The Effect of Pregabalin on Postoperative Pain in the Patients Undergoing Lower Extremity Surgery

Alt Ekstremite Cerrahisi Uygulanan Hastalarda Pregabalinin Postoperatif Analjezi Üzerine Etkisi

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ABSTRACT Objective: Postoperative pain management helps early mobilization, reduces postoperative complications and decreases mortality and morbidity in lower extremity surgery. In this study, we investigated the effect of preoperative pregabalin on postoperative analgesia and opioid related side effects in lower extremity surgery. **Material and Methods:** After obtaining the institutional review board approval and the written informed consent, ASA I-II 60 patients (18-80 years) who underwent lower extremity surgery were included in the study. The patients were divided randomly into two groups. Group I was given oral plasebo, and Group II oral 150 mg pregabalin one hour before surgery. We performed combined spinal epidural anesthesia to both groups with 10-15 mg 0.5% levobupivacaine and 25 μg fentanyl. In the postoperative period, hemodynamic data, pain scores, sedation levels and side effects were observed and recorded. **Results:** The demographic characteristics, hemodynamic parameters, duration of surgery of the groups were similar. Postoperative pain scores were lower at 15th, 30th, 60th minutes in the Group II than Group I ($p<0.05$). The incidence of pruritus was significantly greater in the Group I ($p<0.05$). There was no statistically significant difference in nausea, pruritus and sedation scale of the groups. **Conclusion:** Preoperative 150 mg oral pregabalin improves postoperative pain scores, reduces opioid consumption and opioid related side effects.

Key Words: Pregabalin; anesthesia and analgesia

ÖZET Amaç: Alt ekstremite cerrahisinde postoperatif ağrı yönetimi erken mobilizasyon, postoperatif komplikasyon, mortalite ve morbiditede azalma yönünden önemlidir. Bu çalışmada alt ekstremite cerrahisi yapılacak hastalara preoperatif uygulanan oral pregabalinin postoperatif analjezi ve opioid iliskili yan etkiler üzerine etkisi araştırılmıştır. **Gereç ve Yöntemler:** Fakülte etik kurul onayı ile hastaların yazılı onamları alındıktan sonra alt ekstremite cerrahisi geçirecek 18-80 yaş arası ASA I-II 60 hasta çalışma kapsamına alındı. Hastalar randomizasyon yöntemi ile iki gruba ayrıldı. Cerrahiden bir saat önce Grup I'e oral plasebo, Grup II'e oral 150 mg pregabalin verildi. Her iki gruba da kombine epidural spinal anestezi (10-15 mg %0,5 levobupivakain ve 25 μg fentanil) uygulandı. Postoperatif dönemde hemodinamik veriler, ağrı skorları, sedasyon düzeyleri ve olası yan etkiler kaydedildi. **Bulgular:** Demografik veriler, hemodinamik parametreler, cerrahi süre her iki grupta benzerdi. Postoperatif ağrı skorları 15, 30, 60. dakikalarda pregabalin uygulanan grupta istatistiksel olarak daha düşük bulundu ($p<0,05$). Postoperatif kaşıntı insidansı Grup II'de istatistiksel olarak anlamlı düşük bulunurken ($p<0,05$) bulantı, kaşıntı ve sedasyon skorları benzerdi. **Sonuç:** Preoperatif 150 mg oral pregabalin uygulamasının postoperatif ağrı skorlarını iyilestirdiği, opioid tüketimini azalttığı ve böylece opioid iliskili yan etki sıklığını azalttığı kanısına varıldı.

Anahtar Kelimeler: Pregabalin; anestezi ve analjezi

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Management of postoperative pain is crucial in patients undergoing lower extremity surgery. An acceptable and satisfactory pain treatment obtains acceleration in the postoperative recovery, early mobilization, shorter hospital stay and decreased hospital cost.[1] Furthermore,

optimal management of acute postoperative pain may reduce the development of chronic pain.[2]

Opioid treatment is used safely in the management of postoperative pain but is associated with adverse effects such as vomiting, nausea, pruritus, constipation and urinary retention.[3] Multimodal pain management provides effective postoperative analgesia with minimal side effects using lower doses. Documented benefits of multimodal therapy include improved pain relief, reduction in perioperative stress response, shorter hospital stay, decreased costs of treatment, improved patient satisfaction and reduction in postoperative morbidity and mortality.[4,5]

Pregabalin is an analogue of the inhibitory neurotransmitter γ-aminobutyric acid. It has been established for treatment of neuropathic pain such as postherpetic neuralgia, fibromyalgia, diabetic neuropathy and central neuropathic pain.[6] Its oral absorption is rapid with more than 90% bioavailability, reaches peak plasma levels within 30 min to 2 h, is excreted unchanged by the kidneys and elimination half-life ranges from 5.5 to 6.7 hours.[7-9] Most common adverse effects of pregabalin are dizziness and somnolence and it does not affect arterial blood pressure or heart rate. Several studies reveal that pregabalin reduces postoperative pain and opioid requirement with improves pain scores.[10-15] It is also effective in the treatment of anxiety and confusion.[16,17]

The aim of our study was to investigate the effects of preoperative pregabalin administration on postoperative analgesia and adverse effects in patients subjected to lower extremity surgery under combined spinal epidural anesthesia (CSEA).

MATERIAL AND METHODS

After obtaining the approval of the institutional review board (Cukurova University Faculty of Medicine, Adana, Turkey, 20.01.2011) and the written informed consents, ASA I-II 60 patients (18-80 years) undergoing lower extremity surgery were included in this prospective, randomized, double-blind and placebo controlled clinical study.

Exclusion criteria included morbid obesity (BMI>35), severe systemic diseases (left ventricular ejection fraction < 50%, hepatorenal diseases, congestive heart failure, coagulation disorder, insulin dependent diabetes mellitus, psychological problems, etc.), sensitivity or contraindication to pregabalin, nonsteroidal anti-inflammatory drug administration within 24 hour before surgery, chronic pain (defined as regular use of opioid analgesics for > 3 months), drug or alcohol abuse, the patient's inability to describe postoperative pain to the investigators and contraindication to administration of CSEA.

Using a computer generated randomization table, sixty patients were classified into two groups. One hour before surgery, the control group (Grup I, n=30) received oral placebo, the pregabalin group (Grup II, n=30) received oral 150 mg pregabalin (Lyrica capsule, Pfizer GmbH, Freiburg, German). All patients were instructed preoperatively about the study protocol, use of analgesic and anesthetic techniques, including their side effects and complications.

In the preoperative care unit, intravenous (iv) infusion of saline was initiated via 20-gauge cannulas. In the operating room, after routine monitoring (electrocardiography, noninvasive blood pressure, peripheral oxygen saturation), CSEA was applied at L3-4 or L4-5 intervertebral space using needle-through-needle set to all patients in seated position. Epidural space was identified in the midline using 18 G Tuohy needle by loss of resistance technique. 10-15 mg levobupivacaine (Chirocaine 0.5%, Abbott, Norway) and 25 μg fentanyl (Fentanyl, Johnson& Jonhson, Belgium) were used for spinal anesthesia via 27 G pencil point spinal needle. The epidural catheter was placed 5 cm inside epidural space and fixed after confirming absence of cerebrospinal fluid or blood flow through it. If peroperative pain occurred, epidural 0.25% levobupivacaine 6-10 cc was administered.

After surgery, epidural morphine (3 mg, in the 5 cc volume) was applied to all patients for postoperatively analgesia. In the postoperative recovery unit, hemodynamic parameters, pain levels and side effects were recorded by an

observer, blinded to the study group in the first hour of the 24 hours follow-up.

We used visual analogue score (VAS) (0 mm-no pain, 10 mm-unbearable pain), Ramsay Sedation Scale (1: anxious, agitated, restless, 2: coopere, orient, transquil, 3: responds to command, 4: brick response, 5: a sluggish response, 6: no response), pruritus scale (1:no pruritis, 4: severe pruritis), 5 point scale (1: no nausea, 5: retching and/or vomiting) in postoperative pain, sedation, pruritus and nausea evaluation respectively. We administered iv 2 mg morphine hydrochloride (Morphine ampul, Galen, Turkey) when the patient reported pain, pheniramine maleate (Avil 45.5 mg ampule, Sandoz, Turkey) with pruritus levels equal or higher than 3, metoclopramide (10 mg, iv) for nausea with scores equal or higher than 3. The number of patients requiring analgesic, antihistaminic and antiemetic agents was recorded.

SPSS software was used for statistical analysis of the data. Demographic (age, gender, body weight) data were expressed as number or mean and standard deviation, continuous measures as mean and standard deviation (SD). Demographic data were analyzed using one-way ANOVA. Chi-square test statistics were used for comparisons between groups of categorical measures. Clinical data (VAS, sedation scores) were analyzed using the Kruskal-Wallis test. For comparisons of numerical measures between two groups, the t- test was used under the assumptions of normality and the Mann-Whitney U test under non normality. Repeated measure analysis was used in comparing time variations in continuous measures performed at different times on the same individuals. In all tests, values of $p<0,05$ were considered statistically significant.

RESULTS

All sixty cases completed the study (Figure 1). Patients' demographic characteristics (age, gender, body weight) and duration of surgery were similar (Table 1). No statistically significant differences were found in the hemodynamic data ($p>0,05$).

The VAS scores were significantly lower in Group II at the 15th, 30th, 60th minutes ($p<0,05$) (Table 2). The sedation levels were similar at all time intervals (Table 2). The numbers of patients who needed rescue analgesic and the incidence of nausea were lower in Group II than Group I but they were not statistically significant. Antiemetic and antihistaminic requirement were similar between the groups. The incidence of pruritis was significantly lower in Group II than Group I ($p=0,03$) (Table 3).

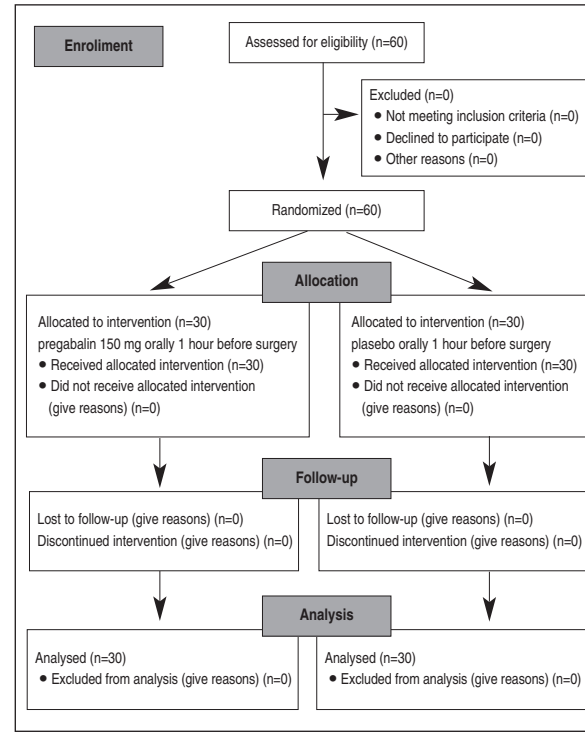

FIGURE 1: Flowchart of the patients.

TABLE 1: Patients' characteristics and duration of surgery.

	Placebo (n=30) (Mean±SD)	Pregabalin(n=30) (Mean±SD)	p
Age (years)	50,5 ± 17.2	43,10 ± 17.3	0,10
Male / female (n)	15 / 15	10 / 20	0,19
Weight (kg)	76,3 ± 14,6	79 ± 13,2	0,52
Duration of surgery (min)	138,2 ± 62,3	136,6 ± 56,6	0,90

Values are mean ± SD or number of patients ($p>0,05$).

DISCUSSION

The aim of our study was to assess the analgesic efficacy, adverse effects and clinical value of pregabalin on CSEA. We found that administration

TABLE 2: The level of pain and sedation of groups.

	5th min Mean±SD	15th min Mean±SD	30th min Mean±SD	60th min Mean±SD	2nd hour Mean±SD	4th hour Mean±SD	6th hour Mean±SD	12th hour Mean±SD	18th hour Mean±SD	24th hour Mean±SD
VAS										
Group I	0,7±1,4	1,0±1,8	0,9±1,9	0,9±1,6	1,4±2,1	1,5±2,0	1,4±1,9	1,4±1,9	1,3±1,7	1,2±1,7
Group II	0,3±1,1	0,2±0,5	0,1±0,4	0,2±0,5	0,8±1,4	1,4±1,6	1,7±2,0	1,4±1,8	0,7±1,1	0,5±0,7
P value	0,32	0,02*	0,03*	0,04*	0,18	0,78	0,47	0,94	0,07	0,05
Sedation										
Group I	2,1±0,5	2,1±0,5	2,1±0,5	2,0±0,2	2,0±0,0	2,0±0,0	2,0±0,0	2,0±0,0	2,0±0,0	2,0±0,0
Group II	1,9±0,2	1,9±0,2	1,9±0,2	2,0±0,2	2,0±1,2	2,0±0,0	2,0±0,0	2,0±0,0	2,0±0,0	2,0±0,0
P value	0,14	0,14	0,14	0,16	1,0	1,0	1,0	1,0	1,0	1,0

Datas were presented as Mean±SD

*p< 0,05, significant compared with Group I

of preemptive single dose pregabalin (150 mg) provided postoperative analgesia, had no significant influence on hemodynamic parameters, and decreased side effects under CSEA compared to placebo.

Pregabalin is a structural analogue of γ-amino-butyric acid (GABA) which has two-two-four greater analgesic effect than gabapentin in neurophatic pain. Pregabalin may also be used as additional analgesic in acute pain therapy, although it is primarily confirmed for the treatment of chronic pain. The effect of pregabalin on acute postoperative pain has been evaluated in recent studies. It was concluded that preemptive implementation of pregabalin may provide postoperative analgesia, reduce opioid requirements and decrease side effects.[10,14,15,18-20] All of these studies were in patients under general anesthesia. Conversely, there are also studies showing that preoperative pregabalin does not affect postoperative pain.[21,22]

Variable doses of pregabalin for pain relief are used in the literature. Peng and colleagues noted that 75 mg of pregabalin was more effective than 50 mg in the early postoperative period.[14] Agarwal et al. reported that preoperative single dose of 150 mg pregabalin reduced fentanyl requirement compared with plasebo in laparoscopic cholecystectomy.[10] Bornemann-Cimenti and colleagues showed that preemptive implementation of pregabalin (300 mg) reduced opioid consumption in the first 48 hours in transperitoneal nephrectomy.[20] Hill and colleagues concluded that pregabalin was more effective than

TABLE 3: The incidence of nausea, pruritis and supplement analgesia

	Group I (n=30)	Group II (n=30)	p
The incidence of nausea (n)	12 / 30	7 / 30	0,13
Antiemetic requirement (n)	5 / 30	2 / 30	0,21
The incidence of pruritus (n)	16 / 30	8 / 30*	0,03*
Antihistamic requirement (n)	2 / 30	0 / 30	0,24
The incidence of supplement analgesia (n)	10 / 30	4 / 30	0,06

Data were presented as number of patients

p< 0,05, significant compared with Group I

ibuprofen for analgesia maintenance under local anesthesia.[23] Conversely, Chang et al. showed that perioperatively administered pregabalin (300 mg; twice a day) did not reduce frequency and severity of post laparoscopic shoulder pain.[21] Similarly, Gonano et al. did not observe an analgesic effect with 300 mg of pregabalin in minor orthopaedic surgery.[24] Also, they found that opioid consumption was lower than the plasebo group but it was not statistically significant.

Effect of pregabalin in regional anesthesia was not well established. Pregabalin application has been showed to reduce opioid consumption and improved postoperative analgesia after total knee arthroplasty.[25] Compared to our study, postoperative analgesia was provided with epidural PCA devices and pregabalin dose was 75 mg, pre and postoperatively twice a daily (for two days) in this study. In addition, the number of patients in each group was lower than our study. Similarly, we also

found that pregabalin reduces postoperative pain at the 15th, 30th and 60th minutes postoperatively.

Pregabalin is used for generalized anxiety disorder but few studies are available about its anxiolytic effect after surgery. Gonano and colleagues found that rapid anxiolytic effect was provided with 300 mg pregabalin before surgery.[24] White et al. found that the sedation scores were higher with 300 mg pregabalin when compared to 75 and 150 mg doses.[26] Although the most common side effects are dizziness, blurred vision and somnolence, pregabalin is well tolerated and its adverse effects are dose-dependent, mild-to-moderate and usually transient. We used 150 mg doses of pregabalin in our study and none of patients complained about any side effects.

Jain et al. reported that, pregabalin also reduced opioid related side effects but, they did not evaluate opioid related pruritus.[25] Ehrchen et al. reported the beneficial effect of pregabalin in chronic pruritus.[27] Remerand and colleagues showed that pregabalin did not reduce postoperative nausea, vomiting and pruritus.[28] We could not find any research about the effects of pregabalin in regional or intraveonus opioid related pruritus. In our study, we observed less opioid related adverse reactions in pregabalin group.

As a conclusion, pregabalin helps to decrease opioid consumption, reduces opioid related side effects and thus improves patient comfort without hemodynamic changes in regional anesthesia.

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