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ANALGESIC EFFICACY OF PRE-EMPTIVE FLUPIRTINE MALEATE FOR POST OPERATIVE ANALGESIA IN PATIENTS UNDERGOING TOTAL ABDOMINAL HYSTERECTOMY UNDER GENERAL ANAESTHESIA

Anaesthesiology

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ABSTRACT

Background: Pre-incisional analgesic drug administration showed more effectiveness in decreasing the postoperative pain. Flupirtine have been used for various painful conditions including postoperative pain and beneficial in controlling acute and chronic pain like trauma, migraine, cancer pain and low backache. **Material And Methods:** This prospective study was conducted in the Department of Anaesthesiology and Critical Care, Sher-I-Kashmir Institute of Medical Sciences, Srinagar from 2017 to 2020 after approval from IEC. In the study 50 patients undergoing abdominal hysterectomy under General Anaesthesia were included and divided in to two groups, Group A received 100mg oral flupirtine maleate tablet and Group B had received multivitamin tablet 90 minutes prior to induction of anaesthesia. Patients were assessed by VAS scale at various intervals of time. The time to request for first rescue analgesic and total analgesic consumption was recorded in both the groups. **Observations:** There was statistically insignificant difference between the two groups in respect of pre-operative vitals (HR, SBP, DBP, MAP, SPO2 and RR). There was significant difference ($p<0.05$) among the two groups as regards the post-operative heart rate, systolic blood pressure & diastolic blood pressure, mean arterial pressure. The mean value of VAS shows statistically significant difference between two groups at various intervals of time post-operatively ($P<0.001$). In Group-A, 20% of patients experienced side effects whereas in Group-B, 16% patient's experienced side effects. **Conclusion:** The study concludes that pre-emptive administration of oral flupirtine before induction of anesthesia provides effective analgesia in first -3 hours of postoperative period and reduces the amount and frequency of rescue analgesics needed in postoperative period.

KEYWORDS

pre-incisional analgesic, flupirtine, abdominal hysterectomy

INTRODUCTION:

Post-operative pain management is the most important component of adequate postsurgical patient's care [1]. Prevention and treatment of postoperative pain continues to be a major challenge in postoperative care and plays an important role in the early mobilization and well-being of surgical patient.

The basic remedies for postoperative analgesia are still confined to regional anesthesia, opioids, NSAIDs and local anesthetics, but they are inevitably associated with risk of- respiratory depression, itching. retention of urine and their actions may be short lived [2]. The need for post-operative pain relief and choice of drugs depends upon extent and duration of surgery, site of operation, time lapse since operation and patient's personality.

Pre-emptive analgesia is an antinociceptive treatment that prevents establishment of altered central processing of different input which amplifies postoperative pain and thereby thought to consequently decrease the incidence of hyperalgesia and allodynia after surgery and also effective in reducing chronic postoperative pain [3]. Different drugs have been tried as pre-emptive analgesia such as Diclofenac, Ketorolac, Ibuprofen, Fentanyl,Morphine Pregabaline and Gabapentin through systemic and oral routes [4].

Pre-emptive analgesic modalities can be used either singly or in combination. Pre-incisional analgesic drug administration showed more effectiveness in decreasing the postoperative pain by protecting the CNS from noxious stimuli induced deleterious effect, and which may lead to increased pain and hyperalgesia.

Flupirtine is a non-opiate, non NSAID, centrally acting analgesic and unique as first in class of selective neuronal potassium channel opener that also has NMDA receptor antagonist properties [5]. it has been tried for chronic as well as acute postoperative pain [6,7].

Flupirtine maleate is a water soluble compound, undergoes rapid gastric absorption (bioavailability 90%) after oral administration with peak plasma concentration of approximately 0.8-2mg/ml, achieved in about 1.6-2 hours. [8,9].

Flupirtine have been used for various painful condition including postoperative pain. It has beneficial effect in controlling acute and chronic pain like trauma, migraine, cancer pain and low backache. Its muscle relaxant and neuroprotective effect was an additional beneficial effect. It is found that use of this drug in the perioperative period is quite safe and devoid of side effects.

Therefore, this study was done to evaluate the analgesic efficacy of pre-emptive oral flupirtine maleate for post-operative analgesia in patients undergoing abdominal hysterectomy under general anaesthesia.

MATERIAL AND METHODS

This prospective study was conducted in the Department of Anaesthesiology and Critical Care, Sher-I-Kashmir Institute of Medical Sciences, Srinagar from 2017 to 2020. After approval from IEC, 50 patients undergoing abdominal hysterectomy under General Anaesthesia were included in the study as per following inclusion and exclusion criteria:

Inclusion Criteria:

1. ASA-I and II
2. Aged 30-60 years

Exclusion Criteria

1. History of allergy to the drug used in the study
2. History of Analgesic intake 3 days before surgery
3. Coagulopathy
4. Gastritis
5. Previous Cerebrovascular accident
6. Dementia or similar cerebral condition
7. Patients on anticonvulsants, anti-depressants
8. Chronic Analgesic use
9. Alcohol or drug abuse

In the study patients were divided in to two groups, Group A received 100mg oral flupirtine maleate tablet and Group B had received multivitamin tablet 90 minutes prior to induction of anaesthesia with a sip of water.

On arrival to operation theatre 18 G I/v cannula was secured and 500ml of normal saline was infused. Basic standard monitoring ECG, NIBP, $ETCO_2$ and pulse oximetery) was done till completion of surgery. Glycopyrolate 10 µ/kg was given before anaesthesia and then anaesthesia was induced with propofol 2.5mg /kg, fentanyl 2 µ g/kg

and endotracheal intubation was facilitated with atracurium 0.5mg/kg. Airway was secured with cuffed endotracheal tube and patient put on mechanical ventilation. Anaesthesia was maintained with 66% N_2O in Oxygen and Isoflurane 1% to MAC > 1. Muscle relaxation was maintained with atracurium 5mg every 20 minutes.

For intraoperative analgesia morphine 0.1mg /kg was given before incision. Patients received ondensteron 0.lmg /kg towards the end of surgery. Neuromuscular blockade was reversed with neostigmine 60 µg/kg and glycopyrrolate 10 µg/kg and patient put on 100%Oxygen after extubation till full recovery. The period after full recovery from anaesthesia was considered as postoperative period.

Patients were assessed at 0,1,2,4,8,6,12,24 and 36 hrs after recovery from anaesthesia for pain by VAS scale (VAS 0- no pain, VAS 1-3-mild pain, VAS 4-6 moderate pain, VAS 7-9 severe pain, VAS 10 worst pain). Rescue analgesia if needed was given in the form of Diclofenac 50mg I/M if VAS > 4. The time to request for first rescue analgesic and total analgesic consumption was recorded in both the groups.

The recorded data was compiled and entered in a spreadsheet Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc. Chicago, Illinois, USA) for analysis of results.

OBSERVATIONS AND RESULTS:

It was observed in our study that the age of patients in both the groups was between 31-60 years with mean 45.5±7.79 years in Group-A whereas in Group B, the mean age was 46.4±8.12 years. Mean age in both the groups was comparable and the difference between the age in two groups was statistically insignificant (P>0.05).

In our study, physical status of both the groups was comparable with insignificant statistical variation. In both the groups maximum number of patients belonged to ASA Grade-II.

Table 1: Duration of Surgery (minutes) In Two Groups

Duration of Surgery (Minutes)	N	Mean	SD	Range	P-value
Group-A	25	124.8	29.21	90-180	0.633
Group-B	25	121.2	23.76	90-175	

The duration of surgery in both groups was comparable and showed statistically insignificant difference (p>0.05). The mean duration of surgery in Group-A and Group-B was 124.8 minutes and 121.17 minutes respectively.

As depicted in fig. 1, there was statistically insignificant difference between the two groups in respect of pre-operative vitals (HR, SBP, DBP, MAP, SPO2 and RR).

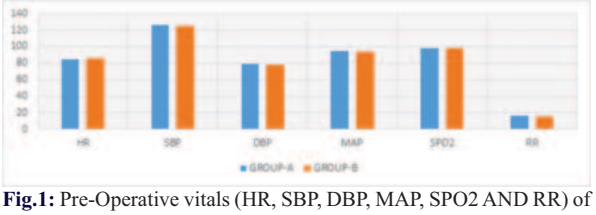

Fig.1: Pre-Operative vitals (HR, SBP, DBP, MAP, SPO2 AND RR) of patients in two groups

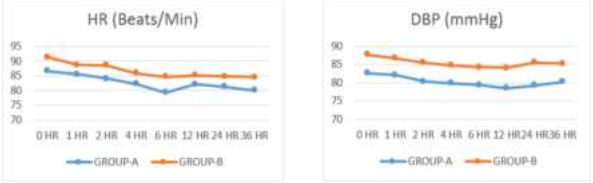

Fig 2: Post-operative comparison of HR (Beats/Min) and DBP (mmHg) in two groups at various intervals of time

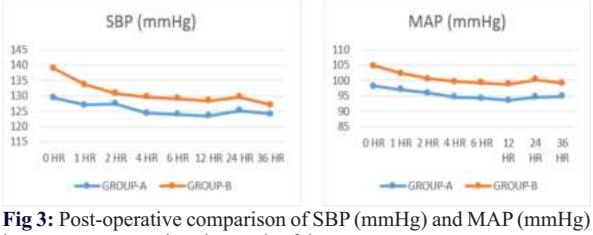

Fig 3: Post-operative comparison of SBP (mmHg) and MAP (mmHg) in two groups at various intervals of time

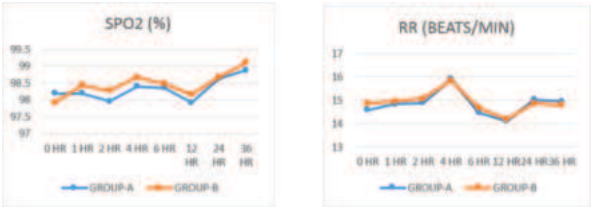

Fig 4: Post-operative comparison of SPo2 (%) and RR (Beats/min) in two groups at various intervals of time

It was found in our study that there was significant difference (p<0.05) among the two groups as regards the post-operative heart rate, systolic blood pressure & diastolic blood pressure, mean arterial pressure. Further, the difference was statistically insignificant (p>0.05) among the two groups as regards of post-operative respiratory rate and SPO2 (fig. 2,3 and 4).

Table 2: Post-operative VAS Score In Two Groups At Various Intervals Of Time.

VAS Score	Group-A		Group-B		P-value
	Mean	SD	Mean	SD	
O HR	0.52	0.65	1.92	0.81	<0.001*
1 HR	1.24	0.97	3.44	1.39	<0.001*
2 HR	3.80	2.02	2.72	1.65	0.045*
4 HR	2.16	1.18	2.52	1.68	0.345
6 HR	1.92	1.73	2.96	1.65	0.034*
12 HR	2.36	2.04	3.48	1.61	0.036*
24 HR	2.64	2.16	4.24	1.01	0.002*
36 HR	1.16	0.75	1.24	0.60	0.677
Overall	1.98	0.54	2.82	0.33	<0.001*

Statistically Significant Difference (P-value<0.05)

The table-2 shows that comparison in Visual Analogue Score for pain between two groups post-operatively for duration of 36 hours. In Group- A VAS Score had a mean of 1.98±0.54, whereas in Group-B it was 2.82±0.33. The mean value of VAS shows statistically significant difference between two groups at various intervals of time post-operatively (P<0.001).

Table 3: Frequency Of Rescue Analgesic Dose In Two Groups

No of Doses	Group-A		Group-B		P- value
	No.	% age	No.	%age	
1 Dose	12	48	0	0	<0.001*
2 Doses	10	40	6	24	
3 Doses	3	12	14	56	
4 Doses	0	0	5	20	
Total	25	100	25	100	

*Statistically Significant Difference (P-value<0.05)

Table-3 depicted that in Group-A, 48% of patients demanded only one dose of rescue analgesia, 40% two doses, 12% three doses and none four doses whereas in Group-B, 56% of patients demands three doses, 24% two doses and 20% demanded four doses of rescue analgesia and the results were statistically significant between the two groups (P<0.001).

The mean of total analgesic consumption in Group-A was 80±32.28 and in Group-B it was 148±33.79. The difference was statistically significant between the two groups (p<0.001).

Table 4: Various Side Effects In Two Groups

Side Effects	Group-A		Group-B		P- value
	No.	% age	No.	%age	
Nausea	3	12	1	4	0.609
Vomiting	2	8	1	4	1.000
Hypotension	0	0	0	0	-
Dry Mouth	0	0	2	8	0.489
Dizziness	0	0	0	0	-

NS- Not Significant (p>0.05)

20% of patients in Group-A experienced side effects like nausea and vomiting and in Group-B, 16% patient's experienced nausea, vomiting and dry mouth and no patient in either of the groups experiences

dizziness and hypotension. The results were statistically insignificant in two groups (p>0.05).

DISCUSSION:

The present study was undertaken to evaluate the analgesic efficacy of pre-emptive oral flupirtine maleate for postoperative analgesia in patients undergoing abdominal hysterectomy under general anaesthesia. In this study we used 100mg oral flupirtine maleate tablet in group A (flupirtine group) (n=25) which was given 90 minutes prior to induction of anaesthesia and group B (control group) (n=25) patients received multivitamin tablet and acts as control for comparison with the study group.

In our study, 2 groups were comparable with respect to age and physical status of the patient and the difference in mean duration of surgery between two groups was statistically insignificant. There was no statistically significant difference in preoperative HR, SBP. DBP and MAP, SPO2 and respiratory rates between the two groups.

In our study, the mean HR, SBP, DBP and MAP of Group- A patients at various intervals of time postoperatively were significantly lower than those of group B and it was found that tachycardia and raised BP coincided with the patient's demand for rescue analgesia. The observations for VAS score for pain corresponded to the above findings. Thus tachycardia and hypertension in group B patients as compared to Group- A patients can be attributed to lesser analgesia in group B patients. The observations were contradictory to those of *Mohanty A et al* who recorded no significant difference between two groups with regard to HR, SBP. DBP and MAP in a similar study [10]. Our results are also contradictory to a similar study done by *Sethy AK et al* who found no significant difference between two groups with regard to hemodynamic parameters i.e; HR, SBP, DBP and MAP [11].

In our study, comparison of mean post-operative respiratory rate and SPO2 showed no statistically significant difference between the two groups. Further, statistically significant difference in visual analogue pain score (VAS) between the two groups at 0, 1,2,4,6,12,24 and 36 hours postoperatively, with lower pain scores in Group-A. Time to the request for first analgesia (hours) between two groups showed statistically significant difference with time interval for first analgesia being more in Group- A.

In our study, the total analgesic consumption and frequency of rescue analgesic doses given during post-operative period showed statistically significant difference. Pre-emptively given oral flupirtine maleate 100mg provided effective analgesia for first 2-3 hours of postoperative period.

Furthermore, the analgesia in flupirtine group was significantly better compared to control group for first two hours postoperatively (p <0.001). The patients in group A had 'better pain control for the entire postoperative period than that of control group. This was most convincingly shown by the visual analogue score as it was low in the first 3 hours of postoperative period. The visual analogue score showed significantly lower values in the study group than that in the control group for the remaining postoperative period as well, except for statistically insignificant difference at 4 hours and 36 hours postoperatively. Patients were followed up for 36 hours postoperatively. The findings of our study correlates with a similar study by *Yadav G et al* wherein it was showed that the time to the first analgesic requirement was significantly prolonged in the flupirtine group as compared with placebo group. There was significant pain reduction in early postoperative period (upto to 4 hour), but no changes occurred thereafter [12].

A mother study done by *Malik A et al* was also comparable with our study. In this study time to the request for first dose of rescue analgesia and number of such doses during first 24 hours postoperatively and patient satisfaction were noted and it was observed that mean time to first dose of rescue analgesic drug required was 2 to 2.5 hours postoperatively in patients who received flupirtine preoperatively as compared to patients in control group who demanded first dose of analgesic almost immediately after surgery. This difference was statistically significant [13].

Other studies like *Abrams S M et al* stated that, flupirtine when given orally attained peak plasma concentration at 1.5 to 2 hours and the analgesic effects lasted for 6.5 to 8 hours [14]. Hence it was assumed that, in our study flupirtine attained peak plasma concentration during intraoperative period and provided adequate analgesia during the postoperative period. This was indicated by stable vitals which were noted, till the early postoperative period. But significant difference was not noted in the late postoperative period. The time to the request for rescue analgesia was longer in group A (flupirtine) patients (p<0.001). Our study, was also comparable to studies done by *vanitha Ahuja* and *ambarish sharma* [15,16].

In our study, we found statistically insignificant difference in the incidence of side effects between the two groups. But a higher incidence of nausea and vomiting was found in group A (flupirtine). Our study correlates with a similar study by *Ohja P.K et al* showed that flupirtine works as an excellent alternative analgesic in patients at risk of NSAIDs associated gastropathy and was significantly better tolerated with fewer side effects than usually associated opioids, such as nausea, vomiting and dizziness [17].

Other studies by *Yadav G et al* showed side effects were comparable between the study (flupirtine) and control group except for higher sedation in flupirtine group. *Malik et al* showed no difference between the two groups with regard to pain and sedation scores as well as requirement of analgesia and incidence of side effects [12,13].

CONCLUSION

The study concludes that pre-emptive administration of oral flupirtine (100mg) 90 minutes before induction of anesthesia provides effective analgesia in first -3 hours of postoperative period and reduces the amount and frequency of rescue analgesics needed in postoperative period in patients undergoing total abdominal hysterectomy under general anesthesia. It was further found that flupirtine as single dose had no significant side effects, with its use.

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