Original Article

Optimizing the Dose of Preemptive Oral Pregabalin for Postoperative Pain Control after Abdominal Hysterectomy under Spinal Anaesthesia

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ABSTRACT

Objectives: *Acute postoperative pain is a challenge to all clinicians which has prompted many authors to study the effect of neuropathic pain killers like gabapentin and pregabalin as preemptive drugs for management of acute postoperative pain. The dose of preemptive oral pregabalin though studied by few authors has not yet been optimized. Hence the present study has been undertaken to arrive at optimal dose of preemptive oral pregabalin.*

Methods *:This was a randomized double blind prospective study with 90 patients of American society of anesthesiology (ASA) Grade I and II aged between 35 to 60 years divided into 3 groups with Group I receiving placebo, Group II receiving 150mg oral pregabalin and Group III receiving 225mg oral Pregabalin.*

Statistical tools*: Statistical analysis was done by using averages, means and percentages.*

Results*: The time to visual analogue scale (VAS) > 3 was significantly increased in group III and group II than group I. The total dose of tramadol consumed in 24 hours duration was significantly less in group III and group II than group I. Sedation scores were more in patients of group III. Side effects like dizziness were more in Group III than in Group II. Patient satisfaction score was more in Group II than in Group III.*

Conclusion*: Preemptive oral pregabalin 150mg is very effective in providing good postoperative analgesia with better patient satisfaction.*

Keywords*: Preemptive analgesia, Pregabalin, Spinal Anaesthesia.*

INTRODUCTION

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or expressed in terms of such damage is the definition given by International Association for the Study of Pain. [1] Pain has been the centre of attention bothering all clinicians since human evolution, as defeating it has always been a challenge since times immemorial. Although the field of anaesthesia has progressed so well since the time of invention of ether anaesthesia, post operative pain management even today offers challenges to the practicing anesthetist. The main problem with pain is that, it is a highly subjective phenomenon.

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The main stay of treatment of acute postoperative pain has been opioids and non-steroidal anti-inflammatory drugs (NSAIDS). Increasingly there has been awareness among the clinicians that acute postoperative pain has also got a hyperalgesic component which has prompted many authors to study the effect of neuropathic pain killers like gabapentin and pregabalin as preemptive drugs for management of acute postoperative pain.

Gabapentin, an analogue of Gama amino butyric acid (GABA) has been demonstrated by many authors in reducing postoperative pain as well as requirement of analgesics in the postoperative period. [2,3,4] Pregabalin, a successor of gabapentin has also been studied by few authors to have an analgesic sparing effect when used preemptively before surgical incision. [5,6,7] However, there has been a paucity of studies to arrive at an optimal preemptive dose of pregabalin for postoperative pain control.

Hence the present study was aimed at comparing different doses of pregabalin 150mg and 225mg with placebo as preemptive analgesics for postoperative pain control for abdominal hysterectomy surgeries under spinal anaesthesia.

MATERIAL AND METHODS

The objective of the present study was to determine and compare placebo with oral pregabalin 150mg and 225 mg for postoperative pain control in patients undergoing abdominal hysterectomy under spinal anaesthesia. The study involved patients belonging to physical status of ASA Grade I and II. The study protocol was approved by the institutional ethical committee and written informed consent was obtained from all the patients.

Inclusion Criteria

1. ASA Grade I and II patients aged between 35-60 years undergoing elective abdominal hysterectomy under spinal anaesthesia.

2. Exclusion Criteria (other than those to spinal anaesthesia)

1. Patients with history of known allergy to any drugs especially pregabalin
2. Uncontrolled hypertension
3. Ischemic heart disease
4. Uncontrolled Diabetes mellitus
5. Cerebrovascular disease
6. Renal and hepatic disease
7. Bronchial asthma
8. Drug and alcohol abuse

This was a randomized double blind prospective study with 90 patients of ASA Grade I and II aged between 35 to 60 years divided into 3 groups. Randomization was done using random number table. All patients were kept nil orally for 10 hours prior to surgery and were administered Tab. ranitidine 150 mg and Tab. alprazolam 0.5mg on the night before surgery. All the patients were educated about 0-10 centimeters of VAS(Visual Analogue Scores) on a scale and were asked to mark on the scale about the intensity of the pain in the postoperative period.

One hour prior to spinal anaesthesia

GROUP I -received color matched empty capsules.

GROUP II -received 150mg of oral pregabalin and

GROUP III - received 225mg of oral pregabalin.

The person administering the study drugs and the patients were both unaware as to which group they belonged to.

Anaesthesia technique was standardized to all the 3 groups. Baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP) and SpO_2 were recorded. All the patients were preloaded with RL (ringer's lactate) 15 ml/kg iv before administering spinal anaesthesia. Inj. ondansetron 50µg/kg i.v was administered to all the patients prior to anaesthesia. All patients were subsequently administered spinal anaesthesia in left lateral position in L_3-L_4 space with the table in neutral position with Inj. bupivacaine heavy (0.5%) at a dose of 0.3mg/kg body weight with the maximum dose limited to 20 mg. All the patients were catheterized with appropriate sized Foley's urine catheter to monitor the urine output. Oxygen was administered to all the patients via facemask at 4 litres/min.

The parameters recorded intraoperatively were any incidence of

1. Bradycardia (HR<60bpm) requiring a dose of Inj. atropine 0.6mg i.v.
2. Fall in the blood pressure (SBP< 90mmHg, MAP < 60 mmHg), requiring bolus doses of Inj.mephentermine 6mg i.v. and
3. Any adverse effects like dizziness, sedation and blurred vision.

Sedation was assessed perioperatively by using Ramsay's sedation score.[8]

SCORE	RESPONSE
1	anxious, agitated and restless
2	cooperative, oriented and tranquil
3	responds to oral commands only
4	brisk response to light glabellar tap
5	sluggish response to light glabellar tap
6	no response to light glabellar tap

Duration of surgery in all the 3 groups was recorded. Postoperatively the patients were shifted to post anaesthesia care unit(PACU) and once the patients were awake, oriented and responding to oral commands with stable hemodynamics, were shifted to postoperative ward.

Postoperatively one resident anesthetist who was unaware as to which group the patient belonged to recorded the following data. All patients were given Inj. tramadol 1.5mg/kg i.v as rescue analgesic once VAS exceeded 3.

1. Time to two segment regression (in minutes).
2. Time to VAS >3 (time to rescue analgesics in minutes).
3. Total number of times VAS>3 in 24 hours duration.
4. Total dose of Tramadol administered in 24 hours (in mg).

Any adverse effects like dizziness, sedation, blurred vision were recorded in the first 24 hours of post operative period.

A patient satisfaction score as adopted by Wichai Ittichaikulthol et al was measured at 24 hours postoperatively.[9] This is a numerical score from 1 - 4.

1	Poor
2	Fair
3	Good
4	Very good.

Statistical analysis was done by using means, averages and percentages for easy understanding of the results.

RESULTS

A total of 107 patients were enrolled for the study out of which 90 patients completed the trial as 8 patients refused to participate in the study and 9 patients could not understand the VAS scoring system.

The demographic data along with the dose of bupivacaine and the duration of surgery is presented in **Table 1**. From table 1 it is evident that there is no difference in the demographic parameters among the 3 groups. Only when duration of surgery is considered, it was noted that surgical duration was less in group III compared to group II and group I.

On comparison of intraoperative hemodynamics between the 3 groups, 13 patients of Group III required Inj. mephentermine to maintain blood pressure compared to 7 patients of Group II and Group I each.

The time to two segment regression(in minutes) was significantly increased in group III(182.8 min) than group II(138.8 min) and group I(126.8 min) , whereas between group II and group I it was significantly more in group II than in group I.

The time to VAS > 3 (time to rescue analgesic in min) was significantly increased in group III than group II and group I (**Figure 1**), whereas between group II and group I it was significantly more in group II than in group I.

The number of times VAS > 3 was significantly less in group III than group II and group I (**Table 2**), whereas between group II and group I it was significantly less in group II than in group I.

The total dose of tramadol consumed in 24 hours duration was significantly less in group III(139.75 mg) than group II(155.65 mg) and group I(281.22 mg), whereas between group II and group I it was significantly less in group II than in group I.

Sedation scores were more in patients of group III (16.67% with score of 4 and 6.67% with score of 5) as compared to group II where only 10 % of the patients had a score of 4. None of the patients of group I had a score above 3 (**Table 3**).

56.67 % (17 patients) of patients in Group III complained of side effects like dizziness whereas only 23.33% (7 patients) in Group II and 10% in Group I (3 patients) reported dizziness.

Comparing overall patient satisfaction scores, 33.34% (10 patients) had a score of 4(very good) in Group II and 10 % (3 patients) in Group III (**Table 4**).

DISCUSSION

Postoperative pain is a very unpleasant subjective suffering by the patient. Various authors have studied the pain pathways and the pathophysiology of nociception after surgical stimulus. Surgical stimulus releases various catabolic neurohumoral substances like bradykinin, prostaglandins and substance P which stimulate peripheral nerve endings. The nerve impulses in turn are transmitted through the A delta and C fibers of the spinal cord to the central nervous system. Repeated stimulation of

Table 1 – Demographic Data with Dose of Bupivacaine and Duration of Surgery

Particulars	Group I	Group II	Group III
Age (in years)	47	43.4	45.4
Weight (in kilograms)	62.6	59.8	61.7
Height(in centimeters)	155.3	157.6	156.2
Dose of bupivacaine (in mg)	18.1	17.6	18.1
Duration of surgery (in minutes)	55.1	51.8	46.5

Table 2- Total No of times VAS >3 in 24 hrs (No of Patients)

No of Times	GROUP I	GROUP II	GROUP III
1	0	12	16
2	5	14	13
3	20	4	1
4	5	0	0

Table 3- Sedation Score (Ramsay Sedation Scale) (No. of patients)

SEDATION SCORE	GROUP I	GROUP II	GROUP III
1	6	1	1
2	8	8	10
3	16	18	12
4	0	3 (10.0%)	5 (16.67%)
5	0	0	2 (6.67%)
6	0	0	0

Table 4 - Patient Satisfaction Score at 24 Hrs Post-Operative (No of Patients)

Score		GROUP I	GROUP II	GROUP III
1	POOR	9	1	6
2	FAIR	15	7	9
3	GOOD	6	12	12
4	VERY GOOD	0	10 (33.34%)	3 (10.0%)

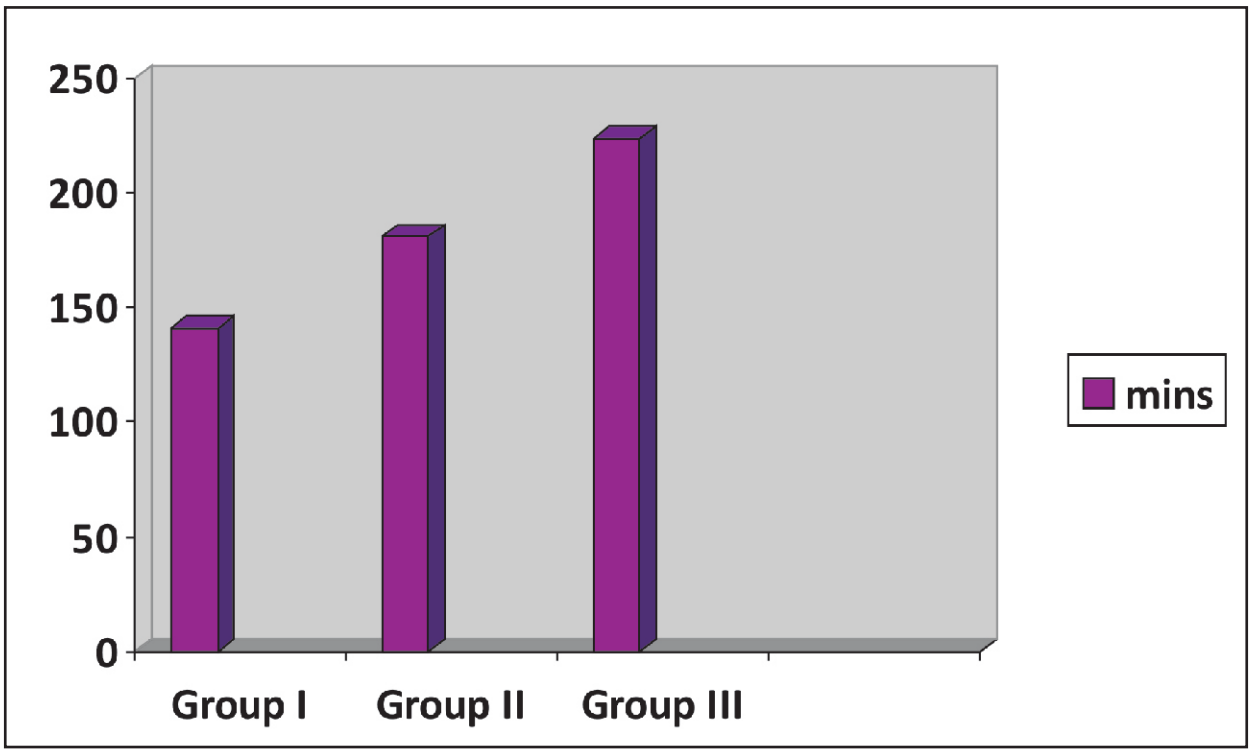

Fig 1: Time to VAS > 3 (Time to rescue analgesic in mins)

peripheral nerves can decrease the threshold for the stimulation of the nerves leading to augmentation of stimuli and ultimately leading to central sensitization of pain. Thus the brain starts perceiving even mild pain as severe as a result of this phenomenon.[10,11,12]

Various techniques have been developed to relieve postoperative pain like intravenous and intramuscular opioids, epidural infusions, patient controlled intravenous and epidural infusions, additives to intrathecal bupivacaine and fentanyl patches. Increasingly clinicians have realized that acute pain can induce a chronic pain syndrome [13,14] and hence many authors have studied the effects of drugs like gabapentin, a known anti epileptic used in treatment of chronic neuropathic pain, for control of acute pain in postoperative period.

A new concept of pain control has recently been increasingly used in the form of preventive or preemptive analgesia. This is nothing but administration of analgesic drugs prior to surgical incision so as to reduce the transmission of impulses from periphery to CNS. Studies have proven the efficacy of this technique in reduction of postoperative pain and accelerated recovery. This technique has also shown to reduce central sensitization and hence reduce the intensity of postoperative pain.[15,16,17,18]

Gabapentin, an anti epileptic agent with GABAmimetic action and is being used to treat partial seizures has been extensively studied for control of postoperative pain by administering it preoperatively. Its efficacy as a preemptive analgesic during both regional and general anaesthesia has been well established by many authors.[2,3,4]

Pregabalin, a successor of gabapentin was introduced and approved by FDA in 2005 for clinical use. Its indications are

1. Partial seizures of temporal lobe epilepsy
2. Diabetic neuropathic pain
3. Fibromyalgia
4. Generalized anxiety disorder(approved in European union).[19]

Its mechanism of action is similar to gabapentin, in that it binds to alpha 2 delta site of voltage gated calcium channels in the brain and exerts its antinociceptive and antiseizure properties. Pregabalin also decreases the release of neurotransmitters such as glutamate, noradrenaline and substance P which is responsible for its antinociceptive action.[19]

Few authors have studied pregabalin as a preemptive analgesic in a dose of 150mg and 300mg and have shown both doses to be effective in reducing postoperative pain as well as requirement of analgesics in postoperative period.[5,6] Few authors have noted increased incidence of adverse effects like dizziness and blurred vision with a dose of 300mg compared to 150mg.[7] There are no studies regarding the usage of pregabalin in the dose of 225mg. Hence in our study we chose to compare pregabalin 150mg with 225mg and placebo for postoperative pain control.

In our study pregabalin in doses of 150mg and 225 mg was more effective than placebo in reducing postoperative pain and also decreased the analgesic requirements in the first 24 hours of the postoperative period. But we noted increased sedation scores and dizziness with pregabalin 225mg than with 150mg. Also at 24 hours postoperative period, patients who received 150mg of oral pregabalin expressed more satisfaction than the other 2 groups. Thus pregabalin in a dose of 150 mg used preemptively offers good analgesia with better patient satisfaction.

CONCLUSION

Pregabalin in doses of 150mg and 225mg used preemptively offers good postoperative pain control and decreases the requirement of analgesics in the first 24 hours after spinal anaesthesia. Higher doses of pregabalin 225mg is associated with increased incidence of adverse effects with lesser patient satisfaction. Hence from our study we conclude that preemptive oral pregabalin 150mg is very effective in providing good postoperative analgesia with better patient satisfaction.

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