To study the effect of oral pregabalin as premedicant on post-operative analgesia in patients undergoing hysterectomy after spinal anaesthesia

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Abstract
Background and Aim: Post-operative pain is one of the main areas on which research is being under taken nowadays. This has led to the emergence of concept of preemptive analgesia to prevent post-operative pain by inhibiting the nociceptive stimuli. This study aims at assessing whether pregabalin as pre-medicant has any superadded benefit on prolonging the analgesic effect of spinal anaesthesia and post-operative analgesic requirements in patients posted for hysterectomy.

Material and Methods: A total of 60 patients of ASA grade I and II posted for elective hysterectomies were randomly allocated in two groups of 30 each. The blinded drug selected for the study was given orally one hour before surgery. Group A received pre-medicant with placebo capsule and Group B received pregabalin capsule 75mg. Spinal anaesthesia was performed using 26 G spinal needle at L2-3/L3-4 interspace with 3ml of 0.5% bupivacaine heavy injected. VAS score at first rescue analgesia, mean time of onset of sensory and motor block, duration of analgesia and total requirement of rescue analgesia were observed as primary outcome. Haemodynamic parameters and side effects were recorded as secondary outcome.

Results: The mean duration of effective analgesia was comparable in group A (141±6.7 mins) and group B (149.33±10.807 mins). The mean VAS scores in pregabalin group were significantly reduced compared to the placebo group (p<0.05). The mean number of doses of rescue analgesia in the first 24 hours in group A and B was 3.16±0.08 and 2.23 ±0.05 respectively ( p=0.001). There were no significant hemodynamic changes in group A and B. Incidence of perioperative adverse effects were similar in both the groups.

Conclusion: Oral pregabalin 75mg as premedicant has comparable duration of spinal analgesia. However the VAS scores and number of doses of rescue analgesics used were significantly less in the pregabalin group compared to the placebo group.

Keywords: Pregabalin, Hysterectomy, Postoperative analgesia, Visual analog scale score.

Introduction
Postoperative pain is generally inadequately treated and it persists even after tissue heals, sometimes leading to chronic pain. It can cause autonomic disturbances and haemodynamic derangements which may have detrimental effect on the recovery of the patient. Hence it has to be taken care prior to start of the surgery.

Hysterectomy is done in the women of age between 28 to 80 years with DUB, fibroids etc. Hysterectomies cause severe postoperative pain, which may persist for 3-5 days, thus delays recovery and prolongs hospital stay. It is most commonly performed under regional anaesthesia. One of the main disadvantage of spinal anaesthesia is its limited duration of action and lack of postoperative analgesia.

The management of pain often includes opioid therapy but because of the known side effects of these drugs consideration of non-opioid strategies for pain management is important. The use of non-opioid analgesic regimen may limit the use of these drugs. The goal is to find non-opioid drugs with reasonable costs, lesser side effects, long duration of action and easy availability.

Preemptive analgesia is a new clinical domain and implies the use of analgesic regimen before the onset of nociceptive stimuli, aiming at preventing the sensitization of nervous system to subsequent stimuli that could augment pain. Many different drugs such as paracetamol, lornoxicam, ketamine, clonidine, dexmedetomidine, gabapentin, pregabalin as well as regional blocks have been used for preemptive analgesia.

Pregabalin is a gamma-aminobutyric acid (GABA) analogue with anticonvulsant and anxiolytic properties. It was used as spasmolytic agent and for the management of generalized or partial epileptic seizures resistant to conventional therapies. Recently, a large number of clinical trials suggest that pregabalin could be effective in early postoperative pain. Nowadays, pregabalin is very commonly used in reducing neuropathic and inflammatory pain, tissue irritation, neuralgia fibromyalgia and postoperative pain. However, limited data is available for supporting the evidence for postoperative analgesic efficacy of pregabalin.

The main objective of this study was to compare the effect of pregabalin as oral premedicant with the placebo group for prolongation of postoperative analgesic phase and requirement of rescue analgesia as primary outcome. Hemodynamic parameters and side effects were recorded as secondary outcome in our study.
Materials and Methods

After obtaining approval from hospital ethics committee, this randomised double blind study was conducted in 60 adult patients in age group 18-70 years belonging to ASA status I and II posted for elective hysterectomies under spinal anaesthesia in our institute. Prior to the procedure, a written informed consent was obtained from all the patients. Patients were explained about spinal anaesthesia and linear Visual Analog Scale using a 10 centimeter line, where 0 denoted “no pain” while 10 “worst imaginable” pain.

Patients having known allergy to study drug, raised intracranial tension, neurological disorder, spinal deformity, local infection, patient on anticoagulant therapy and those on chronic pain medication were excluded from study.

Pre-anaesthetic checkup was done, a day prior to surgery and were kept fasting overnight. They were advised tablet alprazolam 0.5 mg for night sedation. No other premedication was given except for the study drug as premedicant.

Patients were randomly allocated into two groups of 30 each by computer generated 60 coded slips in blinded manner. The anaesthesiologist giving the drug and those who monitored the patients were blinded to the study drug used.

Group A: received placebo in the form of multivitamin capsule one hour before the procedure.

Group B: received 75 mg of pregabalin capsule one hour prior to procedure.

After shifting the patient to operation theatre standard monitoring including PR, NIBP, pulse oximetry(SpO2) and ECG leads were attached and baseline vitals were recorded. Intravenous access was established using 18 G cannula and after preloading with ringer lactate solution at the rate of 15ml/kg, under all aseptic precautions spinal anaesthesia was performed at L2-3 or L3-4 interspace using 26G Quincke’s needle in lateral position. 3 ml of 0.5% bupivacaine heavy was injected, after confirming free flow of cerebrospinal fluid. Thereafter, patients were made to lie supine and given O2 at the rate of 4l/min via face mask.

Sensory block was assessed by pinprick sensation using 26 G needle every minute till maximum level was achieved. Motor block was assessed using a modified bromage scale. Haemodynamic monitoring (PR, BP, SpO2, RR) were assessed and noted every 5 minutes intra-operatively. Mephenteramine 6mg bolus was given intravenously, when mean arterial pressure was less than 20% of baseline value. Similarly, if pulse rate falls below 60 beats per minute, injection atropine 0.6mg was given. Patients were then shifted to PACU after the completion of surgery. Duration of absolute analgesia is defined as the time from intrathecal injection until pain score ≤4. In the postoperative period, pain intensity was measured using Visual Analogue Scale immediately at the end of operation(0 hour) then every 2 hourly till 12 hours and 24 hours after the operation.

Rescue analgesia was given when 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 in the first 24 hours. Side effects such as nausea, vomiting, dizziness, sedation and respiratory depression were also documented.

Decoding of the drug was done at the end of study. All the results were tabulated and analysed statistically using software SPSS version 17 for Windows Statistical Software Package (SPSS Inc., Chicago, IL, USA). Comparison of quantitative data was done by one way analysis of variance(ANOVA) and independent sample t-test was used for the comparison between the groups. Chi square test was used for the non-parametric data. P value of less than 0.05 was considered statistically significant and 0.001 highly significant.

Results

The demographic profile of both the groups were comparable with respect to age, weight, height and duration of surgery (p>0.05) (Table 1). Baseline pulse rate, MAP and SpO2 were comparable in both the groups. There was no statistically significant changes in these parameters.

<table>
<thead>
<tr>
<th>Table 1: Demographic data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
</tr>
<tr>
<td>Group A (n=30)</td>
</tr>
<tr>
<td>Group B (n=30)</td>
</tr>
<tr>
<td>NS</td>
</tr>
</tbody>
</table>

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

The mean time of onset of sensory block was 4.57±0.81 and 5±0.37 minutes in group A and B respectively. There was no significant difference in onset of sensory block between group A and B (p>0.05) (Table 2). The mean time of onset of motor block was 11.67±0.75 and 11.73±0.69 mins in group A and B respectively. There was no significant difference in onset of motor block (p>0.05).
Duration of absolute analgesia is the time interval between administration of intrathecal injection until first dose of rescue analgesia. The mean duration of effective analgesia in group A was 141.67 ±14.04 versus 149.33±10.80 minutes in group B (Table 2). Thus duration of analgesia was comparable in both the groups.

Rescue analgesia was given with injection diclofenac sodium 75 mg intramuscularly when VAS>4. The mean VAS scores in pregabalin group were significantly reduced compared to placebo group (p <0.05) (Table 3, Fig. 1). The mean number of doses of rescue analgesia used in first 24 hrs. were significantly reduced (3.16±0.08 versus 2.23±0.05) in group A and B respectively (p <0.001) (Table 4).

There were no significant hemodynamic derangements in both the groups. Incidence of adverse effects such as nausea, vomiting, convulsions, anaphylaxis, sedation, respiratory depression, hypotension and bradycardia were not observed in any of the patients in both the groups and hence were non-significant.

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**Table 2: Characteristics of sensory and motor blockade**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A (n=30)</th>
<th>Group B(n=30)</th>
<th>Group A vs B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory level</td>
<td>T₈(T₇-T₉)</td>
<td>T₈(T₇-T₉)</td>
<td>NS</td>
</tr>
<tr>
<td>Onset of sensory block(mins)</td>
<td>4.57±0.817</td>
<td>5.00±0.371</td>
<td>NS</td>
</tr>
<tr>
<td>Onset of motor block(mins)</td>
<td>11.67±0.758</td>
<td>11.73±0.691</td>
<td>NS</td>
</tr>
<tr>
<td>Mean duration of analgesia</td>
<td>141.67±14.040</td>
<td>149.33±10.807</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data: mean ±SD, NS: non-significant (p>0.05).

**Table 3: Comparison of Postoperative Mean VAS Score**

<table>
<thead>
<tr>
<th>Post-operative period(hr)</th>
<th>0 hr</th>
<th>2 hrs</th>
<th>4 hrs</th>
<th>6 hrs</th>
<th>8 hrs</th>
<th>12 hrs</th>
<th>24 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (n=30)</td>
<td>4.70 ±3.175</td>
<td>5.17 ±3.249</td>
<td>3.90 ±2.383</td>
<td>4.90 ±2.510</td>
<td>3.37 ±2.042</td>
<td>3.50 ±1.834</td>
<td>0.37 ±0.490</td>
</tr>
<tr>
<td>Group B (n=30)</td>
<td>3.20 ±2.99</td>
<td>3.10 ±2.99</td>
<td>3.47 ±3.08</td>
<td>2.63 ±2.78</td>
<td>2.63 ±2.25</td>
<td>2.47 ±1.79</td>
<td>0.30 ±0.53</td>
</tr>
</tbody>
</table>

p value between placebo and pregabalin group <0.05

**Table 4: Mean No. of doses of rescue analgesia**

<table>
<thead>
<tr>
<th>Total No. of doses</th>
<th>Group A(n=30)</th>
<th>Group B(n=30)</th>
<th>Group A vs B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.1667±0.0841</td>
<td>2.233±0.5040</td>
<td>HS</td>
</tr>
</tbody>
</table>

Data: mean ±SD, NS: non-significant (p>0.05), HS: Highly Significant (p<0.001)
Discussion

Postoperative pain has to be judiciously and adequately managed. It may delay recovery, increase hospital stay and patient’s expenditure. Good analgesia postoperatively minimizes patient discomfort, facilitates early mobilization and discharge from hospital. It also prevents acute pain developing into chronic pain. Experimental models of neuropathic and inflammatory pain have shown that amino butyric acid analogues such as pregabalin and gabapentin contain analgesic components and are anti-nociceptive. It is postulated, that CNS sensitivity may lead to postoperative pain augmentation. Administering gabapentinoids before surgery, inflammatory trauma or surgical stimulation may reduce the degree of sensitivity of the CNS. In recent years, pregabalin has been used as an adjunct in dealing with postoperative pain. Pregabalin is a gamma amino butyric acid (GABA) analogue, an anticonvulsant drug. It binds with high affinity to the α2-δ protein, found in the central nervous system’s voltage gated calcium channels, which reduces calcium entry to the nerve terminal of central nervous system and lowers substance P, glutamate and noradrenaline levels that play role in creating the sense of pain. Pregabalin has anti-allodynic and anti-hyperalgesic properties useful for treating neuropathic pain and may also be beneficial in acute postoperative pain management. The time to the requirement of first dose of rescue analgesia from the time of onset of sensory block is the duration of analgesia assessed. Our analysis showed comparable duration of analgesia in patient receiving pregabalin and placebo as pre-medicant. However, pregabalin group maintained VAS score in lower range in comparison to placebo group. The total number of doses for rescue analgesia used were also less in pregabalin group when compared to placebo group. A meta-analysis by Tiippane et al and Cliff KS et al regarding perioperative administration of gabapentinoids was conducted. They observed reduced postoperative pain scores, increased time to first rescue analgesic request and decreased supplemental postoperative analgesic requirements in the pregabalin group.

Eman et al observed the effects of oral pregabalin (150mg) given in the women undergoing abdominal hysterectomy. They concluded that premedication with the pregabalin reduces postoperative pain scores and total analgesic consumption without increasing the side effects in the postoperative period. A comparative study by Prasad et al on preoperative oral clonidine (150mcg) and pregabalin (150mg) in patients undergoing vaginal hysterectomy under spinal anaesthesia found that VAS scores were significantly less in pregabalin and clonidine group compared with the placebo group.

Bafna U et al did a randomized trial on patients undergoing elective gynaecological surgeries and observed that preemptive use of gabapentin 600mg and pregabalin 150mg orally significantly prolongs the duration of analgesia and reduces the postoperative requirement of rescue analgesics. All these studies signify that oral pregabalin as pre-medicant reduces VAS scores and request for analgesic requirement to a great extent in postoperative period in patients after spinal anaesthesia. Their findings were in concordance with our study.

There were no significant changes in hemodynamic parameters in both the groups. No differences regarding intraoperative adverse effects such as nausea, vomiting, dizziness, sedation and respiratory depression were seen in either of the group.

Thus, we conclude that the use of pregabalin as premedicant in a dose of 75mg has comparable duration of spinal analgesia, however it showed good quality of analgesia as evidenced by improved postoperative VAS scores and decreased use of rescue analgesics in 24 hours without increasing the incidence of adverse effects.

References
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