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The effect of tramadol and tramadol + gabapentin combination in patients with lumbar disc herniation after epidural steroid injection

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Background/aim: To compare the effects of tramadol-only treatment and tramadol + gabapentin treatment in patients who had received an epidural steroid injection.

Materials and methods: Forty patients with hernia disc-originated acute lumbar discogenic pain were evaluated. All patients received a single dose of steroid and local anesthesia mixture epidurally via the lumbar approach. In both groups, Group T (tramadol, n = 20) and Group TG (tramadol + gabapentin, n = 20), the injection dose was adjusted to 4 mL of triamcinolone acetonide and 0.25% bupivacaine mixture. Orally, 75 mg/day tramadol or 75 mg/day tramadol + 900 mg/day gabapentin were added to the treatment. Leukocyte, erythrocyte sedimentation rate, C-reactive protein, and urine serotonin levels were measured prior to and after treatment. The effectiveness of the treatment was evaluated by visual analog scale (VAS), Oswestry Disability Index (ODI), and straight leg elevation test (SLET).

Results: Similar improvements in VAS, ODI, and SLET values were observed in both groups in the second week. The inflammation markers were not different after treatment, neither within the groups nor between the groups.

Conclusion: This study revealed that tramadol + gabapentin treatment was not superior to tramadol treatment.

Key words: Lumbar disc herniation, epidural steroid injection, tramadol, gabapentin, lumbar radicular pain

1. Introduction

Lumbar radicular pain is an important problem, particularly in developed and developing countries, and causes serious physical, psychological, and economic losses (1). One of the most frequent reasons for lumbar pain is disc hernias. Mechanical pressure is not the only factor that causes patient complaints. Local inflammatory processes around the nerve root also contribute to the situation (2,3). Epidural steroid injection (ESI) is an alternative and effective method in reducing the inflammation of the nerve root (4). Inflammatory mediators have been reported on in few studies in the literature, while no information about the relationship of the levels of these mediators in clinical situations is present (5).

In herniated discs, nociceptive agents such as prostaglandin E, serotonin, and histamine, which are secreted from the area of the damaged disc, cause inflammation and nerve root irritation. Corticosteroids exhibit a stronger antiinflammatory effect and inhibit

phospholipase A2, which catalyzes arachidonic acid and a prostaglandin formation step from the membrane phospholipids (6). Because of local inflammation, inflammatory mediators such as interleukin 6 are produced by monocytes and macrophages from the inflammation region. These mediators may cause systemic inflammatory reactions in high concentrations. Thus, C-reactive protein (CRP) is thought to increase during lumbar pain. Laboratory measurements of acute phase proteins are important indicators for the degree of inflammation and response to treatment. CRP is a sensitive marker of inflammation and tissue damage, but erythrocyte sedimentation rate (ESR) is not a specific marker (7).

In many experimental studies, serotonin was demonstrated to have a role in neuropathic pain, and 5-hydroxytryptamine 2A (5-HT_{2A}) receptors are reported to have a role in spinal and peripheral sensitivity that promotes analgesia by inhibiting neurotransmission of nociceptive signals (8). Therefore, significant clinical

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effect is observed by using selective serotonin reuptake inhibitors in dissipating many pain symptoms (9). Tramadol, belonging to the weak opioid group according to analgesic classification, is in fact a synthetic drug with both opioid and nonopioid effect mechanisms. In addition to its weak μ -opioid receptor agonist effect, it inhibits presynaptic reuptake of noradrenaline (NA) and serotonin (5-HT) and, at the same time, stimulates the secretion of 5-HT (10,11). Gabapentin is known as an anticonvulsant, shown to have antihyperalgesic and antiallodynic effects in animal and human studies (12,13).

In addition to ESI, treatment can be supported with nonsteroidal antiinflammatory drugs (NSAIDs), muscle relaxants, or antidepressants in patients with discogenic lumbar pain. It has been reported that the treatment success rate and the quality of life increase with ESI and amitriptyline treatment (14).

This study aimed to compare the effects of an oral tramadol-only treatment with a tramadol + gabapentin combination on analgesia, clinical course, serotonin level, and inflammatory response in patients who had received an ESI.

2. Materials and methods

The study was undertaken at the hospital of the Gaziantep University Medical Faculty, following approval by the local ethics commission. This prospective, single-blind study included 40 patients between the ages of 20 and 55 with herniated disc-derived acute lumbar radicular pain present for no more than 3 months and a quality of life score over 20% according to the Oswestry Disability Index (ODI; 1–100; <20%: minimal disability, >35%: serious disability), no surgical history, and radiologically confirmed structural pathology without any neurological deficits.

The patients were evaluated for 3 months. The exclusion criteria were the discovery of bilateral or unilateral multiple root pressure; neurological deficits; history of previous lumbar vertebral surgery; serious cardiac, pulmonary, hematological, gastrointestinal, liver, or kidney disease; glaucoma; urinary retention; statin group drug usage; hormone replacement therapy; and known allergy to drugs used in the study.

Detailed locomotor system examinations; anterior-posterior, lateral, and oblique lumbosacral vertebra radiographies; lumbar MRI investigations; and routine hematological and biochemical tests that had been performed on the patients in the previous 3 month period were evaluated before the process. The initial interventions and probable complications were briefly explained, and written informed consent was obtained.

Patients who provided informed consent were randomized into 2 groups as Group T (tramadol, n =

20) and Group TG (tramadol + gabapentin, n = 20). The randomization was provided by an independent computer consultant. Both groups were administered a single dose of steroid and local anesthetic mixture epidurally by the lumbar approach. Before the procedure, blood vessel cannulation was performed and the patients were monitored (ECG, arterial blood pressure measurements, pulse oximetry). In the prone position, subsequent to local cleaning, the hernia level was determined by fluoroscopy. The fluoroscopy-assisted lumbar transforaminal injection was made in the epidural space using a 22-G spinal needle. The injection dose was adjusted to 4 mL from a triamcinolone acetonide (80 mg, Kenacort ampule, Bristol-Myers Squibb) and 0.25% bupivacaine (10 mg) mixture. Triamcinolone was preferred to betamethasone because of its fast analgesic activity and its effectiveness for ESIs due to its short-term advantages (15). Once it was confirmed that the needle was not in the subarachnoid space, 4 mL of the prepared mixture was injected. After 15 min, a superficial sense examination was performed by the pin-prick method and the epidural analgesia was monitored.

We used an oral form of short-acting tramadol (75 mg) once a day and 900 mg of gabapentin divided into 3 doses in 1 day. This 75 mg/day tramadol and the 75 mg/day tramadol + 900 mg/day gabapentin combination were initiated with oral administration to Group T and Group TG, respectively. We started treatment with a minimal effective dose but planned to increase the doses 2-fold if patients were suffering from pain higher than a visual analog scale (VAS) score of 3, but VAS scores were not higher than 3 during follow-up. We therefore did not decrease the tramadol dose due to the addition of gabapentin because we were using the lower doses.

Venous blood was collected by venipuncture into sterile, siliconized Vacutainer tubes for leukocyte (WBC), ESR, and CRP measurements, and spot urine samples were obtained to detect serotonin levels before treatment and 2 weeks after treatment.

WBC levels were determined with a complete blood count, using the Roche Sysmex XT-2000 I hematology analyzer (Roche, Mannheim, Germany). ESR was determined by the Westergren method. Serum high-sensitivity CRP levels were nephelometrically determined with a Behring Nephelometer 100 Analyzer (Dade Behring, Marburg, Germany).

An isocratic high-performance liquid chromatographic (HPLC) system with an electrochemical detector was used for the HPLC analysis of serotonin in the urine. Accessories for electrochemical detectors were obtained from Chromsystems (urine serotonin normal range: 28.4–125 μ mol/day, intraassay: CV < 2%, interassay: CV < 3%, linearity: up to 1000 μ g/L, limit of quantification: 5 μ g/L,

run time: approximately 8 min, injection volume: 20 μ L, potential: approximately 400 to 500 mV, internal standard: solution of N-methyl serotonin).

In both groups, the analgesia level was evaluated by VAS (0: no pain, 10: maximum pain), while daily activities (walking, sleeping, social activities) were evaluated by ODI (1–100; <20%: minimal disability, >35%: severe disability) to determine quality of life, and objective determination was evaluated by the straight leg raising test (SLET) (0°: worst, 85°: best) before treatment and 2 weeks after the procedure.

Evaluations of data were expressed for the 2 different periods: the baseline sample, and 2 weeks after the beginning of treatment (second week).

Power analysis was performed to determine the proposed sample size in the design stage of the study. The statistical analyses of the data were performed using the Mann–Whitney U test for comparisons between groups and the Wilcoxon test for the intragroup comparisons using SPSS 11.0 for Windows. The intragroup comparisons were performed according to the data at the beginning of the study; the comparisons between groups were performed based on the difference in percentages of the data at the beginning and after the procedure.

3. Results

In total, 40 patients with hernia disc-originated acute lumbar discogenic pain (27 females, 13 males) were enrolled in the study and included in this analysis. The mean age of patients was 45.82 ± 12.20 years (mean \pm SD). The patients were separated into 2 groups, Group T (tramadol, n = 20) and Group GT (tramadol + gabapentin, n = 20). The demographic and epidemiologic characteristics of the patients in both groups were similar (Table 1). Vertebral levels of disc herniation were between L₃ and S₁, duration of pain was 0–12 weeks, and the mean values of VAS, ODI, and SLET scores for each group were similar.

Evaluations concerning patient responses to treatments are shown in Table 2. In the second week, VAS, ODI, and SLET values were evaluated, and no statistically significant difference was found between the groups ($P > 0.05$). Second-week VAS and ODI values decreased and SLET values increased significantly in both groups according to the intragroup comparison ($P < 0.05$).

The ESR, CRP, and serotonin values of the patients did not show any intergroup differences before treatment and 2 weeks after the treatment (Table 3). In the intragroup evaluation, a significant increase was found in WBC values of both groups after treatment (Group T: $7.44 \pm 2.08 \times 10^3/$

Table 1. Demographic and preoperative epidemiologic data of the patients.

	Group T (n = 20)	Group TG (n = 20)
Age (years)	47.70 \pm 10.54	43.95 \pm 13.86
Sex (female/male)	14/6	13/7
Vertebral level of disc herniation, N (%)		
L ₃ –L ₄	4 (20%)	4 (20%)
L ₄ –L ₅	11 (55%)	12 (60%)
L ₅ –S ₁	5 (25%)	4 (20%)
Duration of acute pain, N, mean		
<2 weeks	8	10
2–6 weeks	7	7
7–12 weeks	5	3
VAS	7.05 \pm 1.70	7.10 \pm 1.20
ODI	38.00 \pm 9.78	35.25 \pm 9.10
SLET (0°–85°)	43.25 (20–60)	44.50 (20–50)

VAS = Visual analog scale, SLET = straight leg elevation test, ODI = Oswestry Disability Index.

Group T: 75 mg/day tramadol group (orally).

Group TG: 75 mg/day tramadol + 900 mg/day gabapentin group (orally).

Table 2. Changes in visual analog scale, straight leg elevation test, and Oswestry Disability Index during follow-up.

		Baseline	Second week
VAS	Group T	7.05 ± 1.70	1.95 ± 1.27*
	Group TG	7.10 ± 1.20	1.15 ± 1.08*
SLET	Group T	43.25 (30–60)	63.50 (30–75)*
	Group TG	44.50 (35–60)	60.25 (50–70)*
ODI	Group T	38.00 ± 9.78	26.75 ± 9.63*
	Group TG	35.25 ± 9.10	25.00 ± 8.11*

VAS = Visual analog scale, SLET = straight leg elevation test, ODI = Oswestry Disability Index.

Group T: 75 mg/day tramadol group (orally).

Group TG: 75 mg/day tramadol + 900 mg/day gabapentin group (orally).

*P < 0.05 (significant differences within group).

Table 3. ESR, WBC, CRP, and serotonin levels of groups.

		Baseline	Second week
ESR (mm/h)	Group T	18.20 ± 10.99	16.85 ± 10.99
	Group TG	20.75 ± 16.34	17.75 ± 9.39
WBC (× 10 ³ /μL)	Group T	7.44 ± 2.08	10.28 ± 2.49*
	Group TG	8.82 ± 1.95	11.29 ± 2.46*
CRP (mg/L)	Group T	7.68 ± 11.86	4.01 ± 1.95
	Group TG	8.91 ± 12.64	5.32 ± 5.63
Serotonin (μg/L)	Group T	200.78 + 146.50	148.47 + 87.66
	Group TG	178.98 + 144.96	204.68 + 125.74

ESR = Erythrocyte sedimentation rate, WBC = leukocyte count, CRP = C reactive protein.

Group T: 75 mg/day tramadol group (orally).

Group TG: 75 mg/day tramadol + 900 mg/day gabapentin group (orally).

*P < 0.05 (significant differences within group).

μL vs. 10.28 ± 2.49 × 10³/μL; Group TG: 8.82 ± 1.95 × 10³/μL vs. 11.29 ± 2.46 × 10³/μL), while no difference was found in ESR, CRP, and serotonin values (P < 0.05).

4. Discussion

In this study, the use of tramadol-only and a tramadol + gabapentin combination in defined doses resulted in similar clinical improvement, inflammatory response, and serotonin levels in patients that received an ESI. Furthermore, the WBC count increased in the second week.

Data showed that a low dose of a combination of tramadol and gabapentin shows a synergic effect in preventing pain caused by formalin and may provide a therapeutic advantage in the clinical treatment of inflammatory pain (16). In the nonsurgical management of pain in patients with unilateral cervical or lumbosacral radiculopathy, a mixture of local anesthetic, tramadol, and methylprednisolone was administered via ESI and accepted as an alternative technique for pain relief (17).

No study was found that investigated tramadol + gabapentin treatment in addition to ESI. Tramadol and its

metabolite, O-desmethyltramadol, showed antinociceptive and antihyperalgesic effects via 5-HT₇ receptors by the activation of the serotonergic pathway (18).

Bloms-Funke et al. reported that tramadol increased intracellular 5-HT and NA in the ventral hippocampi of freely moving rats according to *in vivo* measurements (19).

A majority of the serotonergic fibers that play an important role in pain modulation are placed anatomically in the dorsal raphe of the brain. Furthermore, it is clear that serotonin is secreted from the posterior horn by the following conditions: stimulation of the sciatic nerve, carrageenan-induced inflammatory pain, and chronic pain (20).

The use of 5-HT_{2A} inhibitors has relieved symptoms in patients with a herniated lumbar disc (21). Kato et al. reported that exogenous 5-HT secretion increases during intervention of the nucleus pulposus of rats (22). Ayres et al. demonstrated the genetic polymorphism of catecholamine carriers, which play a crucial role within the nervous system in terms of the reuptake of dopamine and serotonin, in cases of acute clinical pain (23).

Generally, CRP levels are higher in patients with acute lumbar sciatic pain. However, only one study could be found concerning patients with chronic lumbar pain and radicular pain. In another study, CRP and ESR levels were expected to increase dependent on increased inflammatory reactions, but they did not increase (7).

Ackerman et al. performed 3 sessions of lumbar ESI (LESI) at 2-week intervals on patients with herniated discs with various pathological intervertebral disc alterations and used systemic inflammatory serum markers (complete blood count, CRP, ESR) in determining the efficiency of LESI. Complete blood count and ESR values were found

to be in the normal ranges and CRP was higher before the LESI treatment (5).

Deniz et al. reported increased leukocyte levels in patients with herniated discs, accompanied by sensory loss as an examinational finding. They also reported a statistically significant increase in ESR compared with the control group in patients with herniated discs, accompanied by reflex impairment as an examinational finding. However, they also found that acute phase reactants were related to examinational findings rather than to radiological findings (24). Crawford et al. demonstrated no increase in ESR and leukocyte levels of a patient with an acute herniated disc imaged with MRI (25).

Anderson et al., in their studies of cattle, reported leukocytosis (neutrophilia, eosinopenia, lymphopenia, monocytosis), an increase in the neutrophil/lymphocyte ratio, an increase in the CD4 lymphocyte percentage, and a decrease in the total CD8 lymphocyte count depending on dexamethasone usage (26). There are studies that suggest a possible systemic effect of steroids used in ESI. In these studies investigating the systemic effects of epidural and intraarticular glucocorticoid injections, a significant increase was reported in the glucose levels of diabetic and nondiabetic patients (27–29). In our study, a clinically insignificant increase in WBC values was found after both groups received ESI. This increase may be explained through the systemic effects of steroids.

In conclusion, in our study, we observed similar effects of a tramadol + gabapentin combination and tramadol-only usage in defined doses on the clinical improvement, inflammatory response, and serotonin levels in patients with herniated lumbar discs who received an ESI.

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