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Comparison of Effect of Pre-Emtive use of Oral Flupirtine and Oral Pregabalin for Post Operative Analgesia in Abdominal Hysterectomy

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Abstract: ***Background and Aims: Uncontrolled postoperative pain, characteristic to abdominal hysterectomy, results in delaying postoperative recovery and mobilisation. Hence we undertook a prospective randomized trial to analyze and compare the role of flupirtine and pregabaline as a preemptive analgesic. Material and Methods: After receiving approval from ethical committee, 64 cases were allocated to two groups using sealed envelope method to receive capsule flupirtine (200 mg) or pregabaline (150 mg) orally, 1.5 hrs. before the abdominal hysterectomy surgery. Time to first rescue analgesia, assessment of postoperative pain in terms of visual analogue score was primary outcome with presence of any side effect as secondary outcome. Data were analyzed using SPSS 21 software, chi-square test, unpaired t test. Results: Duration of analgesia was found to be significantly more in flupirtine group 6hrs.postoperatively as compared to pregabaline group, with no significant difference in demographics, onset of regional anaesthesia (motor and sensory block) and duration of sensory and motor block in both groups. Time to first rescue analgesia was prolonged in the flupirtine group. Total analgesic requirement was more in pregabalin group. Conclusions: Flupirtine is more acceptable as preemptive analgesic in providing adequate pain relief during postoperative period in abdominal hysterectomy surgery and it lacks the typical side effects of continued administration. Limitation: This study was of small group and single dose drug administration.***

Keywords: Flupirtine, Pregabaline, abdominal hysterectomy, preemptive analgesia.

1. Introduction

In the era of multimodel analgesia. Analgesic care starts from pre-operative period in the form of preemptive analgesia to prevent acute and chronic post-operative pain.

Preemptive analgesia is treatment initiated before the surgical procedure; it refers to block afferent nerve fibers before a painful stimulus. They can be administered through various routes e.g. orally, intrathecally, intravenously. Due to this protective effect on nociceptive system, preemptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery. [1, 2, 3]various drugs such as local anaesthetics, opioids, NSAIDS, COX-2 inhibitors, gabapentin, pregabalin, flupirtine, clonidine have been used as preemptive analgesics.[4] Very few studies are available for use of flupirtine as preemptive analgesia and no study available comparing flupirtine and pregabaline to the best of our knowledge, thus purpose of this study was to access and compare flupirtine and pregabaline as preemptive analgesic agents.

2. Material and Method

After Ethical Committee approval (Ref. No.2517 MC/EC/2016) and written/informed consent, 64 American Society of Anesthesiologists physical Status I or II female patients, aged 35-60 years, weight 40-70 kgs, height >145 cms posted for abdominal hysterectomy, were included in this trial between 16 March 2016 to 15 May 2016. Patients with general contraindication for spinal anesthesia (like sepsis. bacteremia) skin infection at the site, severe hypovolemia, coagulopathy, CNS symptoms like hallucination, depression, disorientation were excluded.

The study was a hospital based, randomized, double blind, comparative, interventional study. Using sealed envelope method randomization was done and patients were assigned into flupirtine group (group A=32) or the pregabaline group (group B=32) to receive either capsule flupirtine 200 mg or physically similar capsules pregabaline 150 mg, respectively. An anesthesia resident, who was not part of the study, administered one capsule to all patients with a sip of water 1.5 h before surgery. Neither patient nor the observer was aware of the type of medications.

In the preoperative ward, all patients were instructed on the proper use of visual analogue score (VAS) for assessing pain. After taking the patient in operation theatre, all standard moniters were attached and baseline parameters were recorded. Wide bore 18 gauge cannula line was secured and crystalloid maintainance fluid was started. Blood pressure was monitored non invasively every 5 minutes throughout surgery and heart rate with ECG and oxyhemoglobin saturation monitored continuously during surgery.Spinal anesthesia was givenunder all aseptic precautions at the L3-L4 interspace, with the patient in the left lateral position. 20 mg Bupivacaine was injected over 30 seconds through a 25-gauge spinal needle. Patient then placed in supine position immediately after spinal injection.

Sensory loss assessment included the pin prick test at every 2 minutes till the highest level achieved and confirmed by 3 consecutive pin prick at the same level. Motor blockage will be assessed by Bromage Scale (BS), after achieving all criteria surgery was initiated. Intra operatively blood pressure, oxygen saturation and ECG were monitored continuously. Intra operative hypotension as any episode of systolic blood pressure below 80 mm of Hg or at least one episode of systolic blood pressure more than 20% below baseline was treated by incremental doses of inj. phenylephrine 0.12-0.5 mg intravenously[5]. Decrease in heart rate below 50 beats/min was considered as bradycardia and treated with incremental doses of atropine 0.6mg

intravenously. Intraoperative nausea or vomiting was treated with 4mg inj. Ondansetron.

After completion of surgery patient was shifted to post operative care unit. This time was considered as zero hours and patient was kept in post operative care room for 24 hours. Postoperative pain was assessed, using the 11-point VAS score on which 0 indicated "no pain" and 10 represented "worst imaginable pain." The sedation was assessed using the RSS (1 = patient is anxious and agitated or restless, or both, 2 = patient is 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). Data for pain and sedation score were recorded at 0, 1, 2, 4, 6, 12, and 24 h, postoperatively. For any pain complaint VAS score>4, inj. diclofenac 75 mg IM was administered with shortest interval of 6 hours between two doses and injection tramadol 50 mg IV administered as rescue analgesic.

Our outcome was to determine the time for first rescue analgesia requirement and incidence of side-effects if any. Statistical analysis was done using SPSS software version 21.0 and P value < 0.05 was considered to be significant.

3. Results

There were no significant differences regarding demographics [P =0.486], duration of anaesthesia. The VAS (median ± interquartile range), was significantly lower in A group when compared with the B group ($P < 0.0001$) after the first 6 postoperative hours [$P > 0.05$] (figure 2). Time to first rescue analgesia was significantly longer in A group as compared with B group [$P = 0.001$; Figure 3]. Side-effects did not vary significantly between the groups.

Table 1: Comparison of demographic and regional block characteristics among the groups

	Group A				Group B				
	Sample size	Mean ± Stdev	Median	Min-Max	Sample size	Mean ± Stdev	Median	Min-Max	Pvalue
Age	32	40.72 ± 5.16	40	35-55	32	41.47 ± 5.16	40	34-50	0.529
Wt.	32	58.91 ± 4.32	58.5	50-65	32	60.97 ± 4.25	62	50-68	0.059
PR Pre operative	32	88.19 ± 8.68	87	71-104	32	90.31 ± 11.85	93	70-120	0.416
SBP Pre operative	32	127.91 ± 7.77	129	115-140	32	123.94 ± 8.24	122.5	108-140	0.079
DBP Pre operative	32	82.12 ± 9.69	81.5	55-100	32	81.5 ± 6.44	81	63-91	0.762
MAP Pre operative	32	98.06 ± 9.13	97.5	80-115	32	95.59 ± 6.97	96	78-106	0.229
Highest Sensory Level T	32	6.53 ± 0.92	6.5	5-8	32	6.47 ± 0.92	6	5-8	0.744
Onset Sensory MIN	32	10.88 ± 1.07	11	8-12	32	10.88 ± 0.94	11	9-12	0.855
Onset Motor MIN	32	7.47 ± 0.98	7.5	6-9	32	7.84 ± 0.95	8	6-10	0.158
Duration of Analgesia	32	12.49 ± 1.89	12.3	9-17	32	7.22 ± 0.82	7.3	5.3-9	<.0001
Duration Of Sens. Block	32	179.59 ± 6.64	180	168-190	32	175.97 ± 5.33	175.5	168-188	0.024
Duration Of Motor Block	32	153.06 ± 6.31	154	140-165	32	148.97 ± 3.16	149	143-156	0.005

Data are expressed as mean +/- standard deviation with P < 0.05 was considered significant.

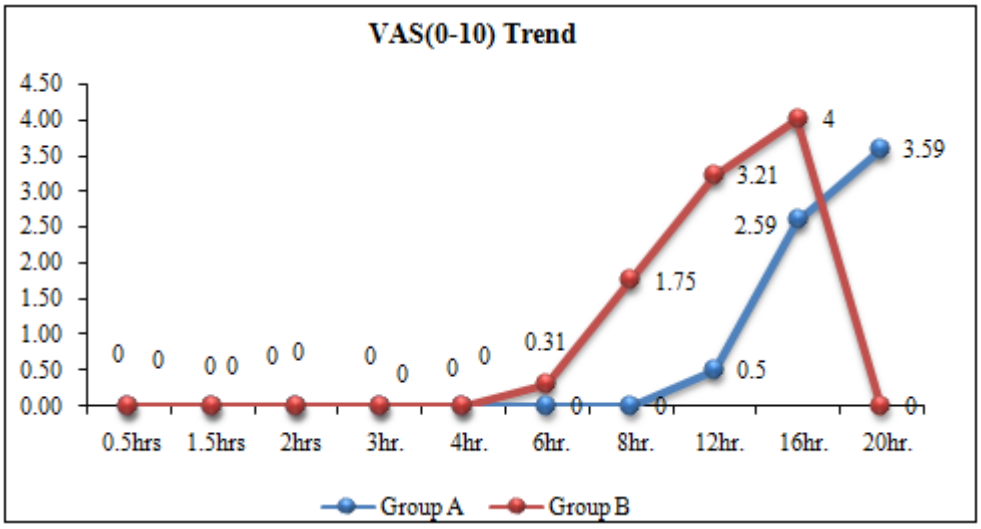

Figure 2: Significantly high visual analogue score in pregabaline group during 6, 8, 12, 16 and 20hr. postoperatively when compared to flupirtine group.

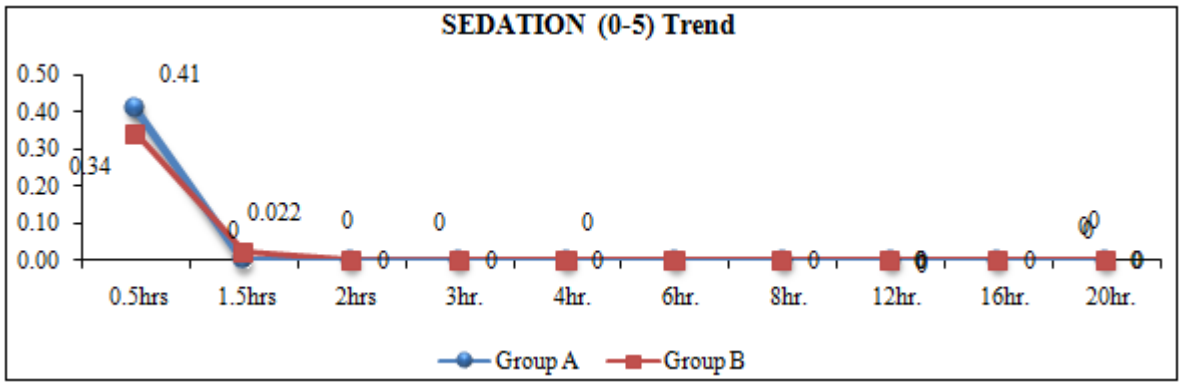

Figure 3: Significantly high incidence of sedation and no difference in postoperative nausea or vomiting in flupirtine group as compared to pregabalin group during the postoperative period.

4. Discussion

The current study indicates that 200 mg flupirtine and 150 mg pregabaline administered orally before incision has preemptive analgesic effect in patient undergoing abdominal hysterectomy surgery. But as observed patients who received flupirtine before the surgical stimulus had lower VAS scores in postoperative period when compared to pregabaline group. Longer time to first analgesic requirement also indicates a preemptive analgesic effect of flupirtine.

Flupirtine maleate, undergoes rapid gastric absorption (bioavailability 90%) after oral administration, with a peak plasma concentration of approximately 0.8-2 mg/L, achieved in 1.5-2 h[6, 7]. Previous studies show that analgesic efficacy of flupirtine is best achieved at a dose of 200 mg with min. side effects.

Previous data indicate that flupirtine exerts its analgesic activity at both spinal and supra-spinal levels. Primary site of action appears to be descending adrenergic pathways, by an indirect action on NMDA receptors through activation of G-protein coupled inward rectifying potassium channels.[8] By acting as potassium channel opener, flupirtine reduces glutamate mediated rise in intracellular calcium concentration, leading to hyperpolarization of neuronal membrane.[9, 10, 11, 12]Flupirtine has been utilized for various painful conditions including postoperative pain. Moore *et al.* showed postoperative pain relief when flupirtine (100 mg) was compared with dihydrocodeine (60 mg) in patients undergoing hysterectomy [13]. Another study also showed similar results when flupirtine was compared with pentazocine [14]. When compared with NSAIDs, flupirtine exhibited better analgesic profile in comparison to diclofenac sodium [15]. Ghanshyam et al concluded that flupirtine is good preemptive analgesic in laproscopic cholecystectomy [16]. Pregabalin is claimed to be more effective in preventing neuropathic component of acute nociceptive pain of surgery, to produce more opioid sparing effect and for amelioration of perioperative anxiety. [17]. usha bafna et al concluded that preemptive pregabalin resulted in more effective prolongation of post-operative analgesia after spinal anesthesia without altering the intraoperative hemodynamics and increasing the incidence of side-effect[18].We chose to compare flupirtine with the pregabaline group to fully quantify its analgesic activity, and any possible side-effect.

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