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The Effect of Gabapentin on Postoperative Pain and Opioid-Related Side Effects in Patients Undergoing Combined Spinal-Epidural Anesthesia (a Preliminary Study)

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Abstract

Purpose: Combined spinal-epidural anesthesia (CSEA) is a technique, which is frequently preferred in lower extremity surgery. It has been reported that preoperative administration of gabapentin, approved for neuropathic and chronic pains, also reduces postoperative pain. In this study, the effect of preoperative administration of gabapentin on postoperative pain in patients who had CSEA during lower extremity surgery is investigated.

Material and Methods: After obtaining the approval of the Ethics Committee and the written consent, 60 patients (ages between 18-65 years) who were lower extremity surgery candidates and classified as ASA I-III, were included in the study. The patients were classified randomly into two groups. Group P (n=30) was given 0.5% levobupivacaine (10-15 mg) and fentanyl (25 μg) by spinal route. In the postoperative period, morphine (3 mg) was administered via epidural catheter after the spinal block has resolved. Group G (n=30) was administered 600 mg of gabapentin 1-2 hours prior to surgery, in addition to the medication of Group P.
In the postoperative period, hemodynamic data (SAP, DAP, HR), pain scores (VAS), sedation scores, pruritus scores, other side effects (nausea, hypotension, respiratory depression, bradycardia), and the need for antihistaminic and additional analgesics were assessed.

Results: The demographic characteristics, hemodynamic parameters, duration of surgery, and sedation scores of the groups were similar. It was found that the postoperative pain scores (VAS) were lower in group G at the 30^{th} and 60^{th} minutes and at 18^{th} and 24^{th} hours ($p<0.05$). In the postoperative period, 10 patients in Group P experienced pruritus at the 18^{th} hour, as did eight patients at the 24^{th} hour, whereas none of the patients in Group G reported pruritus at either the 18^{th} or 24^{th} hours ($p<0.001$, $p<0.005$). The differences between the nausea scores and other side effects of the two groups were not statistically significant.

Conclusion: It was concluded that preoperative gabapentin statistically decreased postoperative pain levels as well as pruritus caused by opioids, but did not improve nausea in patients undergoing lower extremity surgery.

Keywords: Combined Spinal Epidural Anesthesia, Gabapentin, Opioid, Preemptive analgesia, Postoperative Analgesia.

INTRODUCTION

Postoperative pain is a type of acute inflammatory pain which begins with surgical trauma and ends with tissue healing. Various pathophysiological changes

on the pulmonary and cardiovascular systems may be consequences of this pain, which has negative effects on organ systems [11].
Postoperative pain treatment is extremely important for homeostasis, and has a significant role in accelerating recovery, shortening hospitalization, and reducing the costs of treatment [1,20].
It has been reported that, combined use of different analgesics or techniques has an additive or synergistic effect which is capable of providing effective analgesia using lower doses with less side effects (multimodal analgesia) [20].
Gabapentin is found to be effective against neuropathic pains [10], post herpetic neuralgia, and diabetic neuropathy [14]. Gabapentin is also a structural analog of GABA, which is an important neurotransmitter in the central nervous system. Various clinical and animal studies have shown that gabapentin has a high affinity to alpha 2 delta subunits in the presynaptic voltage-dependent calcium channels. It inhibits calcium flow and release of excitatory neurotransmitters, which result in pain courses in central sensitization [5,15]. It is also effective in relieving pain, induced by various chemicals or surgical procedures, and primarily affects via the dorsal root by antihyperalgesic and antiallodynic effects [8,12]. Preemptive administration of gabapentin is reported to decrease both the need for postoperative analgesia and pruritus resulting from opioid use [17].
The aim of our study was to investigate the effects of preoperative gabapentin on adverse effects (nausea, vomiting, and pruritus) related to postoperative analgesia and opioids administered to patients subjected to lower extremity surgery under Combined Spinal Epidural Anesthesia (CSEA).

MATERIALS AND METHODS

Our study was conducted at Cukurova University, Faculty of Medicine, Department of Anesthesiology and Reanimation, after obtaining both the approval of the Ethics Committee of the Turkish Health Ministry and the oral and written approvals of the patients.
Patients included in the scope of our study were selected from among the ASA I-III group of individuals, aged 18-65 who underwent lower extremity surgery under CSEA in our hospital between October, 2009, and June, 2010. Patients who did not accept CSEA, who had severe systemic diseases (heart diseases, hepatorenal diseases, bleeding disorders, psychological problems, etc.), or who were allergic to any medicine were not included the study. All patients were informed preoperatively about the application of CSEA, including its complications, and the side effects (nausea, vomiting, hypotension, respiratory depression, bradycardia, ECG variations) of the medications used, as well as about the Visual Analog Scale (VAS) we used for the evaluation of pain.
The patients were divided into two groups of 30 each. The patients in the gabapentin group (Group G) were given 600 mg gabapentin 1-2 hours before surgery and the placebo group patients (group P) were administered placebo tablets orally.

Patients were admitted to the preoperative care unit, where 0.9 % isotonic fluid infusion was initiated intravenously using 20-gauge cannulas. All patients underwent standard monitoring in the operating room. CSEA was applied via the L3-L4 or L4-L5 intervertebral interstice to all patients in the seated position. An 18-gauge "Tuohy" needle with a side tip was used for the epidural anesthesia and a 27-gauge spinal needle for the spinal anesthesia. Spinal anaesthesia was performed with 0.5 % levobupivacaine (10-15 mg) and fentanyl (25 μg) in both groups. After postoperative removal of the spinal block, morphine (3 mg) was applied via the epidural catheter. All cases were continuously observed utilizing standard intraoperative monitoring techniques.

Following surgery, patients were taken to the recovery unit, where they were monitored for 60 minutes. Morphine (3 mg) was administered via the epidural space after removal of the motor block. The 1^{st}-, 5^{th}-, 15^{th}-, 30^{th}-, and 60^{th}-minute heart rate and systolic and diastolic blood pressure values of the patients were monitored and recorded. Postoperative pain level was evaluated using VAS, sedation level using the six-level Ramsay Sedation Scale, postoperative pruritus using a 4-level scale, and nausea-vomiting using a 5-level scale. An antihistaminic agent was administered to patients who had pruritus levels of 3 or higher. The number of patients requiring antihistaminic agent was determined. Afterwards, an anesthesiologists who was not informed about the study groups of the patients, performed and recorded 2^{nd}-, 4^{th}-, 6^{th}-, 12^{th}-, 18^{th}-, and 24^{th}-hour postoperative follow-ups of the patients in the Orthopaedics and Traumatology Service.

Pain scores were recorded in the 1^{st}, 5^{th}, 15^{th}, 30^{th} and 60^{th} minutes in the recovery room, and also in the 2^{nd}, 4^{th}, 6^{th}, 12^{th}, 18^{th} and 24^{th} hours on the ward.

For an a-level of 0.05 and a power of 77 %, 30 patients were needed in each group to detect a minimum 50 % difference VAS at the postoperative period. SPSS 18.0 software was used for statistical analysis of the data. Categorical measures were expressed as numbers and percentages, continuous measures as averages and standard deviations (or, where necessary, as medians and minimum-maximum). Chi-square test statistics were used for comparisons between groups of categorical measures. For comparisons of numerical measures between groups, the T test was used on individual groups when the hypotheses were seen to be verified and the Mann-Whitney U test when unverified. Repetitive measures analysis was used in comparing time variations in continuous measures performed at different times on the same individuals. In all tests, 0.05 was accepted as the statistical significance treshold.

RESULTS

In this study 60 patients were included; 27 men and 33 women. The average ages of the patients were ascertained to be 49.87 ± 12.30 years and 48.07 ± 11.76 years in groups P and G, respectively. No statistically significant differences were

determined to exist between the groups in terms of gender and age ($p>0.05$). Demographic values are shown in table 1.
The systolic and the diastolic arterial pressures were found to be similar between the groups throughout the study ($p>0.05$).
However, comparison of the VAS values of the two groups recorded in the postoperative period revealed a statistically significant difference. VAS values recorded in 30^{th} minute, 60^{th} minute, 18^{th} hour, and 24^{th} hour were determined to be significantly lower in Group G than in Group P ($p<0.05$). VAS values are shown in Graph 1.
Sedation values were similar in both groups and all patients in both groups were observed to be conscious and cooperative.
The number of patients developing postoperative pruritus was similar in both groups in the first four hours (Table 2). However, the number of patients who had postoperative pruritus in the placebo group was higher than that in the gabapentin group at the 6^{th} and 12^{th} hours (11 vs. 3 patients), ($p=0.03$), at the 18^{th} hour (10 vs. 0 patients), ($p= 0.01$) and at the 24^{th} hour (8 vs. 0 patients), ($p=0.005$), respectively. Administration of the antihistaminic agent was similar between the groups in the postoperative period.
In comparing the nausea-vomiting scores of the two groups in the postoperative period, again we did not find any statistically significant difference ($p>0.05$).

DISCUSSION

Gabapentin was found to be effective in treating neuropathic pains [10], post herpetic neuralgia, and diabetic neuropathy [14]. The effects of gabapentin on postoperative pain were first demonstrated in animal models. Singh et al [13] injected mice subcutaneously with 30 mg/kg, 100 mg/kg and 300 mg/kg gabapentin. They reported that gabapentin did not affect the first nociceptive stimulus, but it did reduce the pain triggered by inflammation.
Pandey et al [3] studied the preemptive optimal dose of gabapentin on single-level lumbar discectomies. They emphasized in their study that the preemptive optimal gabapentin dose for postoperative pain was 600 mg and that it reduced postoperative fentanyl need. In addition, they showed that higher doses of gabapentin did not affect postoperative VAS values. In the study conducted by Grover et al [26] on fifty female patients who underwent mastectomy and axillary dissection, the researchers applied 600 mg of gabapentin 1 hour before operation and they observed significantly lower postoperative morphine consumption in the gabapentin group when compared with the placebo group.
There are also studies noticing both low or high doses of gabapentin. Bang et al [23] compared the analgesic effectiveness of low dose (300 mg) gabapentin with that of placebo in orthopedic surgery (arthroscopic shoulder rotator cuff repair). While postoperative VAS values were found to be lower with gabapentin than with placebo, postoperative 24-hour fentanyl consumption and side effects were shown to be similar for both groups. In another study, Turan et al[2] observed that

postoperative VAS values and morphine consumption were significantly lower in the study group than in the control group as a result of 1200 mg gabapentin administration before spinal surgery.

While these studies support the suggestion that preemptive application of gabapentin reduces postoperative pain and lowers opioid/analgesic consumption, studies on the analgesic effects of gabapentin in regional anesthesia are almost nonexistent. Clarke et al [9] researched the effectiveness of preoperative and postoperative gabapentin application on 128 patients who underwent total hip prosthesis surgery and preoperative multimodal analgesia (paracetamol, celocoxib and dexametazon), and no difference was found in the postoperative pain scores and cumulative morphine consumption of the groups included in the study. Gabapentin has not been shown to have analgesic effects for cases subjected to regional anesthesia for acute postoperative pain, nor did it prove to be effective against chronic pain development.

In our study, 600 mg of gabapentin was applied in the preoperative period, approximately 1 hour before surgery. VAS values in postoperative 30^{th}, and 60^{th} minutes and in the 18^{th} and 24^{th} hours after surgery were seen to be significantly lower in the group treated with preemptive gabapentin when compared with the placebo group (Group P).

One of the reasons gabapentin is preferred is the fact that it does not affect intraoperative hemodynamics. Sedation and dizziness are among its most important side effects. The incidence of sedation with gabapentin has been reported as 23 %[25]. In another study, the most frequent side effects listed were somnolence (20 %), dizziness (18 %), ataxia (13 %), and asthenia (11 %) [15]. In rare cases, it may cause pancytopenia, cholestasis, hypersensitivity syndrome, and dyskinesia [16]. In this study, the two groups were determined to have similar postoperative hemodynamic changes, and no gabapentin-dependent side effect was observed. When the groups were evaluated in terms of sedation values recorded in the postoperative period, all patients included in both groups were seen to be conscious and cooperative, and postoperative sedation scores were calculated to be similar in the two groups.

Preemptively applied gabapentin reduces both the doses of opioids administered for postoperative analgesia and also the side effects caused by opioids. However, the preventive effects of gabapentin on nausea and vomiting are not clear. Guttoso et al [21] showed the antiemetic effects of gabapentin on acute (first 24 hours) and late (2-5 days) nausea and vomiting in breast cancer cases subjected to chemotherapy. Pandey et al [4] applied 600 mg of gabapentin and placebo 2 hours before laparoscopic cholecystectomy and reported less postoperative nausea and vomiting (37.8% - 60%) with use of gabapentin. Similarly, Khademi et al [21] researched the postoperative nausea and vomiting effects of gabapentin on 90 ASA I-II patients aged 18-60 who underwent open cholecystectomy, and reported reduced incidence of postoperative nausea and vomiting (36 % - 65.2 %) with gabapentin use when compared with that of the placebo group. Consumption of metoclopramide also decreased when gabapentin was administered. In our study, although not significant statistically, the number of cases who experienced

postoperative nausea and vomiting were lower in the group which was given gabapentin. Nausea and vomiting rates were between 0% and 23.3 % in the placebo group and between 0 % and 10 % in the study group.

Gabapentin, which inhibits the release of presynaptic glutamate, was shown to be effective in brachioradial pruritus [7,22] (a subgroup of pruritus) as well as in itching seen in uremic patients and after burns [6,19]. It was also reported to be effective in cases of systemic pruritus of unknown origin [18]. In two cases of common itching which did not respond to other treatments, gabapentin was administered with an initial dose of 300 mg/day; treatment continued, the dose being titrated (maximum 1800 mg/day) until the symptoms disappeared.

It has been reported that this anti-pruritus effect of gabapentin may be either central or peripheral. One explanation is that gabapentin secondarily inhibits the calcitonin gene-related peptide released by primary afferent neurons. Opioid receptors may also play a role [16].

Gabapentin is also said to relieve the pruritus caused by opioids. Sheen et al [17] evaluated the effects of gabapentin on intrathecal morphine-related pruritus. The gabapentin group was given 1200 mg of gabapentin two hours before surgery. More pruritus was observed in the placebo group than in the gabapentin group (77.5 % - 47.5 %). In addition, pruritus was found to start later in the gabapentin group (3.1±0.8 hours – 6.2±1.8 hours). Unlike this study, our study included administration of morphine (3 mg) via the epidural space, and early postoperative pruritus was observed in both groups. The reason of early pruritus may be related to the fentanyl we administered by spinal puncture. In the postoperative pruritus follow-up, the number of cases developing pruritus in the 6^{th}, 12^{th}, 18^{th}, and 24^{th} hours was found to be significantly lower in group G, in which gabapentin was administered prior to surgery, than in the placebo group.

CONCLUSION

In summary, preoperative gabapentin lowered postoperative pain scores and effectively inhibited development of opioid-related pruritus, especially in the late postoperative period, and that it did so without causing any hemodynamic changes or other side effects.

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Table1 - Demographic data of the groups (Mean ± SD)

	Group P	**Group G**	**P**
Age (years)	49.87 ± 12.30	48.07 ± 11.76	0.56
Gender (m/f)	13/17	14/16	0.79
Weight (kg)	75 (63-92)	77 (55-102)	0.58

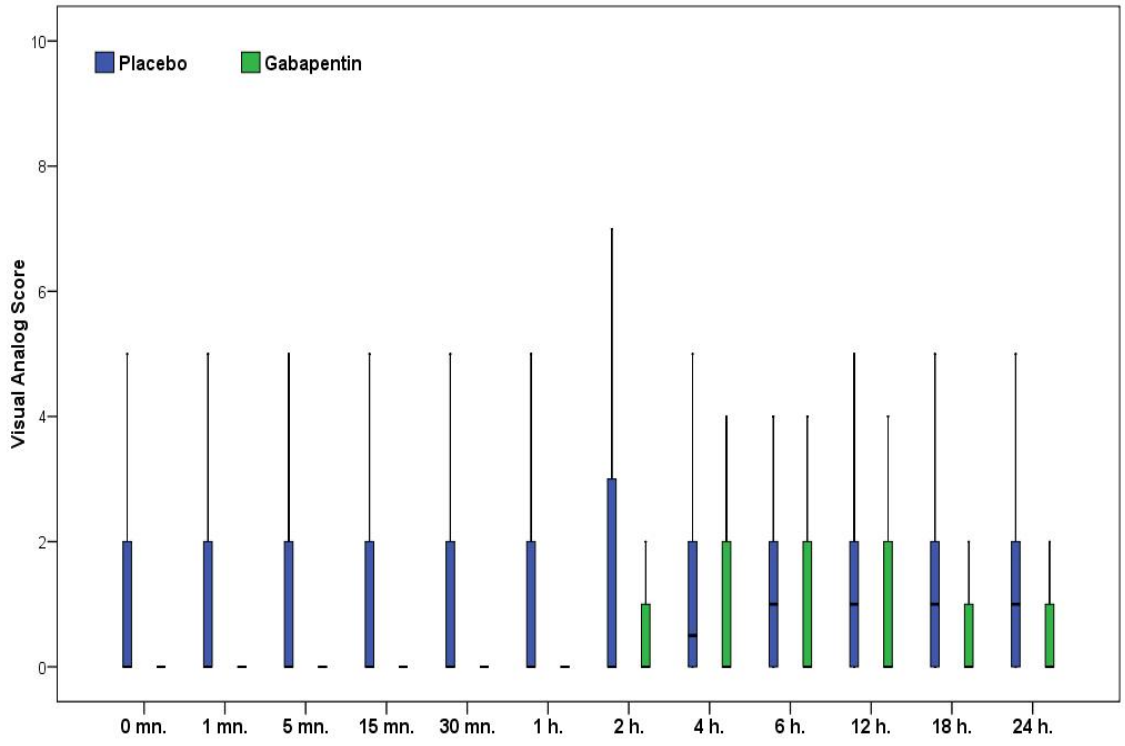
Table 2 - Pruritis (n)

	Group P	**Group G**
Postoperative 1st min.	11	5
Postoperative 5th min.	9	6
Postoperative 15th min.	12	6
Postoperative 30th min.	10	6
Postoperative 60th min.	10	6
Postoperative 1st hr.	11	5
Postoperative 4th hr.	7	5
Postoperative 6th hr.	11	3*
Postoperative 12th hr.	11	3*
Postoperative 18th hr.	10	0**
Postoperative 24th hr.	8	0**

*

***** p= 0.03 Group G compared with group P.
** p= 0.001 Group G compared with group P.
*** p=0.005 Group G compared with group P**.**

Graph 1 - VAS values in groups.



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