

A comparison of effect of preemptive use of oral gabapentin and pregabalin for acute post-operative pain after surgery under spinal anesthesia

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Abstract

Background and Aims: Preemptive analgesia is an antinociceptive treatment that prevents establishment of altered processing of afferent input. Pregabalin has been claimed to be more effective in preventing neuropathic component of acute nociceptive pain of surgery. We conducted a study to compare the effect of oral gabapentin and pregabalin with control group for post-operative analgesia

Materials and Methods : A total of 90 ASA grade I and II patients posted for elective gynecological surgeries were randomized into 3 groups (group A, B and C of 30 patients each). One hour before entering into the operation theatre the blinded drug selected for the study was given with a sip of water. Group A- received identical placebo capsule, Group B- received 600mg of gabapentin capsule and Group C — received 150 mg of pregabalin capsule. Spinal anesthesia was performed at L3-L4 interspace and a volume of 3.5 ml of 0.5% bupivacaine heavy injected over 30sec through a 25 G spinal needle. VAS score at first rescue analgesia, mean time of onset of analgesia, level of sensory block at 5min and 10 min interval, onset of motor block, total duration of analgesia and total requirement of rescue analgesia were observed as primary outcome. Hemodynamics and side effects were recorded as secondary outcome in all patients.

Results: A significantly longer mean duration of effective analgesia in group C was observed compared with other groups ($P < 0.001$). The mean duration of effective analgesia in group C was 535.16 ± 32.86 min versus 151.83 ± 16.21 minutes in group A and 302.00 ± 24.26 minutes in group B. The mean numbers of doses of rescue analgesia in the first 24 hours in group A, B and C was 4.7 ± 0.65 , 4.1 ± 0.66 and 3.9 ± 0.614 . (P value < 0.001).

Conclusion: We conclude that preemptive use of gabapentin 600mg and pregabalin 150 mg orally significantly reduces the postoperative rescue analgesic requirement and increases the duration of postoperative analgesia in patients undergoing elective gynecological surgeries under spinal anesthesia

Key words: Gabapentin, pregabalin, spinal anesthesia

Introduction

Pain is defined by International Association for Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. The relief of post operative pain is a subject, which has been

receiving an increasing amount of attention in the past few years.^[1,2]

Various drugs such as local anesthetics, opioids, non-steroidal antiinflammatory drug, cyclooxygenase-2 inhibitor, gabapentin, pregabalin, clonidine and dexmedetomidine have been used as preemptive analgesics.^[3]

Gabapentin is a structural analog of gamma amino butyric acid. Large placebo controlled, double-blind trials confirmed their effectiveness in relieving neuropathic post-herpetic pain^[4-6] and reflex sympathetic dystrophy.^[7]

Gabapentin and pregabalin both have been used in the treatment of neuropathic pain as well as post-operative pain with good results.^[8-10] However, due to fewer studies^[11] comparing pregabalin and gabapentin for post operative pain management, we planned this study to compare the effect of

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oral gabapentin 600 mg and oral pregabalin 150 mg with the control group for post-operative analgesia in elective gynecological surgeries performed under spinal anesthesia.

Materials and Methods

The Ethical Committee of the Institute approved this prospective, randomized, placebo-controlled study protocol. A detailed physical examination was carried out a day before the proposed surgery. Patients of American society of Anesthesiologists (ASA) grade I or II, aged 30-50 years, weighing 45-65 kg and scheduled for elective gynecological surgeries under spinal anesthesia were included in the study, after obtaining informed consent. Patients with contraindications to spinal anesthesia or major neurological, cardiovascular, metabolic, respiratory, renal disease or coagulation abnormalities were excluded. The sample size calculation was based on the previous study^[11] accepting mean difference between the time of rescue analgesia between gabapentin and pregabalin 5 h (+, -) 6.67 h and assuming alpha error was 0.05 and the power of the study was 80%. Thus, the calculated sample size for each group was 27 patients. So, for the study purpose, it was decided to include 30 patients in each group.

In the holding room, the concept of a visual analog scale (VAS)^[12] [Table 1] was introduced to the patient.

Randomization was carried out by chit in box method. Patients were divided into three groups (group A, B and C). In each group, there were 30 patients. An hour before surgery, vital parameters including pulse rate, blood pressure [BP], and electrocardiography [ECG] of all the patients were recorded in preanesthetic room and then the drug selected for the study was given with a sip of water. Group A — Received identical placebo capsule; Group B — Received 600 mg of gabapentin capsule; Group C — Received 150 mg of pregabalin capsule.

On entering into the OT, intravenous (IV) line was secured by using 18 Gauge cannula and preoperative vitals (pulse, BP, respiratory rate, SpO₂) were recorded. Preloading was done with ringer lactate fluid at the rate of 15 ml/kg/h. Spinal anesthesia was instituted at L3-L4 interspace and a volume of 3.5 ml of 0.5% bupivacaine heavy injected over 30 s through a 25 Gauge spinal needle. Patient was placed in the supine position with a 15° head down tilt immediately after spinal injection to achieve the level of block of T5-T6.

The level of sensory block was assessed using a 26 gauge needle and recorded as loss of sensation to pin prick, checking in a caudal to cephalic direction. Motor block was recorded according to the Bromage scale^[13] [Table 2]. Routine monitoring of pulse, BP, SpO₂, ECG was instituted

Table 1: Pain scoring-visual analog scale

score	Criteria
Score 0	no pain
Score 1, 2, 3	Mild pain
Score 4, 5, 6	Moderate pain
Score 7, 8, 9	Severe pain
Score 10	worst imaginable pain

Table 2: Intensity of motor block, Modified Bromage score (Breen TW 1993)

Score	Criteria
1	Complete block (unable to move feet or knees)
2	Almost complete block (able to move feet only)
3	Partial block (just able to move knees)
4	Detectable weakness of hip flexion while supine (full flexion of knees)
5	No detectable weakness of hip flexion while supine
6	Able to perform partial knee bend

intra-operatively. Fluid administration was continued intra-operatively and a decrease in mean arterial pressure greater than 15% below the pre-anesthetic baseline value was treated with incremental doses of injection Mephentermine 5 mg IV. A decrease in heart rate below 50 beats/min was treated with incremental doses of atropine 0.3 mg IV.

In post-operative period pain assessment was carried out by VAS and duration of motor block was assessed by Bromage scale. Intramuscular diclofenac (75 mg) was given in the gluteal region as rescue analgesic on demand. At that time, VAS score was recorded duration of effective analgesia was measured as time from intrathecal drug administration to patient's 1st request for analgesic either in the recovery room or in ward. Patient was kept under observation for a total period of 24 h to observe for the total number of doses of analgesic required and any side-effects.

Statistical analysis was performed with the SPSS, version 15.0 for Windows Statistical Software Package (SPSS Inc., Chicago, IL, USA). Categorical data, i.e., ASA grade, type of surgery and the incidence of adverse events (hypotension, bradycardia, respiratory depression, nausea and vomiting) were presented as numbers and proportion of these data were compared in all three groups and the difference in proportion was inferred by Chi-square test. Demographic data (age, weight), duration of surgery, VAS score, total duration of analgesia and requirement of rescue analgesia were expressed as mean \pm standard deviation and these data were compared in all three groups and difference in means were inferred by analysis of variance (ANOVA) — test of significance. For significance *P* value \leq 0.05 was considered as significant for both types of data.

Results

A total of 110 patients were assessed for eligibility. Of these 20 patients did not fulfill the study criteria and were excluded. A total of 90 patients were enrolled in the study. All groups were comparable with respect to age, gender, weight, ASA status, type of surgery and duration of surgery [Table 3].

The mean time of onset of analgesia was 9.83 ± 1.55 , 9.96 ± 1.79 and 9.96 ± 1.24 min in group A, group B and group C, respectively. There was no significant difference in the onset of sensory analgesia in between group A and B, group A and C and group B and C. ($P > 0.928$)

In group A, B and C, the mean time of onset of motor block was 14.06 ± 1.57 , 14.6 ± 1.54 and 14.7 ± 1.23 min.

Table 3: Demographic profile of groups

Observation	Group A n = 30	Group B n = 30	Group C n = 30	P value
ASA grade (I/II)	19/11	15/15	20/10	$P > 0.378$ (NS)
Age (year)	42.4 ± 4.74	41.7 ± 5.17	42.0 ± 5.34	$P > 0.86$ (NS)
Weight (kg)	57.33 ± 3.32	56.5 ± 3.77	57.2 ± 3.31	$P > 0.611$ (NS)
Duration of surgery (min)	56.8 ± 7.7	59.2 ± 11.0	57.8 ± 9.1	$P > 0.610$ (NS)
Type of surgery				
TAH+BSO	20	18	20	$P > 0.824$ (NS)
TAH	6	9	7	$P > 0.656$ (NS)
Laprotomy for ovarian cyst	4	3	3	$P > 0.902$ (NS)

NS = Non-significant, TAH = Total abdominal hysterectomy, BSO = Bilateral salpingo-oophorectomy, ASA = American society of anesthesiologists

Table 4: Characteristics of sensory and motor block

parameters	Group A	Group B	Group C	P value
Sensory level (pinprick)				
5 min	T ₉ (T ₇ -T ₉)	T ₉ (T ₇ -T ₁₀)	T ₉ (T ₇ -T ₉)	
10 min	T ₆ (T ₅ -T ₇)	T ₆ (T ₅ -T ₇)	T ₆ (T ₅ -T ₇)	
Mean time of onset of analgesia (min)	9.83 ± 1.55	9.96 ± 1.79	9.96 ± 1.24	$P > 0.928$ (NS)
Total duration of analgesia (min)	151.8 ± 16.2	302 ± 24.2	535.1 ± 32.8	$P < 0.001$ (HS)
Onset of motor block (min)	14.06 ± 0.57	14.6 ± 1.54	14.7 ± 1.23	$P > 0.20$ (NS)

HS = Highly significant, NS = Non-significant

Table 5: Total number of rescue analgesics within 24 h

Number of rescue analgesics given within 24 h	Group A		Group B		Group C		P < 0.001 (HS)
	Number of patients	%	Number of patients	%	Number of patients	%	
3	0	0	5	17	6	20	
4	11	37	17	56	20	67	
5	16	53	8	27	4	13	
6	3	10	0	0	0	0	
VAS score at first rescue analgesic	2.8 ± 0.6		2.4 ± 0.5		2.3 ± 0.7		$P < 0.005$ (S)

VAS = Visual analog scale 0-10cm, HS = Highly significant, S = Significant

(P value = 0.20) There was no significant difference in the onset of motor block in between group A and B, group A and C and group B and C.

A significantly longer duration of effective analgesia in C group was observed compared with other groups ($P < 0.001$). The mean duration of effective analgesia in group C was 535.16 ± 32.86 min versus 151.83 ± 16.21 min in group A and 302.00 ± 24.26 min in group B [Table 4].

The mean numbers of doses of rescue analgesia in the 1st 24 h in group A, B and C were 4.7 ± 0.65 , 4.1 ± 0.66 and 3.9 ± 0.614 respectively. The P value between these groups is < 0.001 [Table 5].

In all three groups, patients were hemodynamically stable in intra-operative and post-operative period. There were no significant differences between groups regarding intra-operative adverse effects [Table 6].

Discussion

In this study total duration of analgesia got prolonged in gabapentin and pregabalin group as compared to control group, more so in pregabalin group. Rescue analgesic requirement in 24 hours was less in gabapentin and pregabalin groups. This benefit was not associated with significant hemodynamic variation and other side effects. Post operative recovery was uneventful.

Table 6: Intra-operative side-effects

Side-effects	Group A	Group B	Group C
Nausea	2	3	2
Hypotension	3	2	3
Bradycardia	3	3	3
Vomiting	0	1	0
Respiratory depression	0	0	0

Preemptive analgesic modalities have been used as single entities and in combination. Regional and opioid analgesia has been studied extensively.^[14] A meta-analysis conducted by Cliff K.-S. Ong, *et al.*^[15] demonstrates the ability of preemptive analgesic interventions to attenuate postoperative pain scores, decrease supplemental postoperative analgesic requirements, and prolong time to first rescue analgesic request. Using these outcome measures, preemptive analgesia showed an overall beneficial effect after epidural analgesia, local wound infiltration, and systemic nonsteroidal anti-inflammatory drug administration. Pre-incisional analgesia has been shown to be more effective in control of post-operative pain by protecting the central nervous system from deleterious effects of noxious stimuli and resulting allodynia and increased pain. Gabapentin and pregabalin have antiallodynic and antihyperalgesic properties useful for treating neuropathic pain and may also be beneficial in acute post-operative pain management.^[10,16]

Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA). It is not converted metabolically into GABA or a GABA agonist. It acts by decreasing the release of neurotransmitter glutamate.^[17] Oral gabapentin as an adjunct to epidural analgesia have been found to decrease pain and analgesic consumption.^[18,19] Hurley *et al.*^[20] in a meta-analysis on 896 patients concluded that perioperative use of oral gabapentin is a useful adjunct for the management of post-operative pain by providing analgesia through a different mechanism than opioids and therefore would make a reasonable addition to a multimodal analgesic treatment plan.

M, Christophe *et al.*^[21] have shown that premedication with 1200 mg gabapentin improved preoperative anxiety, postoperative analgesia, and early knee mobilization after arthroscopic anterior cruciate ligament repair under general anaesthesia.

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.^[22]

Saraswat and Arora^[11] studied preemptive gabapentin and pregabalin for acute post-operative pain after surgery under

spinal anesthesia. In their study, patients received a single dose of gabapentin 1200 mg (group G) or pregabalin 300 mg (group P). The total post-operative analgesic time was 8.9 hours in group G whereas 14.17 hours in group P (highly significant, $P < 0.001$). Similarly in our study, a significantly longer duration of effective analgesia in group C (nine hours) was observed in comparison with other groups ($P < 0.001$). We have used 600 mg of gabapentin in this study, as bioavailability of gabapentin is not dose proportional, i.e., as dose increases bioavailability decreases. In one metaregression analysis it was suggested that the gabapentin-induced reduction in the 24-h opioid consumption was not significantly dependent on the gabapentin dose. The most common adverse effects of the gabapentinoids were sedation and dizziness.^[10] Pregabalin has been used in a dose range of 75 mg to 300 mg, and higher doses of pregabalin were associated with an increased incidence of dizziness thus in our study, we used 150 mg of pregabalin.^[11] In our study incidence of side effects was not significant. In a study of 90 patients of abdominal hysterectomy the incidence of somnolence was 40% in pregabalin group, 33.3% in gabapentin group, 3.3% in control group ($P = 0.002$). Six patients (20%) reported dizziness in pregabalin group, eight (26%) in gabapentin group and one (3%) in control group ($P = 0.093$).^[23]

Conclusions

Both Gabapentin and pregabalin can be used for preemptive analgesia, however 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.

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