

## To Study The Effect of Oral Pregabalin on Duration of Analgesia in Patients Undergoing Hysterectomies Under Spinal Anaesthesia Using Bupivacaine Alone or Bupivacaine Clonidine Combination.



### Medical Science

KEYWORDS :

RUCHI GUPTA

GIFTY SINGH

ANITA KUMARI

#### INTRODUCTION

Hysterectomy has been a common surgery done to a large number of women belonging to late reproductive age group. In India annual incidence is 2,310,263. The mean and median ages of women undergoing hysterectomy are 42.7 and 40.9 years with a range of 28 to 80 years.<sup>1</sup>Hysterectomy can be performed with several different approaches such as vaginal, laparoscopic and open abdominal under general or spinal anaesthesia.

Hysterectomies causes severe postoperative pain, which can persist for up to 3 days, hampering convalescence.<sup>2,3</sup> There are some disadvantages with spinal anaesthesia such as hypotension, bradycardia, post dural puncture headache, nausea, vomiting and neurological complication. One main disadvantage is its limited duration of action, hence lack of postoperative analgesia.

A number of adjuvants to local anaesthetics have been used intrathecally to prolong the intraoperative as well as postoperative analgesia.<sup>4</sup> Opioids are commonly used as intrathecal adjuvants. However, side effects such as pruritus, nausea, vomiting, urinary retention, and delayed respiratory depression have prompted further research toward non-opioid analgesics with less serious side effects.<sup>5</sup>

Clonidine, a selective partial  $\alpha_2$ -adrenergic agonist, is being extensively evaluated as an adjuvant to intrathecal local anaesthetics and has proven to be a potent analgesic free of opioid-related side effects.<sup>6</sup> It is known to increase both sensory and motor blockade of local anaesthetics.<sup>7</sup>Intrathecal clonidine has been used as an adjuvant to local anaesthetics in various surgical procedures without any clinically significant side effects.<sup>8,9</sup>

In recent years, studies have shown that an important factor for reducing surgery related stress is taking control over post-operative pain starting during the preoperative period which has brought about the idea of preemptive analgesia that aims to block postoperative pain by inhibiting this sensitization. Many different drugs such as paracetamol, lornoxicam, ketamine or gabapentin as well as regional blocks have been used for the purpose of preemptive analgesia.<sup>10,11</sup>

Pregabalin is a gamma-amino butyric acid analogue, an anti-convulsant drug. It was developed as spasmolytic agents and for the management of generalized or partial epileptic seizures resistant to conventional therapies. It binds with high affinity to the  $\alpha_2\delta$  protein, found in the central nervous system's voltage gated calcium channels,<sup>12</sup> which reduces calcium entry to the nerve terminals of central nervous system and lowers substance P, glutamate and noradrenaline levels that play roles in creating the sense of pain.<sup>13,14</sup>

The aim of this research was to study the effect of pregabalin as premedicant in combination with bupivacaine and clonidine to prolong the postoperative analgesic phase and the requirement of rescue analgesia. The primary outcome of the study was to evaluate the requirement of rescue analgesia post operatively.

Secondary outcome was to evaluate severity of pain using VAS scores.

#### MATERIALS AND METHODS

A study was planned to carry out a randomized double blind study on 60 adult patients, of ASA physical status I and II, age 18-70 years undergoing hysterectomies under regional anaesthesia after obtaining approval from hospital ethics committee, a prior written informed consent was taken from all the patients.

Exclusion criteria included contraindications to spinal anaesthesia, such as local infections, generalized septicaemia, platelet and clotting factor abnormalities, significant neurological disease with motor or sensory deficit, diagnosed increased intracranial pressure; patients with history of hypertension and on beta blocker therapy; a known history of allergy, sensitivity or any other form of reaction to local anaesthetics of amide type or opioids; psychiatric history or any other concomitant disease which might have led to unreliability; patients with spinal cord deformities like scoliosis, kyphosis in whom there was anticipated difficult spinal.

#### Patients selected were allocated in two groups of 30 each.

Group A: premedication with pregabalin 75mg was given 1hour before surgery and intrathecal 0.5% hyperbaric bupivacaine 3cc and normal saline (insulin syringe) making the total drug volume 3.1cc.

Group B: premedication with pregabalin 75mg 1hour before surgery plus intrathecal 0.5% hyperbaric bupivacaine 3cc and clonidine 15mcg (insulin syringe) making the total drug volume 3.1cc.

All patients included in the study were subjected to a detailed pre anaesthetic check-up, clinical history, general physical and systemic examination and basic routine investigations.

The patients were randomly allotted in two groups by picking up coded slips in blinded manner.

Lumbar puncture was performed at the L2-3/L3-4 interspace using a 26G Quincke needle in sitting/lateral position. The assessment of sensory block by pinprick was performed every minute till maximum level was achieved. Motor block in the lower limb was assessed using a modified Bromage scale. Duration of absolute analgesia defined as the time from intrathecal injection until pain score  $\leq 4$ .

Pain intensity was measured using Visual analogue scale till 24 hours postoperative. VAS (0-10 point scale): 0 – no pain; 1-3-mild pain; 4-7-moderate pain; 8-10-severe pain. Rescue analgesia was given for pain score  $> 4$  in the form of intramuscular diclofenac sodium 75mg. Number of doses in an individual patient and total doses of rescue analgesia were noted.

Complications such as hypotension, bradycardia, sedation, nausea and vomiting, respiratory depression, pruritus, urinary reten-

tion, dry mouth, any other.

Decoding of the drug was done at the end of study and the results were evaluated statistically. Comparison of quantitative data between groups was done by independent samples *t*-test. Chi-square test was used for the analysis of the non-parametric data. *P* value of <0.05 was considered statistically significant.

**RESULTS**

The age, weight, height, ASA status and duration of surgery were comparable in both the groups.(Table 1)

**Table 1: Showing demographic data**

	Age	Height	Weight	Duration surgery
Group A	33 – 56 (43.90 ± 5.48)	160.1667± 4.8215	65.166±2.841	80.50± 17.828
Group B	32 – 60 (45.30 ± 7.10)	160.1667± 4.9971	64.866±1.655	94.00± 23.940
	NS	NS	NS	NS

Data: Mean±SD, NS: Non Significant (*p*>0.05)

Duration of analgesia is the time interval between administration of intrathecal injection until the first dose of rescue analgesia. The statistical analysis was highly significant (*p*<0.001) among both the groups (Table 2). Thus, addition of pregabalin 75mg as premedicant to bupivacaine with clonidine 15mcg increased the duration of analgesia postoperatively.

**Table 2: Showing mean duration of analgesia**

Duration of analgesia	Group A	Group B	Group A vs B
Time (min)	149.33±10.807	287.00±21.838	HS

Data: Mean±SD, HS: Highly Significant (*p*<0.001).

**Table 3: Showing mean VAS scores; Total No. of doses of rescue analgesia.**

	Group A	Group B	Group A vs B
VAS	149.33±10.807	287.00±21.838	HS
Total No. of doses	2.233±0.5040	2.066±0.6171	NS

Data: Mean±SD, HS: Highly Significant (*p*<0.001), NS: Non Significant(*p*>0.05)

Rescue analgesia was given with injection diclofenac sodium 75 mg intramuscularly when VAS>4. The mean VAS scores were significantly different in both the groups. The total doses of rescue analgesia was comparable in group A and B (Table 3).

**DISCUSSION**

Postoperative pain is naturally sensed by nociceptive receptors. However, the trauma of the operation can cause hyperalgesia which prolongs the postoperative pain. Thus, improved postoperative analgesia has been associated with early resumption of mobilization, oral nutrition and early discharge from hospital.

Unlike traditional analgesics which are nociceptive, gabapentoids like gabapentin and pregabalin decrease the stimulation of posterior horn neurons caused by tissue damage compared to the period before afferent entry from tissue damage spot. On this basis gabapentoids (administered before the operation) are recommended to relieve acute surgery pain.<sup>15</sup>In recent years, pregabalin has been used as an adjuvant drug in dealing with postoperative pain.<sup>16,17</sup>

The duration of analgesia was assessed by observing the time to the requirement of first dose of rescue analgesia from the time of onset of sensory block. Strebelet al<sup>18</sup> observed that the first request for supplemental analgesia was significantly delayed by addition of clonidine in 18mg bupivacaine. In some other studies

Clonidine 15-30 mcg was used with opioids and local anaesthetic for prolongation of postoperative analgesia, in labour analgesia, knee arthroscopy, ambulatory inguinal herniorrhaphy<sup>19,20</sup>. Biochemical studies have hypothesized that the analgesic action of pregabalin depends on the reduction of calcium influx at nerve terminals with a reduction in the release of neurotransmitters, including glutamate, noradrenaline, calcitonin gene-related peptide, and substance P.<sup>21,22</sup>

The rescue analgesia time with the use of pregabalin alone showed similar results as seen by a meta-analysis conducted by Cliff K.S. Ong et al<sup>23</sup> demonstrated the ability of preemptive analgesic interventions to attenuate postoperative pain scores, decrease supplemental postoperative analgesic requirements, and prolong time to first rescue analgesic request. Pregabalin has antiallodynic and antihyperalgesic properties useful for treating neuropathic pain and may also be beneficial in acute post-operative pain management.<sup>24</sup> The use of pregabalin preoperatively in low dose of 75mg and clonidine 15mcg with bupivacaine intrathecally in this study gave better results than the use of pregabalin independently. The mean duration of analgesia was prolonged with the combined use of pregabalin orally and intrathecal clonidine. The postoperative pain and analgesia showed significant difference, the time to requirement of rescue analgesia was significantly prolonged. Clonidine inhibits neurotransmission in both A-delta and C fibers and potentiates inhibitory effect of the local anesthetic on the C-fiber activity. Pregabalin is a GABA analog that binds to the α2-δ subunit of the presynaptic voltage-dependent calcium channels that are widely distributed throughout the central and peripheral nervous systems.<sup>25</sup> the enhanced duration of analgesia with the combined use of pregabalin and intrathecal clonidine may be due to the synergistic effect of central action of clonidine and central as well as peripheral action of pregabalin. So, this can explain significant difference in both the groups with group B having decreased mean VAS more than group A. Total dose of rescue analgesia required were similar in both the groups.

The use of pregabalin was not associated with any adverse events in the haemodynamic parameters such as bradycardia, hypotension. Hypotension is the central effects of Clonidine administered by any route. Higher doses of (50 to 450 mcg) clonidine have been associated with hypotension, bradycardia and higher degree of sedation. Julio et al. also found similar with the use of same dose of clonidine.<sup>26</sup> The group receiving pregabalin with intrathecal clonidine in this study although experienced a fall in systolic and diastolic blood pressure but was clinically as well as statistically insignificant. This may be because of lesser dose used in this study (15mcg).

Thus to conclude that the use of pregabalin as premedication along with intrathecal clonidine can prolong the duration of analgesia compared to the use of pregabalin alone in patients undergoing hysterectomies under spinal bupivacaine. The VAS scores are reduced with the use of pregabalin with intrathecal clonidine as compared to the use of pregabalin alone with bupivacaine without increasing the incidence of any adverse effects.

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