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Pregabalin administered as an anxiolytic agent in ultrasound-guided infraclavicular block: a controlled, double-blind, dose-ranging trial

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Abstract. – OBJECTIVE: Adjuvant agents, given with local anesthetics or via venous, oral, or rectal routes for peripheral nerve blocking, have been in use for a long time. Literature studies about pregabalin usage in peripheral nerve blocking are limited in number. In this study, we aimed to reveal the blocking quality of pregabalin administered orally in various doses as an anxiolytic agent and its effective dose range.

PATIENTS AND METHODS: Eighty patients who underwent upper extremity bone surgery were included in the study. The cases were divided into 4 randomized groups of 20 patients. The group that did not receive any medication before the surgery was named the Control Group (Group C), the group that received 75 mg pregabalin per os was named Group P75, the group that received 150 mg pregabalin per os was named Group P150, and the group that received 300 mg pregabalin per os was named Group P300. The study had a controlled and double-blind design. Before, during and after routine peripheral nerve blocking, vital signs, Ramsey Sedation Scale, Patient Satisfaction, Visual Analog Scale, and termination durations of sensorial and motor blocks were recorded.

RESULTS: Motor block initiation durations of all groups given pregabalin were significantly shorter than those of Group C. Sensorial block termination durations were similar in Group P150 and Group P300, and both were significantly longer than those in Group C and Group P75. First analgesic requirement time for Group P150 and Group P300 were significantly longer than that of Group P75. Although there was no significant difference between postoperative patient satisfaction and VAS values, first analgesic requirement times of the pregabalin administered groups were longer than those of the control group.

CONCLUSIONS: The patients, who are about to undergo surgery, generally develop anxiety about death, not waking up from anesthesia, disability, pain and loss of ability to work. Pregabalin is an anti-epileptic, analgesic and anxiolytic agent. With these characteristics, it can be used to reduce pre-operative anxiety, for prophylaxis against convulsions and post-operative analgesia.

One hundred fifty mg of pregabalin provides sufficient and effective analgesia, and this dose positively affects the quality of the block.

Key Words:
Pregabalin, Anxiolysis, Infraclavicular block.

Introduction

Anxiety is observed in patients during the pre-operative phase and affects the surgery and the anesthesia in a negative manner[1]. The fear of pain constitutes an important part of pre-operative anxiety[2]. Currently, to eliminate pre-operative pain and anxiety, some medications are administered to the patients combined with non-pharmacological methods. Medical treatment is still the most commonly used method in cases of acute and chronic pain. Anxiolytics, benzodiazepines and narcotic analgesics are used for this purpose[3].

Pregabalin is a derivative of gabapentin[3]. Although it can be used for anxiety[4,5], it has recently been used for this purpose. Although several studies have been performed investigating the adjuvant effect in chronic pain treatment, the usage for pain and anxiety treatment is increasing[6]. Pregabalin, a GABA analogue is a derivative of gabapentin, and it reduces the release of calcium by binding to the alpha-2 delta sub-unit of calcium channels and increases neuronal GABA levels[7]. Thus, it is considered to maintain the anxiolytic effect via an increase in GABA neurotransmission[8]. Approximately 150-600 mg/day of

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pregabalin is used in anxiolytic, anti-epileptic and chronic neuropathic pain indications[5]. Several studies have used pregabalin for acute pain[6].

In this study, we aimed to observe the effects of pregabalin, which was administered before blocking, on the block quality and post-operative pain in patient groups undergoing infraclavicular blocking and to determine the effective dose range.

Patients and Methods

Approval of the Yuzuncu Yil University Clinical Research Ethics Committee was obtained for this study (08.10.2015/ 13). As a routine procedure, anesthetic examinations of the cases were performed at least one day before the operations. Cases were informed about the study and written consents were collected. Eighty patients of American Society of Anesthesiologists' Physical Classification System (ASA) 1 and 2 who were to undergo upper extremity bone surgery were included in the study. Cases were divided into 4 randomized groups of 20 patients. The group that did not receive any medications before the surgery was named the Control Group (Group C), the group that received 75 mg pregabalin per os was named Group P75, the group that received 150 mg pregabalin per os was named Group P150, and the group that was received 300 mg pregabalin per os was named Group P300. The study had a controlled and double-blind design. Grouping and premedication of the cases and the peripheral nerve blocking and data recording were performed by different doctors. The physicians who performed the procedure did not know the identity of the groups.

One hour before the blocking procedure, cases were taken into the preoperative room and monitored. Their medications were given with some water per os. Routine monitoring (ECG, peripheral oxygen saturation and non-invasive blood pressure measurement) was performed. Intravenous cannulas were inserted, and 500 ml of 0.9 % isotonic solution was given. Cases were prepared for infraclavicular blocking in the supine position. Twenty-five milliliters of solution mixture, including 15 ml of levobupivacaine (Chirocaine® 50 mg/10 ml Propylene ampoule, ABBOTT, Elverum, Norway) and 5 ml of 0.9 % isotonic solution was prepared. Abiding by the principles of asepsis and antisepsis, all three cords were observed using USG-guidance (Esaote® MyLab 5, Florence, Italy) (12 MHz, linear probe; LA4 35) and 15 ml of prepared local anesthetic solution was injected into the posterior cords; 5 ml of solution for each of the anterior and superior cords were injected using the lateral sagittal infraclavicular approach. Next, 100-mm, 22-G needles (Stimuplex® Ultra, Braun, Melsungen, Hessen, Germany) were used for the procedure. Blood pressures (BP), heart rates (HR) and peripheral oxygen saturations (SpO_2) were measured and recorded at intraoperative time points of 0, 5, 10, 20, 30, 40, 50, 60, 70, 80, and 90 minutes and at postoperative time points of 1, 3, 5, 7, 10, 12, 15, 18, and 24 hours. The Ramsey Sedation Scale (RSS) (9) and patient satisfaction (PS) were assessed using 4-point scales (1: very good, 2: good, 3: not bad, 4: bad), and visual analog scale (VAS) assessments of pain (0: No pain, 10: Severe pain) were also recorded. Termination durations of sensorial and motor blocks were recorded at the clinics where the cases were followed. Sensorial blocks were assessed using the pin-prick test, and motor blocks were assessed using the Modified Bromage Scale (MBS). The scales that were used in the study are presented in Table I.

Statistical Analysis

Descriptive statistics for the emphasized characteristics were expressed as the mean, standard deviation, minimum and maximum. According to these characteristics, variance analysis with two factors or repeated measures analysis of variance was performed to compare the groups and the durations. Subsequent to variance analysis, Tukey's test of additivity was used to analyze the data for the different groups and periods. The level of significance in the calculations was assumed to be 5 %, and SPSS 13.0 (SPSS Inc., Chicago, IL, USA) was used for calculations.

Results

When the groups were compared in terms of age, height, weight and operation duration, no significant difference was found ($p>0.05$) (Table II).

No significant difference between the systolic, diastolic and mean arterial pressures of the groups was found ($p>0.05$) (Figure I). Between the intraoperative 10^{th} and 20^{th} minutes, the heart rates and peripheral oxygen saturations of Group P150 and Group P300 were sig-

Table I. Tests used in the study.

Ramsey Sedation Scale (RSS)	Patient Satisfaction (PS) Scores (MBS)	Modified Bromage Scale (VAS)	Visual Analog	'Pin-prick' test
1-Completely awake and oriented	1-Very good	0-No motor block (arm, forearm totally flexible)	1-No pain 2-Very mild pain	0-No sensorial block
2-Drowsy	2-Good	1-Partial block (arm partially flexible, forearm totally flexible)	3-Mild pain 4-Mild to moderate pain	1-Tactile sensation without pain
3-Closed eyes, eye opening to commands	3-Not bad	2-Almost complete block (no arm flexion, forearm diminished flexion, fingers are brisk)	5-Moderate pain 6-Moderate pain	2-No tactile sensation and pain
4-Closed eyes, eye opening to light physical stimulus	4-Bad	3-Total block (no arm and forearm flexion, fingers are immobile)	7-Severe pain 8-Very severe pain	
5-Closed eyes, no response to light physical stimulus			9 & 10-Unbearable pain	

Table II. Demographical data and operation durations of the cases.

	Group C (mean±SD)	Group P75 (mean±SD)	Group P150 (mean±SD)	Group P300 (mean±SD)	p
Age (year)	32.4 ± 14.2	31.0 ± 7.4	31.5 ± 12.1	32.4 ± 14.9	
Height (cm)	169.3 ± 7.7	168.5 ± 7.1	171.1 ± 10.3	165.1 ± 36.8	
Weight (kg)	68.6 ± 8.3	69.8 ± 9.8	72.2 ± 9.1	74.1 ± 7.8	>0.05
Operation durations (min)	83.3 ± 27.5	97.8 ± 56.4	76.5 ± 23.5	68.0 ± 13.8	

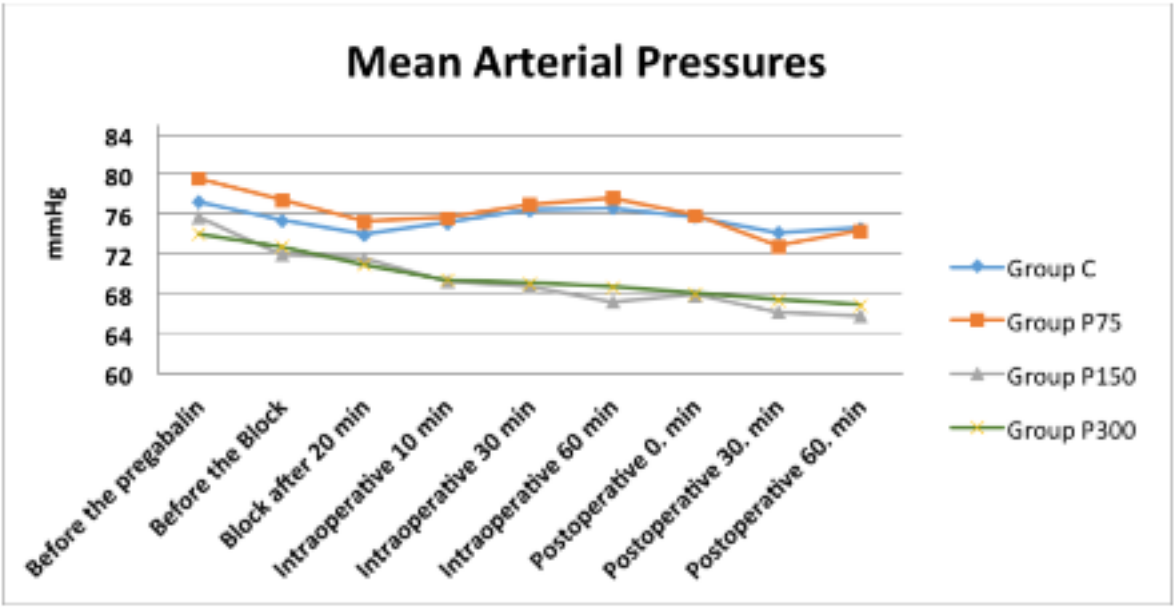

Figure 1. Comparison of the groups according to mean arterial pressures.

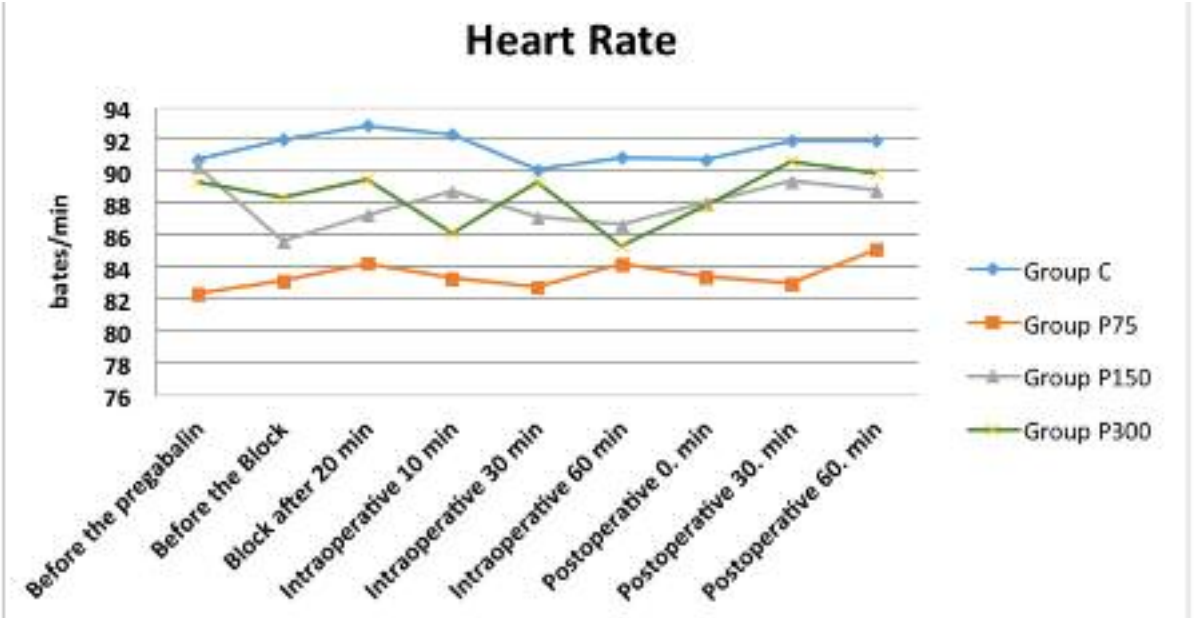

Figure 2. Comparison of the groups according to heart rates per minute.

Table III. Comparison of initiation and termination durations of the groups.

	Group C (mean±SD)	Group P75 (mean±SD)	Group P150 (mean±SD)	Group P300 (mean±SD)	p
Initiation of sensorial block (min)	12.00 ± 2.51	10.30 ± 2.89	10.00 ± 3.45	10.90 ± 3.45	>0.05
Termination of sensorial block (hour)	14.3 ± 2.6	15.7 ± 3.6*&	16.7 ± 3.2*&	16.5 ± 3.2*&	<0.05
Initiation of motor block (min)	15.3 ± 3.4	12.9 ± 4.1&	11.8 ± 4.4*&	12.3 ± 4.7*&	<0.05
Termination of motor block (hour)	13.9 ± 2.9	15.0 ± 3.8	15.9 ± 3.1	15.9 ± 3.3	>0.05

*: Significant regarding Group P75 and Group C,&:

nificantly lower than those of Group C and Group P75 ($p<0.05$) (Figure II).

The motor block initiation durations of all groups given pregabalin were significantly shorter than that of Group C ($p<0.05$). In terms of the motor block termination durations, no significant difference between the groups was found ($p>0.05$) (Table III).

No significant difference in the duration of the sensorial block initiations between the groups was observed. Sensorial block termination durations were similar in Group P150 and Group P300 and both durations were significantly longer than those observed in Group C and Group P75 (Table III).

Although there was no significant difference between postoperative patient satisfaction and VAS values, first analgesic requirement times of the pregabalin administered groups were longer than those of the control group.

In addition, first analgesic requirement time for Group P150 and Group P300 were significantly longer than that of Group P75 ($p<0.05$). No differences were found when the Ramsey sedation scores were analyzed (Table IV).

Discussion

Patients who are about to undergo a surgery generally develop anxiety about death, not waking up from anesthesia, disability, pain and loss of ability to work. 60-80 % of the patients develop anxiety during the preoperative phase[10,11]. Preoperative anxiety affects surgery, anesthesia and post-operative healing in a negative manner[1-3].

Table IV. Values of postoperative VAS, patient satisfaction and first need of analgesics.

	Group C (mean±SD)	Group P75 (mean±SD)	Group P150 (mean±SD)	Group P300 (mean±SD)	p
Postoperative VAS value	0.8 ± 1.2	0.5 ± 0.8	3.0 ± 0.8	0.2 ± 0.8	>0.05
Postoperative patient satisfaction	1.60 ± 0.7	1.8 ± 0.52	1.7 ± 0.5	1.9 ± 0.3	>0.05
First need of analgesics (hour)	12.2 ± 3.3	13.1 ± 4.6[&]	14.5 ± 3.4[&*]	15.0 ± 3.5[&*]	<0.05
Sedation according to Ramsey	2.0 ± 0.2	2.5 ± 0.5	2.5 ± 0.5	2.6 ± 0.5	>0.05

[*]: Significant regarding Group P75 and Group C, [&]: Significant regarding Group C.

Pregabalin is an anti-epileptic, analgesic and anxiolytic agent. With these characteristics, it can be used to reduce pre-operative anxiety, for prophylaxis against convulsions and for post-operative analgesia[15,16]. Although it is used in neuropathic pain treatment, a limited number of studies exist about the usage of pregabalin in acute pain and premedication[15-17]. Pande et al[18] determined that pregabalin is an effective, fast and reliable treatment in common anxiety disorders. In short-term pregabalin treatments, deprivation symptoms related to benzodiazepine were not observed.

Regional anesthesia enables anesthesia without a loss of consciousness and provides longer post-operative analgesia. Currently, success of blockage has increased and complications significantly decreased due to the availability of ultrasonography[14].

Fear conditioning is one of the concepts that may explain the etiology of anxiety disorder. The patients mostly arrive at the operation room conditioned by fear and pain due to the lack of information and the bad experiences they have had or heard. The amygdala and its efferents are responsible for acquiring fear and the subsequent reaction to the fear, supporting the proposal that the amygdala has a regulatory role in the formation of positive symptoms of anxiety[19]. The basolateral amygdala is an important nucleus for integrating memories related to fear and emotions and for organizing the responses against stress[20]. The amygdala interacts with the prefrontal and cingulate cortices and hippocampus while functioning[21]. Interaction disorder between the amygdala and prefrontal cortex prevents the fade-out of fear conditioning[22]. The hippocampus, which causes the recall of fear content, has been anticipated to prevent avoidance of anxiety[19]. This information explains the effect of the amygdala and hippocampus on epilepsy and anxiety disorder.

Patients who have overcome their anxiety are in a state of tranquility, and their hemodynamic parameters maintain a normal level. The RSS is used in this study to assess the anxiety and sedation level of the patient. The RSS values of the groups that were medicated with 150 mg and 300 mg pregabalin were significantly higher compared to the other groups, demonstrating that pregabalin administered at these dosages was effective in the treatment of anxiety.

Patient satisfaction score and the durations of block initiation and termination were used to assess block quality. Cox et al[23] identified the duration of motor block termination in the supraclavicular brachial plexus block as 847 minutes for 0.25% levobupivacaine and 1050 minutes for 0.5% levobupivacaine. Liisanantti et al[24] used a 45 ml volume of 0.5% bupivacaine in the axillary brachial plexus. In this study, high doses of bupivacaine were used, and the mean block duration was 19.3 hours. In the same study, the mean block duration for high dosage levobupivacaine and ropivacaine was 19.5 hours and 17.3 hours for ropivacaine. Cox et al[23] reported the duration of sensorial block termination in supraclavicular brachial plexus block as 892 minutes for 0.25% levobupivacaine and 1039 minutes for 0.5% levobupivacaine. In another study[25], the duration of sensorial block termination was 17 hours in peripheral nerve blocks after the application of 2 mg/kg of 0.5% levobupivacaine. In our study, bupivacaine was used in the blocking process. The duration of sensorial block initiation was measured as 12 minutes, and the termination duration was measured as 855 minutes in the control group. However, the duration of motor block initiation in all groups was significantly lower compared to the control group, and there was no difference between the groups that were given 150 mg and 300 mg pregabalin. The durations of sensorial block initiation and termination were similar in all groups. According to the sensorial block termination duration, the groups that were medicated with 150 mg and 300 mg pregabalin had a longer effect period.

Pregabalin positively affected motor block and sensorial block durations when it was administered at 150 mg and 300 mg doses, which is similar to the RSS data, and it was reported that there was no difference between the two dosages. It was concluded that 150 mg of pregabalin was adequate and effective in motor and sensorial blocks.

Intraoperative stability and the minimal distortion of hemodynamics are the leading objectives of anesthesiologists. In this study, no difference between the groups according to the mean arterial pressures and RSS were observed. In addition to peripheral SpO_2, the heart rate values were lower in the groups receiving 150 mg and 300 mg pregabalin. Thus, stable hemodynamics in the groups receiving 150 mg and 300 mg pregabalin motivated the proposal that pregabalin has positive analgesic and anxiolytic affects. Although there was no significant difference between the RSS values of the groups, it was observed that 150 mg and 300 mg pregabalin provide sufficient sedation to decrease peripheral oxygen saturation. Consistent with conclusions in the literature[26-28], these findings indicated that hemodynamics are stable after using preoperative gabapentin in regional anesthesia, and 150 mg pregabalin does not alter hemodynamics or respiratory parameters[16].

The mechanism and pathogenesis of pain have been recently well studied. Estimation of the patients' pain severity is one of the major difficulties for health care workers[29]. A simple descriptive scale, VAS, and some quantitative scales are used to measure the level of pain. Using these tests, the pain level is converted to objective values to effectively control the pain severity. Among these tests, the VAS is used to convert qualitative assessment to quantitative assessment[30]. In many studies, it was observed[31] that the VAS was used to determine the pain level. Pregabalin was compared to placebo in the treatment of artificial electrical pain in healthy volunteers, and it was observed[32] that VAS values significantly decreased in those given pregabalin compared with those who received the placebo. In our study, the VAS was used to determine the pain level of the patients. The VAS values of Group P150 and Group P300 were lower compared to the control group (Group C) at postoperative minute 0 and during the first moment of feeling pain. A significant decrease was not observed in Group P75. Furthermore, 150 mg of pregabalin was proposed to be adequate and effective in motor and sensorial block in terms of the VAS scores.

Administration of 150 mg and 300 mg pregabalin was similar in terms of the RSS values, motor and sensorial block initiation and termination durations, and VAS scores. These features were significantly more effective compared to Group C and Group P75.

It was observed that 150 mg and 300 mg of pregabalin demonstrated superior analgesia and exhibited more optimal effects on block quality, but there was no difference in the effects of dosages of 150 mg and 300 mg of pregabalin. It was also observed that preoperatively administered 150 mg and 300 mg pregabalin had favorable effects on postoperative pain and peripheral block quality, but this favorable effect was adequate with 150 mg of pregabalin.

Conclusions

It was observed that preemptive usage of pregabalin resulted in increased motor block initiation duration, sensorial block termination duration, sedation, and delayed postoperative first pain feeling; and 150 mg and 300 mg of pregabalin yielded better results compared to Group C and Group P75. Furthermore, it is concluded that 150 mg of pregabalin provided sufficient and effective analgesia and that the pregabalin dose affects the quality of the block.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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