative, oriented, and tranquil, 3 = patient responds to commands only, 4 =patient exhibits brisk response to light glabellar tap or loud auditory stimulus, 5 = patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus, 6 = patient exhibits no response[11].

In the preoperative room patients were given oral medication (flupirtine or placebo) 1 hour prior to surgery by the person not involved in the study. On the operation table patient's base line vital parameters such as pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure(MAP) and peripheral arterial oxygen saturation(SPO2) as well as electrocardiogram(ECG) were recorded. Patient were then pre medicated with IV glycopyrrolate 0.2mg and fentanyl 2mcg/kg body wt. General anesthesia (GA) was induced with IV propofol 2mg/kg body weight followed by suxamethonium1.5mg/kg for tracheal intubation. Anesthesia was maintained with nitrous oxide-oxygen (N2O:O2 65:35%) and isoflurane (0.6 to 1%). Vecuronium 0.1mg/kg was used to provide muscle relaxation during surgery.

Intra operatively patients were monitored with continuous ECG, pulse rate, SpO2, end tidal carbon di oxide concentration (ETCO2) and BP every 5 min. Blood loss and urine output were also monitored. Ringer lactate (RL) was used as replacement fluid.

At the end of surgery residual effect of vecuronium was reversed with glycopyrrolate-neostigmine combination in the usual dose. Patients were then shifted to post anesthesia care unit (PACU). In PACU patients's VAS, RSS, vital parameters were recorded as well as side effects if any in both the groups. This was taken as 0 time. Subsequently, VAS was recorded every half an hour for first 4 hours and then 4hourly up to 24 hours postoperatively. The incidence and severity of postoperative nausea or vomiting (PONV) was also noted as assessed by four points scale on which 1 means no nausea or vomiting , 2 means mild PONV (Patient having only mild nausea, or one emetic episode or nausea lasting for <10 min and no antiemetic required), 3 means moderate PONV (patient has 1-2 emetic episodes or moderate to severe nausea and antiemetic therapy required in form of ondansetron 0.1mg/kg and 4 means severe PONV (>2 emetic episodes or nausea more than twice and patient required more than one antiemetic)[12].

Whenever patient complained of pain (VAS>3), 1gm paracetamol was infused intravenously over 20 min as rescue analgesic. The number of rescue analgesic doses required during study period were noted.

STATISTICALANALYSIS:

Descriptive statistical analysis was carried out. Data entry was done using MS Excel 2007 computer software. Data were analyzed using SPSS version 17. Numerical variables are presented as mean and standard deviation (SD). Categorical variables are presented as frequency (%). The difference between the two groups with regards to continuous variables was assessed by Student's - t test and categorical variables by Chi-square test. Non parametric parameters were analyzed by Mann-Whitney Test. For all the tests, p value of 0.05 and less was considered statistical significant and a value of 0.001 and less was considered as statistically highly significant.

RESULTS

There was no statistically significant difference between the two groups with respect to age, weight of patients and duration of anaesthesia among the patients of two groups as shown in Table 1. The time to first rescue analgesic drug in both the groups is also depicted in Table 1 and figure 1.This difference between the two groups is clinically as well as statistically highly significant (p<.001). The surgical procedures performed in both the groups were comparable. The surgical procedures performed were Laparoscopic diagnostic hysteroscopies, laparoscopic tubal ligations and laparoscopic cystectomies.

VAS scores at different time intervals are depicted in figure 2. Three patients in flupirtine group had pain at operation site immediately after surgery requiring rescue analgesic in form of one gram paracetamol IV infusion over 20 minutes. As compared, 17 patients in placebo group required IV paracetamol infusion as rescue analgesic over 20 minutes for pain relief. This difference between the two groups at zero hour was statistically highly significant (p <.001) .At this time mean RSS of patients in group F was 3.03 and in group P was 1.76 (figure 3) indicating that most of the patients in flupiritne group were comfortable and responding to commands while majority of patients in placebo group were restless and anxious . At subsequent time intervals up to first four hours there was statistically significant difference in VAS score between the two groups. VAS score was later on comparable in both the groups up to 24 hours. Total number of five patients in flupiritine group and 19 patients in placebo group required two rescue analgesic dose of paracetamol IV in 24 hours. This difference was statistically significant. The overall incidence of side effects was low in both the groups as only three patients in F group and five patients in P group had postoperative nausea and vomiting. This difference was statistically not significant. There were no other side effects noted in this study.

Table 1

Comparison of Demographic & Treatment characteristics

Parameters	Group F	Group P	P Value
Age	26.76 ± 4.86	28.76 ± 6.01	0.150
Weight	49.4 ± 7.15	51.86 ± 8.91	0.224
Duration of Anaesthesia (in mins)	33.9 ± 6.82	32.2 ± 6.66	0.383
Time of Rescue anaigesic (in mins)	128 ± 38.83	40 ± 17.45	< 0.001

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Figure 1

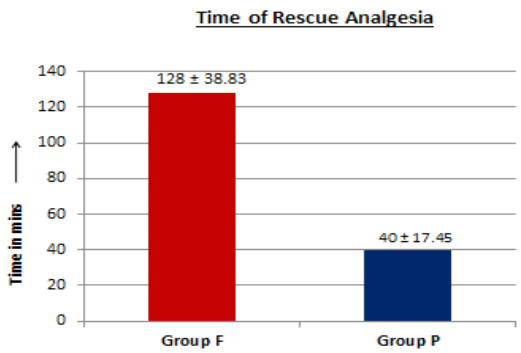


Figure 2.

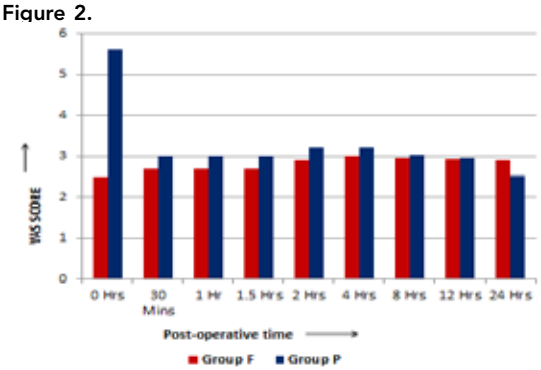
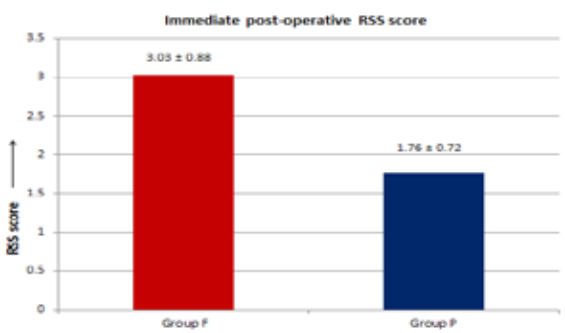


Figure 3.



Discussion

Gynaecological laparoscopy is a commonly performed procedure for diagnostic surgeries for infertility, ovarian surgeries etc. Inadequate analgesia, nausea & vomiting can cause distress to patient & augment post-operative complications. This study tells that 200mg flupirtine giving orally 2 hours before incision has preemptive analgesic effect in patient undergoing laparoscopic gynaecological surgeries. This is supported by the observation that patients who received flupirtine before surgical stimulus had VAS scores lower during early postoperative period in contrast to group P who had higher VAS scores. This study also supports the fact that giving the analgesic drugs before the operation or earlier during the operation will ensure that drug absorption & distribution to the effect site has occured by the time patient is waking after general anaesthesia.

Flupirtine maleate, a water soluble compound, undergoes rapid gastric absorption (bioavailability 90%) after oral administration, with a peak plasma concentration of approximately 0.82mg/L, achieved in about 1.62h[13-14]. Flupirtine has dose dependent analgesic effect, but not in linear fashion for range of therapeutic effects(100-400mg)[13-14]. Increase in oral dose of flupirtine increases the side effects like drowsiness, muscle relaxation and concentration impairment effects, least desirable during the immediate postoperative period[13-14]. Keeping this in mind we chose therapeutic dose of flupirtine (200 mg) with maximum therapeutic analgesia,but it showed significant sedation related side effects.

Past studies proved that flupirtine has analgesic activity at both spinal and supraspinal levels. Primary site of action appears to be descending adrenergic pathways, by an indirect action on NMDA receptors through activation of Gprotein coupled inward rectifying potassium channels[15]. 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)[16]. Acting as potassium channel opener, flupirtine reduces glutamate mediated rise in intracellular calcium concentration, leading to hyperpolarization of neuronal membrane[17-20].

Moore et al. showed equivalent postoperative pain relief when flupirtine (100 mg) was compared with dihydrocodeine (60 mg) in patients operated for hysterectomy[21]. A similar study was done which showed same results when flupirtine was compared with pentazocine[22]. In one study flupirtine was compared with NSAIDS which showed it exhibited better analgesic profile in comparison to diclofenac sodium[23]. Yadav et al conducted a double blind prospective study assessing the role of flupirtine as a preemptive analgesic in patients undergoing laparoscopic cholecystectomy and concluded that it is effective as preemptive analgesic in providing adequate pain relief during immediate postoperative period and it is more acceptable as it lacks the typical side effects of continued administration[24].

Here we compared flupirtine with the placebo group to see its analgesic activity and any side effects compared to placebos.

A lot of studies indicate that flupirtine is well tolerated with least side effects if its given to the patient on a short term basis. Common side effects with long term administration include sedation, gastrointestinal upset, headache, disorientation, and hallucinations[13-14]. In this study we used flupirtine as only a preemptive analgesic drug with no repeated doses and we found no significant side effects except for significant sedation in group F as compared with placebo group.

CONCLUSION

Our study conclude that flupirtine is a very much effective preemptive analgesic drug in providing adequate pain relief during the immediate postoperative period after gynaecological laparoscopic surgery.The preemptive analgesic effect of flupirtine is more acceptable as it does not show the typical side effects which we see during continued administration except some sedation.

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