Comparing the therapeutic effects of pregabalin and gabapentin after transforaminal epidural nerve block in lumbar radiculopathy

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Abstract
Lumbar radiculopathy can be presented as low back pain and radiating pain. Transforaminal epidural steroid injection (TFESI) has been used to treat radicular pain, and after the injection, additional medications such as gabapentinoids including pregabalin (PGB) and gabapentin (GBP) can be administered to relieve remnant pain. However, little is known about the effectiveness of gabapentinoids in relieving pain after transforaminal epidural steroid injection. This study was conducted to compare the effect of pregabalin and gabapentin in lumbar radiculopathy patients who underwent transforaminal epidural steroid injection.

One hundred seven patients who received TFESI and had taken PGB or GBP after the intervention at Daegu Catholic University Medical Center from January 2013 to August 2021 were included in this study. Visual Analogue Scale (VAS) was evaluated in all patients. Among 107 patients, 57 (53.3\%) patients took PGB and 50 (46.7\%) patients took GBP after TFESI. The PGB and GBP groups showed reduced VAS scores according to visit (\(P<.001\)). However, no statistically significant differences in VAS scores according to the types of medication (\(P=.811\)) and change aspects according to visit were observed between the PGB and GBP groups (\(P=.947\)). The study findings suggest that both pregabalin and gabapentin can be equally used to reduce pain in lumbar radiculopathy patients who underwent TFESI. Further studies with larger sample size are needed to generalize the findings of this study.

Abbreviations: GBP = gabapentin, PGB = pregabalin, TFESI = transforaminal epidural steroid injection, VAS = Visual Analogue Scale

Key Words: gabapentin, lumbar radiculopathy, pregabalin, transforaminal epidural steroid injection

1. Introduction
Lumbar radiculopathy is one of the most common causes of neuropathic pain, characterized by low back pain and radiating leg pain induced by impaired spinal root function.\textsuperscript{[1,2]} It can result from a degenerative process within the spinal column, including herniated disk and degenerative spondyloarthropathies causing nerve root compression, which can provoke inflammatory responses and changes in sensory neurons.\textsuperscript{[1,3]}

Most patients with lumbar radiculopathy can be managed conservatively.\textsuperscript{[1,3]} However, more than half of these patients suffer from pain lasting more than 2 years.\textsuperscript{[2]} Therapeutic lumbar epidural steroid injection was developed as a minimal invasive treatment for radicular pain and is the most commonly performed initial procedure for treating radicular pain today.\textsuperscript{[2-4]} Steroids can be delivered into the epidural space through various approaches, such as caudal, interlaminar, and transforaminal approaches. Transforaminal epidural steroid injection (TFESI) under fluoroscopic guidance has been preferably used because it can deposit a small dose of medication in the most proximal targeted pain-generating area.\textsuperscript{[5]}

After steroid injection, additional medication can be considered to relieve remnant radicular pain.\textsuperscript{[4]} Among many medications available for managing neuropathic pain, gabapentinoids, including gabapentin (GBP) and pregabalin (PGB), are considered as the first-line treatment in most clinical guidelines.\textsuperscript{[7]} PGB is commonly used to alleviate radicular pain and accompanying symptoms in patients with cervical or lumbar radiculopathy.\textsuperscript{[4,5]} GBP is also widely used as a medication to treat neuropathic pain and known to decrease neuropathic pain in patients with acute and chronic lumbar radiculopathies caused by lumbar disk hernia and those with lumbar spinal stenosis.\textsuperscript{[7,10]}

Several studies have compared the effects of PGB and GBP, but no consensus or guidelines have been established about efficacy of PGB and GBP after TFESI at the optimal dosage regimen.
Therefore, this study was conducted to compare the therapeutic effects of PGB and GBP in patients with lumbar radiculopathy who underwent TFESI.

2. Materials and Methods

2.1. Study design and setting
This was a retrospective study conducted to compare the effects of GBP and PGB after TFESI. Data of patients with lumbar radiculopathy admitted to Daegu Catholic University Medical Center from January 2013 to August 2021 were obtained. This study was approved by the Institutional Review Board of Daegu Catholic University Medical Center (DCUMC IRB No. CR-21-085-1). The informed consent form was not given since this study was a retrospective study.

2.2. Patient selection
Patients aged between 18 and 65 years were included. All patients were diagnosed with lumbar radiculopathy based on physical examinations or radiological evaluation at DCUMC. Lumbar radiculopathy was defined as ICD-10 codes M511.000 (lumbar and other intervertebral disk disorders with radiculopathy), M511.004 (disk herniation of the lumbar spine with radiculopathy), M511.005 (herniated nucleus pulposus of the lumbar spine with radiculopathy), M4726.000 (other spondylosis with radiculopathies of the lumbar region), M5416.000 (radiculopathy of the lumbar region), and M5416.000.01 (lumbar radiculopathy).

TFESI was conducted under fluoroscopic guidance at DCUMC. With a patient lying in the prone position, skin was disinfected, and local anesthetic was administered. Spinal needle was advanced and the needle position was checked by fluoroscopy followed by 1.5 mL of water-soluble radiocontrast injection. After confirming the needle tip position is adjacent to the nerve root, a mixture of steroid (1 mL of dexamethasone) and anesthetic (3 mL of 2% ropivacaine mixed with 3 mL of normal saline) was slowly injected.

All patients who received TFESI had taken PGB or GBP after the intervention. As PGB, either Lyrica (Pfizer Inc., New York) or Lyribeat (Daewoong Bio Inc, Seoul, Korea) was prescribed 50 to 300 mg/day. As GBP, either Neurontin (Pfizer Inc.) or Neurocover (Samjin Pharmaceuticals Co., Seoul, Korea) was prescribed 100 to 600 mg/day.

Patients who received additional block or surgery after taking PGB or GBP, those diagnosed with rheumatoid arthritis, and those who had a history of infection, fracture, or tumor around the lumbar spine identified through magnetic resonance imaging or computed tomography were excluded from this study.

Outpatient clinic follow-up data of patients were collected 3 months after TFESI, including medication types, medication doses, and Visual Analogue Scale (VAS) scores.

Among 2238 patients who underwent TFESI, 1453 were excluded because they have received <3 prescriptions during the follow-up period. Furthermore, 36 patients were excluded because they did not receive the same consecutive dose of PGB or GBP. Ninety-three patients were further excluded because they have not received 3 consecutive optimal dosage regimens. Furthermore, 507 patients were excluded because time points for visits 2 and 3 did not match. Another 42 patients were excluded from the study because they have received medications other than PGB and GBP. Therefore, 107 patients were finally included in this study (Fig. 1).

2.3. Optimal dosage regimen
The optimal dosage regimen of drugs was individualized according to the response and tolerance of the patients. The dose was monitored via outpatient clinic follow-ups and could be increased or decreased based on the response of the patients. If the same dose is maintained for 3 consecutive outpatient visits, the dose was assumed as the optimal dosage regimen.

Visit 1 was defined as the time when the patients first took PGB or GBP after TFESI. Visits 2 and 3 were determined based on the consecutive outpatient visits. Visit 2 was defined as the 30th day from visit 1. Visit 3 was defined as the 90th day from visit 1.

2.4. Visual Analogue Scale
VAS is a widely used tool to quantify the intensity of pain in several populations and diseases, including radiculopathy.\(^{[13]}\) Scores are determined using a ruler, anchored by scores from 0 to 10 (10 cm) or from 0 to 100 (100 mm), in which “no pain” is anchored as 0 and “worst pain” is anchored as 10 or 100, respectively.\(^{[13,14]}\) In this study, a VAS ranging from 0 to 10 was used to measure the intensity of radicular pain.

2.5. Statistical analysis
The general characteristics of the patients were summarized using descriptive analysis. Quantitative variables were presented as mean and standard deviation, and qualitative variables were presented as frequency and percentage. The 2-sample t-test and chi-square test were used to compare the general characteristics of the patients according to the types of medication. Two-way repeated measures analysis of variance was performed to compare VAS scores according to visit, medication type, and interaction (visit difference according to type of medication). Additionally, adjusted result was analyzed using age and sex as covariate variables. Multiple-comparisons analysis was performed using Bonferroni correction. The data obtained were analyzed by a medical statistician. All statistical analyses were performed using Statistical Package for the Social Sciences for Windows (version 19.0, IBM Corp., Armonk, NY). Moreover, all tests were 2-sided, and P values of <0.05 were used to indicate statistical significance.

3. Results
This study group comprised 107 patients (57 [53.3%] patients in the PGB group and 50 [46.7%] patients in the GBP group). Among them, 52 were females and 55 were males. The mean age of the patients in the PGB group was 60.67 ± 17.34 years, and that of the patients in the GBP group was 68.10 ± 10.89 years. The total dose at the optimal dosage regimen was 143.86 ± 50.29 mg/day for PGB and 370.00 ± 199.23 mg/day for GBP. Statistically significant differences in sex, age, and total dose were observed between the 2 groups (Table 1).

On visit 1, the mean VAS scores in the PGB and GBP groups were 4.956 ± 1.499 and 4.876 ± 2.127, respectively. On visit 2, the mean VAS scores in the PGB and GBP groups were 4.325 ± 1.659 and 4.219 ± 2.015, respectively. On visit 3, the mean VAS scores in the PGB and GBP groups were 4.031 ± 1.568 and 4.074 ± 1.820, respectively. The PGB and GBP groups showed reduced VAS scores according to visit (P < .001). However, no statistically significant differences in VAS scores according to the types of medication (P = .811) and change aspects according to visit were observed between the PGB and GBP groups (P = .947) (Fig. 2).

Since there were differences in general characteristics between the 2 groups, it was necessary to confirm the results adjusting these variables. Therefore, adjusted result was obtained using general characteristics of patients, including age and sex as covariates. No statistically significant difference in VAS scores was observed in the adjusted result (P = .946) (Table 2).
4. Discussion

The important points discovered by the authors through this single-center retrospective study are as follows. Both GBP and PGB were found to be effective in reducing pain at the optimal dosage regimen in patients with lumbar radiculopathy after receiving TFESI. However, there was no significant difference in the pain reduction effect between GBP and PGB.

Neuropathic pain, defined as “pain caused by lesions or diseases in the somatic nervous system” is caused by various diseases, such as radiculopathy, myelopathy, and peripheral neuropathy.[15] Lumbar radiculopathy is a type of neuropathic pain involving pathological processes that affect spinal nerve roots. It can be caused by herniated nucleus pulposus, spinal stenosis, and a combination of degenerative spondylosis, ligament hypertrophy, and spondylolisthesis.[16] As a result, neural and neurovascular structures are compressed, causing disruptions in nerve transmission and alter their functions.[15,16]

The use of antiepileptic drugs in treating various neuropathic pain syndromes is based on the similarities in pathophysiology and biochemical mechanisms between neuropathic pain and epilepsy.[17] Gabapentinoids, commonly used as anticonvulsant drugs, are also effective for resolving neuropathic pain and
managing postoperative pain. Gabapentinoids inhibit the influx of calcium into nociceptive neurons by binding to the αδ subunit of voltage-dependent calcium channels, not gamma-aminobutyric acid (GABA) receptors or sodium channels. The binding of gabapentinoids to the receptor inhibits the secretion of excitatory neurotransmitters, such as glutamate, norepinephrine, and substance P, in the spinal and supraspinal pathways. Paradoxically, due to the effect of these drugs as “neuromodulators,” they are currently used more widely for managing neuropathic pain, not for epilepsy.

GBP was first synthesized in 1976 as a substance similar to GABA for treating rigidity and epilepsy. Currently, GBP is the first drug of choice to be selected for acute or neuropathic pain treatment due to its low toxicity and few interactions with major drugs. GBP was originally developed to improve the pharmacokinetic properties of GBP, simultaneously maintaining the biological activity. It is licensed for treating both peripheral and central neuropathic pain in adults. PGB and GBP are structurally similar and are thought to have similar effects by combining with the αδ site of the presynaptic voltage conversion calcium channel of the central nervous system, preventing neuropathic cascades. PGB inhibits alpha-2-delta (αδ) subunits and certain calcium channels, thereby used to treat neuropathic pain. GBP is an αδ ligand and inhibits its interaction with other proteins but does not act as a direct channel blocker. Therefore, PGB has higher affinity for calcium channels and gastrointestinal absorption rate, allowing systemic concentration of PGB increases faster than GBP.

Several studies have compared the beneficial effects of PGB and GBP in neuropathic pain. Kelvin et al have shown that both PGB and GBP had significant efficacy in reducing pain intensity in adults with chronic sciatica. However, GBP had superior effects over PGB with lesser adverse effects. Mohsin et al have shown that both drugs had equivalent preventive effects without major side effects on patients who underwent lumbar microdiscectomy. In this study, both GBP and PGB were effective in reducing pain in lumbar radiculopathy patients who underwent TFESI with no significant difference in efficacy.

Almost two-thirds of patients taking gabapentinoids experience one or more adverse events. The common adverse events are dizziness, somnolence, drowsiness, visual blurring, and peripheral edema. These adverse effects tend to occur at the start of administration and often decrease after weeks of treatment; however, most events are temporary and usually self-limited. In this study, we attempted to compare pain between the 2 groups at the optimal dosage regimen, in which the adverse effects were thought to be minimized.

This study has several limitations. First, since this study was a retrospective study, the information on the use of concomitant medications and other parameters, such as functional level or quality of life of patients, were unobtainable. In clinical practice, both medications are commonly used with other medications to achieve synergistic effects and reduce adverse effects. In this study, we attempted to compare pain between the 2 groups at the optimal dosage regimen, in which the adverse effects were thought to be minimized. Finally, because there were several operators, standardizing the procedure for TFESI was impossible.

5. Conclusion

This study was conducted to compare the therapeutic effect of PGB and GBP in lumbar radiculopathy patients who underwent TFESI. The study findings suggest that both PGB and GBP can be used to reduce pain in patients with lumbar radiculopathy who underwent TFESI. However, there was no significant difference in the efficacy of pain reduction between 2 drugs. Further studies with larger sample sizes are needed to generalize the findings of this study.

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