Observational Study

Clinical Evaluation of Transforaminal Epidural Steroid Injection in Patients with Gadolinium Enhancing Spinal Nerves Associated with Disc Herniation

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Background: Transforaminal epidural steroid injection (TFESI) of corticosteroid is frequently employed to mitigate the painful and disabling symptoms of lumbar disc herniation. However, the treatment outcome of TFESI in patients with radicular pain and inflamed neural structures as assessed by contrast-enhanced magnetic resonance imaging (MRI) has not been forthcoming.

Objectives: To investigate functional improvement and pain reduction following TFESI in patients found to have nerve inflammation as evidenced by gadolinium-enhanced (MRI).

Study Design: Retrospective assessment.

Setting: Tertiary spinal intervention center, Daegu, Korea.

Methods: Thirty-seven patients were selected by strict inclusion criteria. Patients were classified into enhancing and non-enhancing groups as evidenced by gadolinium-enhanced MRI. The enhancing group was further divided into pre-dorsal roog ganglion (DRG) only enhanced group and pre-DRG and post-DRG enhanced group. Clinical outcomes were evidenced by numeric rating scale (NRS) and Oswestry disability index (ODI) at pretreatment, one week, and 4 weeks after treatment.

Results: The improvement of NRS and ODI in the enhanced group was greater than those of the non-enhanced group, at one week and 4 weeks after TFESI ($P < 0.05$). However there was no significant difference in improvement of NRS and ODI between pre-DRG only enhanced group and pre-DRG and post-DRG enhanced group at one week and 4 weeks after TFESI.

Limitations: Retrospective chart review with a small sample size.

Conclusion: The improvement of NRS and ODI in the enhanced group was significantly greater than those of the non-enhanced group after TFESI. Radicular pain and functional impairment in the presence of gadolinium enhancing spinal neural structures and lumbar disc herniation may be more responsive to TFESI than patients without enhancing neural structures.

Key words: Transforaminal epidural steroid injection, radicular pain, herniated lumbar disc, spinal nerve enhancement, contrast enhanced MRI

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Herniated lumbar disc (HLD) is the most common cause of lumbar radicular pain. Studies have shown the radicular pain in HLD results from both chemical inflammation and mechanical compromise of neural structures (1-3). Marshall et al (4) and Olmarker et al (5) demonstrated proinflammatory cytokines and neural inflammatory reactions associated with radicular pain. Cavanaugh (6) showed that isolated mechanical compression of spinal nerve roots was not sufficient to produce radicular pain.

Computed tomography (CT), CT myelography, and conventional magnetic resonance imaging (MRI) are widely used to evaluate patients with lumbar radicular pain. These studies aid in determining numerous anatomic spine pathologies including disc herniation type, size, location, and the presence of associated neural involvement (7). Clinical symptoms and neurological signs may not correlate well with imaging and these studies may fail to identify a cause for the symptoms (8,9). Gadolinium-enhanced MRI can visualize inflammatory nerve pathology better than other imaging modalities (10). This enhancement with gadolinium may be related to a breakdown of the blood-nerve barrier secondary to inflammatory reactions and granulation formation with neo-vascularization (11,12). Gadolinium-enhanced MRI has been shown to identify inflamed neural structures associated with pathogenic leakage of nucleus pulpous (7). Gadolinium adds significant cost and there is a risk of acute renal failure in patients with renal compromise. Allergic reaction can also occur. With these considerations in mind, gadolinium-enhanced MRI in patients who have not undergone spinal surgical intervention and who are experiencing significant low back pain and or radiculopathy may be useful. The ability of gadolinium to image inflamed structures is useful in the diagnosing pain relating to neural inflammation and chemical radiculitis associated with herniated lumbar disc (13).

Injection of steroids into the epidural space surrounding inflamed neural structures is performed to lessen pain and radiculopathy symptoms associated with HLDs. Systematic reviews have shown that epidural steroid injections can provide short-term pain relief (14-16). Delivery of steroid medications into the lumbar epidural space may be accomplished utilizing an interlaminar, transforaminal, or caudal injection technique. Fluoroscopically guided transforaminal epidural steroid injections (TFESI) have demonstrated good results in managing radicular pain (17,18). A proposed advantage of TFESI over interlaminar and caudal techniques is the deposition of a small volume of concentrated medication in close proximity to possible pain generators (17). However, to our knowledge, there has not been a study relating treatment outcomes of TFESI and nerve root enhancement on contrast-enhanced MRI. The aim of this retrospective study was to evaluate the treatment outcomes of TFESI in patients who had enhancement of lumbar nerve roots and spinal nerves by gadolinium-enhanced MRI.

Methods

Patients

Between January 2005 and August 2012, at The Yeung Nam University Medical Center, Spine Clinic, 352 patients who had lower extremity radicular pain underwent a gadolinium-enhanced MRI to find the cause of symptomatic radicular pain. All patients also went through pain drawing, neurologic examination, and electromyography; therefore, referred pain generators that can mimic radiculopathy were ruled out. Of these 352 patients, 182 underwent a TFESI for treatment of lower extremity radicular pain. We retrospectively reviewed these 182 patients' medical records to evaluate treatment outcome as it related to MRI findings (Fig. 1). The Institutional Review Board of the hospital approved this retrospective study.

Inclusion criteria:

1) Lower extremity radicular pain related to single level HLD as evidenced by clinical examination, medical history, and lumbar MRI findings.
2) The HLD was at L3-4 or L4-5.
3) Patient had undergone a single TFESI for treatment.
4) Patient age range: 18~69 years.

Exclusion criteria:

1) Radicular pain had been present greater than 6 months.
2) Far lateral disc herniation, multi-level disc herniation, spinal stenosis, spondylolisthesis, or previous back surgery.
3) Insufficient documentation of outcome data or lack of 4 week follow-up period.
4) Patient received other concomitant procedure that would interfere with the evaluation of the TFESI therapeutic effects.
5) Patient had been diagnosed with a mental health disorder.

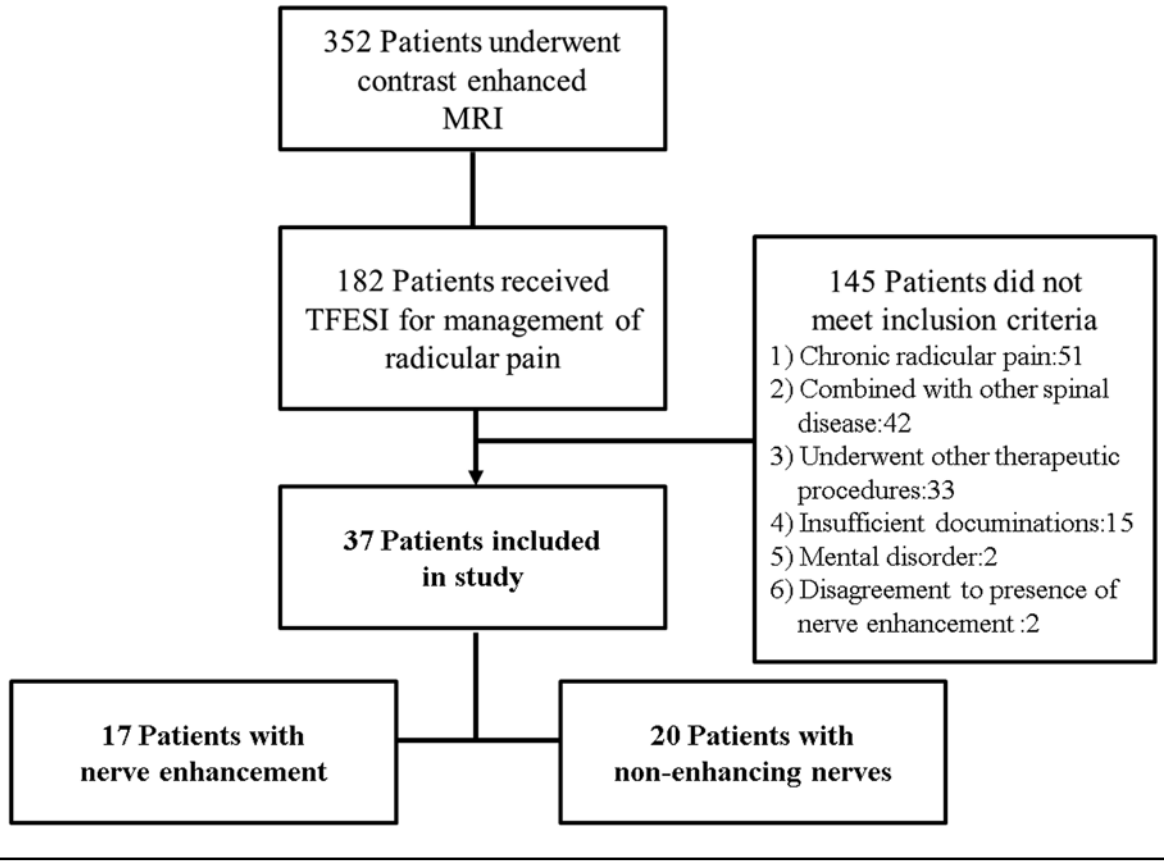

Fig. 1. *Schematic presentation of patient selection by retrospective chart review.*
Note: MR, magnetic resonance; HLD, herniated lumbar disc.

Contrast Enhanced MRI Evaluation

MRI data were obtained using a 1.5-T scanner (Magnetom Vision, Siemens, Erlangen, Germany) with a spine array coil. Spin-echo sequences, axial and sagittal T1- [583/12 (repetition time ms/echo time ms)], turbo T2-weighted images (3800/128), and contrast (Magnevist), 0.2mL/kg of gadopentetate dimeglumine (Bayer Healthcare Pharmaceuticals) enhanced axial T1-weighted images were obtained.

All MRIs were reviewed by a radiologist and a physiatrist, both expert in reading spinal MRIs. The readers were blinded to the corresponding patient's history and clinical outcome. Nerve root enhancement was judged by making a comparison between the non-enhanced and enhanced T1-weighted images. The patients were grouped into enhanced or non-enhanced (Fig. 2). The enhanced group was further divided into those patients where only the nerve before the dorsal root ganglion (DRG) enhanced (pre-DRG [Fig. 3]) and those patients where the nerve before and after the DRG enhanced (pre-DRG and post-DRG enhanced group [Fig. 4]). Two cases where there was disagreement between the 2 reviewers regarding the presence of enhancement were excluded from the study.

TFESI Procedure

All injections were performed by a single interventional physiatrist who specializes in spinal injections. Strict aseptic technique was utilized in the performance of the TFESI procedures. Patients were placed prone and C-arm fluoroscopy (Siemens, Erlangen, Germany) was utilized for level identification and needle guidance. Lidocaine 1% was administered at the needle insertion site and the tip of a 25-gauge, 90-mm spinal needle with a bend at the tip to allow for guidance was positioned between the lateral vertebral body and the 6 o'clock position below the pedicle. Lateral fluoroscopic imaging demonstrated

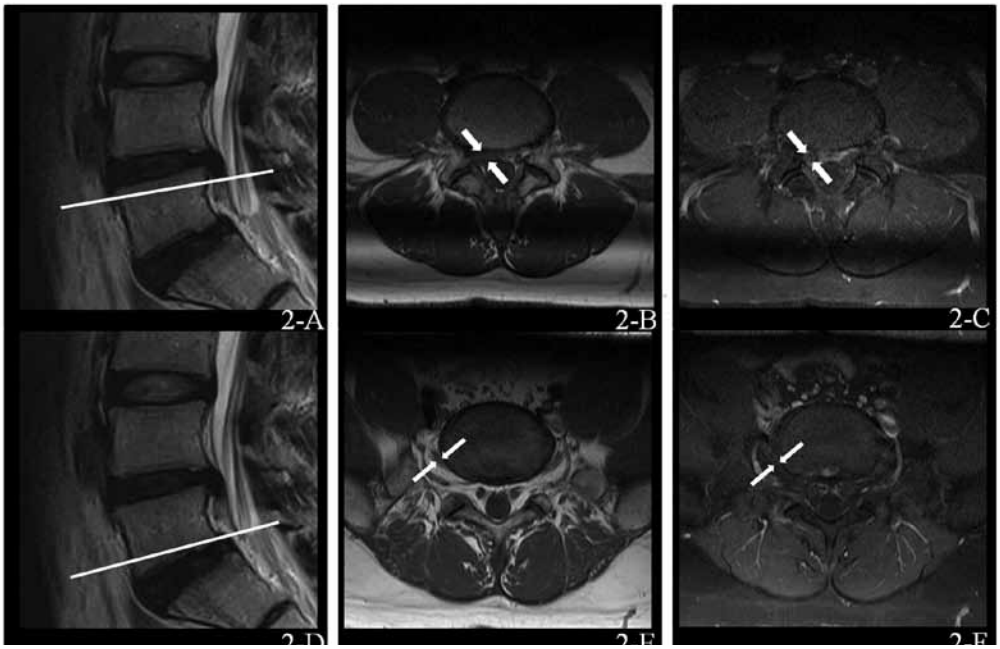

Fig. 2. *Non-enhanced nerve root in lumbar disc herniation. Contrast-enhanced MRI of a 37-year-old man shows a right paramedian extruded disc herniation without nerve root enhancement. At L5 pre-dorsal root ganglionic level (2-A), axial unenhanced T1-weighted (2-B), and contrast-enhanced T1-weight image (2-C) does not show nerve root enhancement. And, at L5 post-dorsal root ganglion level (2-D), axial unenhanced T1-weighted (2-E), and contrast-enhanced T1-weight image (2-F) also does not show nerve root enhancement.*
Note: Wide filled arrow, herniated lumbar disc; Narrow filled arrow, post-dorsal root ganglion.

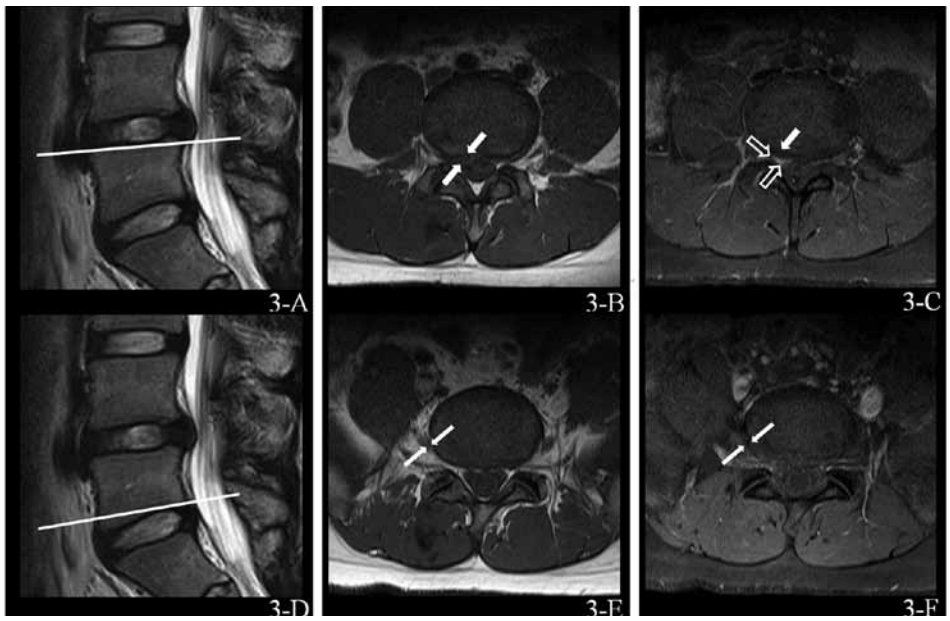

Fig. 3. *Pre-dorsal root ganglion enhancement in lumbar disc herniation.*
Contrast-enhanced MRI of a 20-year-old man shows a right paramedian extruded disc herniation with nerve root enhancement (pre-DRG only enhanced). At L5 pre-DRG level (3-A), axial unenhanced T1-weighted (3-B), and contrast-enhanced T1-weight image (3-C) represent prominent L5 pre-DRG enhancement. At L5 post-DRG level (3-D), axial unenhanced T1-weighted (3-E), and contrast-enhanced T1-weight image (3-F) does not show nerve root enhancement.
Note: Wide filled arrow, herniated lumbar disc; Wide open arrow, enhanced pre-DRG nerve roots; Narrow filled arrow, post-DRG nerve roots.

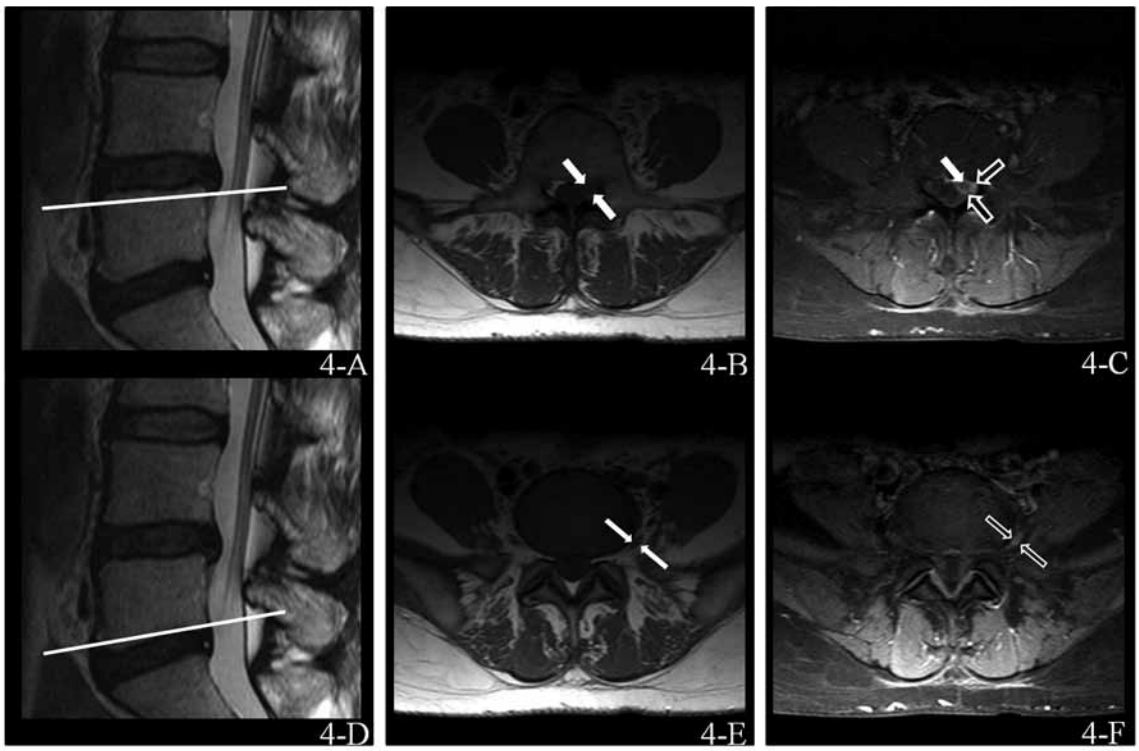

Fig. 4. *Pre- DRG and post-DRG enhancement in lumbar disc herniation.*
Contrast-enhanced MRI of a 21-year-old man shows a left paramedian extruded disc herniation with nerve root enhancement (pre-DRG and post-DRG enhanced). At L5 pre-DRG level (4-A), axial unenhanced T1-weighted (4-B), and contrast-enhanced T1-weight image (4-C) represent prominent L5 pre-DRG enhancement. At L5 post-DRG level (4-D), axial unenhanced T1-weighted (4-E), and contrast-enhanced T1-weight image (4-F) also represent L5 post-DRG enhancement.
Note: Wide filled arrow, herniated lumbar disc; Wide open arrow, enhanced pre-DRG nerve roots; Narrow filled arrow, post-DRG nerve roots; Narrow open arrow, enhanced post-DRG nerve roots.

the needle tip between the spinal laminar margin and the posterior vertebral body. Under anterior-posterior (AP) fluoroscopy, 0.3 mL of non-ionic contrast material (Iohexolbonorex, Daihan Pharm Co, Seoul, Korea) was injected to confirm the absence of vascular uptake and spread of contrast into the foramen. After that, 20 mg (40 mg/mL) of triamcinolone (Shin Poong Pharm Co, Seoul, Korea) with 0.5 mL of bupivacaine hydrochloride (0.5%, Hana Pharm Co, Seoul, Korea) were injected. After the procedures, all patients were observed in the short-stay unit for a minimum of 30 minutes prior to discharge.

Outcome Measurement

Clinical outcomes were assessed by the Numeric Rating Scale (NRS-11) and Oswestry Disability Index (ODI). The NRS-11 ranged from 0 to 10, where 0 indicates no pain and 10 indicates the worst pain imaginable. The ODI consisted of 10 questions and was used to evaluate functional disabilities caused by the patient's radicular pain. Each variable was rated on a 0 – 5 point scale and the total score ranged from 0 to 50. A high ODI score indicates a more severe functional disability related to the pain. The measurements were obtained by a third party who was blinded to the patient's condition prior to and at one week and four weeks after treatment.

Statistical Analysis

The Independent t-test was used for comparing demographic data. Two-Factor Repeated-Measures Analysis of Variance was used to evaluate the improvement of NRS and ODI at one week and 4 weeks after TFESI. All data were analyzed using the SPSS 14.0 for Windows. A *P*-value of less than 0.05 was regarded as statistically significant.

Results

Demographic Data

Demographic findings are summarized in Table 1. Thirty-seven patients were included in this study; 22 were men and 15 were women. Seventeen patients showed nerve enhancement and 20 patients did not demonstrate enhancement. No statistical difference in demographic data was observed between nerve enhanced and non-enhanced group. Among the patients with nerve enhancement, 10 patients had pre-DRG only enhancement and 7 patients showed pre-DRG and post-DRG enhancements patterns. No statistical difference in demographic data was observed between the groups.

Treatment Outcomes

At one week after TFESI, significant improvements were observed in both NRS and ODI compared with pretreatment scores. These improvements remained significant 4 weeks after treatment in both the nerve enhanced and non-enhanced groups ($P < 0.05$). The improvement in NRS was greater in the nerve root enhanced group than the non-enhanced group at one week and 4 weeks ($P < 0.05$). Average NRS scores of the enhanced group declined significantly from 6.2 ± 1.4 at pretreatment to 3.7 ± 1.6 and 2.9 ± 1.6 at one week and 4 weeks after treatment, respectively. Average NRS score of the non-enhanced group declined from 5.4 ± 1.5 at pretreatment to 4.3 ± 1.3 and 3.8 ± 1.3 at one week and 4 weeks after treatment, respectively. Among the nerve root enhanced group, there was no significant difference in improvement of NRS between the pre-DRG only enhanced group and the pre-DRG and post-DRG enhanced group ($P > 0.05$). Average NRS scores of the pre-DRG only enhanced group declined from 6.3 ± 1.4 at pretreatment to 3.9 ± 1.7 and 3.6 ± 1.4 at one week and 4 weeks after treatment and those of the pre-DRG and post-DRG enhanced group declined from 6.2 ± 1.4 at pretreatment to 3.4 ± 1.7 and 2.1 ± 1.5 at one week and 4 weeks after treatment, respectively (Fig. 5).

In ODI, there was greater improvement in the nerve root enhanced group than non-enhanced group at one week and 4 weeks after TFESI ($P < 0.05$). The average ODI of the enhanced group declined significantly from 23.0 ± 9.0 at pretreatment to 12.9 ± 7.8 and 10.0 ± 6.1 at one week and 4 weeks after treatment, respectively. However, the average ODI of the non-enhanced group declined from 22.7 ± 5.6 at pretreatment to 19.6 ± 6.4 and 16.3 ± 6.0 at one week and 4 weeks after treatment, respectively. There was no significant difference in improvement of ODI between the pre-DRG only enhanced group and the pre-DRG and post-DRG enhanced group ($P > 0.05$). Average ODI scores of the pre-DRG only enhanced group declined from 21.4 ± 8.2 at pretreatment to 12.8 ± 7.9 and 10.3 ± 7.1 at one week and 4 weeks after treatment and those of the pre-DRG and post-DRG enhanced group declined from 25.3 ± 10.3 at pretreatment to 13.0 ± 8.1 and 9.5 ± 4.8 at one week and 4 weeks after treatment, respectively (Fig. 6).

Discussion

In this study, we evaluated the treatment outcome of TFESI according to the presence of nerve enhancement as evidenced by gadolinium MRI. NRS and ODI were significantly improved over pretreatment levels following TFESI regardless the presence of nerve enhancement. Improvement in NRS and ODI in the enhanced group was greater than the non-enhanced group at one week and 4 weeks following TFESI. However, the presence of enhancement pre- and post-DRG did not significantly change patients response over pre-DRG only enhancement. There was no statically difference of NRS and ODI between the pre-DRG only

Table 1. *Baseline demographic characteristics.*

Variables	Enhanced nerve root	Non Enhanced nerve root	*P*-value
Patients number	17	20	
Gender (male: female)	11 : 6	11 : 9	0.56
Level of disc herniation (L3-4 : L4-5)	2 : 15	3 : 17	0.48
Age (years)	51.1 (12.2)	48.9 (15.7)	0.63
Duration of symptom (weeks)	6.2 (6.1)	4.9 (4.7)	0.44
Initial numeric rating scale	6.2 (1.4)	5.4 (1.5)	0.09
Initial Oswestry disability index	23.0 (9.0)	22.7 (5.6)	0.91

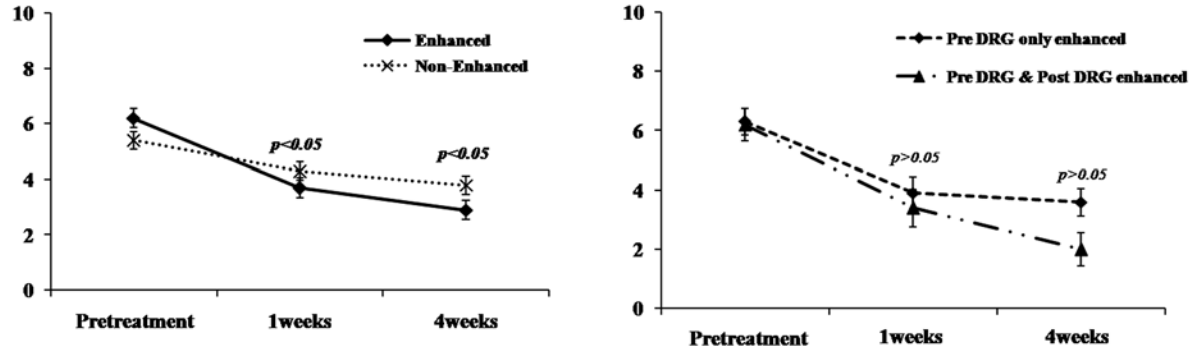

Fig. 5. *Comparison of Numeric Rating Scale according to nerve roots enhancement.*
(A) At one week and 4 weeks after treatment, change of NRS in nerve root enhanced group was significantly greater than those with non-enhance group ($P < 0.05$).
(B) At one week and 4 weeks after treatment, there was no significant difference in improvement of NRS according to spreading pattern of nerve root enhancement ($P > 0.05$).
Note: Full line, nerve root enhanced group; Dot line, nerve root non-enhanced group; Narrow broken line, Pre-DRG only enhanced group; Wide broken line, Pre-DRG and post-DRG enhanced group; Vertical bar means the standard error. *P* value, comparison of the improvement of NRS according nerve roots enhancement at one week and 4 weeks after TFESI.

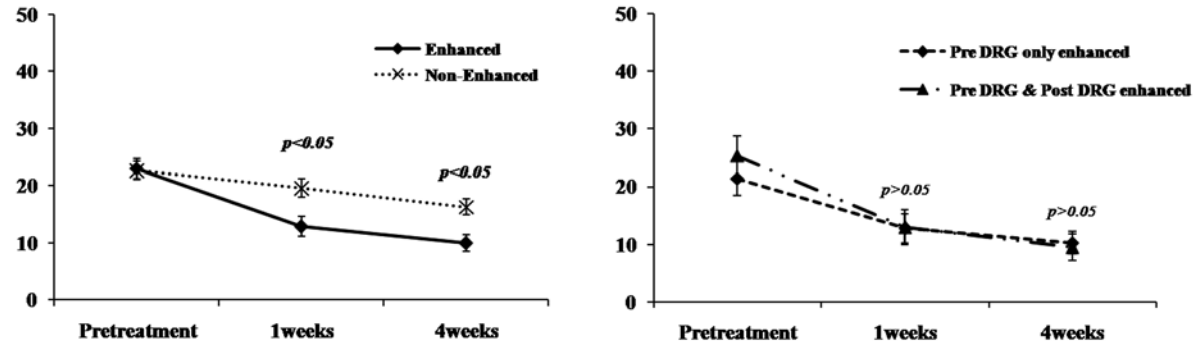

Fig. 6. *Comparison of Oswestry disability index according to nerve roots enhancement.*
(A) At one week and 4 weeks after treatment, improvement of ODI in nerve root enhanced group was significantly greater than those with non-enhanced group. ($P < 0.05$).
(B) At one week and 4 weeks after treatment, there was no significantly difference in improvement of ODI according to spreading pattern of nerve root enhancement. ($P > 0.05$).
Note: Full line, nerve root enhanced group; Dot line, nerve root non-enhanced group; Narrow broken line, pre-DRG only enhanced group; Wide broken line, pre-DRG and post-DRG enhanced group; Vertical bar means the standard error. *P* value, comparison of the improvement of ODI according nerve roots enhancement at one week and 4 weeks after TFESI.

enhanced group and the pre-DRG and post-DRG enhanced group at one week and 4 weeks after TFESI.

Contrast-enhanced MRIs have value in identifying inflammation of spinal neural structures. Nerve enhancement with contrast-enhanced MRIs is associated with accumulation of granulation tissue, inflammatory cytokines, and disruption of endoneurial capillaries (18,19). Inflammation mediated by proinflammatory cytokines results in the breakdown of the blood-nerve barrier, increased vascular permeability, and enhancement of nerve tissue in contrast MRIs. Jinkins (10) demonstrated that gadolinium-enhanced MRI could serve as a marker for spinal nerve and nerve root pathology. Toyone et al (20) revealed that severity of radicular

pain was well correlated with nerve root enhancement. However there has been no study relating clinical outcome of TFESI and nerve enhancement.

For radicular pain, TFESI has demonstrated effectiveness compared to physical therapy and caudal epidural steroid injections (13-15). Triamcinolone acetonide, a synthetic glucocorticoid corticosteroid with marked anti-inflammatory action, has been utilized "off-label" for injections into spinal neural foramen to attenuate the proinflammatory cytokines and inhibit chemical inflammation. Using precise fluoroscopic guided technique. including verification of contrast spread and absence of vascular uptake prior to injecting the steroid, improves safety and allows for a high concentration of steroid agent to be deposited precisely at the affected spinal nerve.

Thomas et al (21) suggested that TFESI was more effective than interlaminar injection for pain reduction and functional ability improvement. Riew et al (22) showed that TFESI had a surgery sparing effect which was sustained at a 5 year follow-up period in radicular pain. Previous studies have not considered nerve root enhancement in relation to the effectiveness of TFESI. Gadolinium MRI enhancing spinal nerves associated with intervertebral disc pathology likely represents nerves in an inflamed state and would be expected to respond to local steroid administration.

Regardless of nerve enhancement, NRS and ODI were significantly reduced at one week and 4 weeks after TFESI. This sort of improvement has been demonstrated in previous studies (14-18,21,22). Our findings suggest that improvements of radicular pain and functional ability were greater in the group demonstrating nerve enhancement over the group in which nerve enhancement was not seen. This would suggest an inflammatory mechanism, exclusive or in addition to others such as mechanical or vascular, be present. Contrast-enhanced MRI is often used post-surgery to evaluate for the presence of inflammation and granulation and may prove useful when spinal nerve mediated pain is suspected. The authors consider that gadolinium-enhanced MRI is also useful in a non-operated degenerative lumbar spine to suspect and find the different causes of low back pain, such as pathologies of nerve roots, facet joints, and annular tear (chemical radiculitis). The enhanced spinal nerves are thought to be a neural inflammatory state.

In this study, and as in a common practice, local anesthetic was combined with the steroid medication. Local anesthetic alone may provide anti-inflammatory effects and injection near an inflamed neural structure may offer a "wash out" of inflammatory products (23-26). To better address these possible mechanisms a future study employing saline, local anesthetic alone, and local anesthetic with steroid all in an equal volume may be useful. Patients with radicular pain over 6 months were excluded and we chose a short 4 week follow-up period. This was done to more accurately study the inflammatory component of the nerve pathology and the anti-inflammatory effects of transforaminal injection of steroid combined with local anesthetic.

In this study, treatment outcome of the pre-DRG and post-DRG enhanced group tended to be slightly superior to that of the pre-DRG only enhanced group; however, there was no statistical difference of treatment outcome between 2 groups. We had expected the response of TFESI in the pre-DRG and post-DRG enhanced group might be stronger than that in the pre-DRG only enhanced group. It is because cases with post-DRG enhanced nerve always accompanied the pre-DRG without exception, therefore, the pre-DRG and post-DRG enhanced nerve might represent a more inflammatory status than the pre-DRG only enhanced nerve. The reason for no statistical difference in treatment outcome in both groups is thought to be the small sample size.

Limitation

This study is limited by its retrospective design, small number of patients, and brief follow-up window. Patients with HLD at L5-S1 were not included due to the less than optimal images obtained at this level making accurate and consistent determinations of post-DRG enhancement difficult. In this retrospective study, all patients were injected with both steroid and local anesthetic; therefore, one cannot conclude the observed effect was due solely to the steroid or the local anesthetic.

Conclusion

In summary, the improvement of NRS and ODI in the enhanced group was significantly greater than those of the non-enhanced group after TFESI. Radicular pain in the presence of enhanced nerve roots and lumbar disc herniation may be more responsive to TFESI than when enhancement is not present. Despite the retrospective method and brief follow-up duration, these findings suggest the presence of nerve enhancement in contrast-enhanced MRIs may help predict the treatment outcome of TFESI in HLD-associated radicular pain. A controlled, prospective, long-term follow-up,

larger scale study utilizing local anesthetic only and local anesthetic with steroid is required to confirm our results and address the limitations.

Disclaimer

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Conflict of interest

Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

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