

Evaluation of the efficacy and safety of combined pulsed radiofrequency and transforaminal epidural steroid injection in herpes zoster-related pain

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SUMMARY

Objectives: In this study, we aimed to evaluate the effectiveness of pulsed radiofrequency (PRF) and transforaminal anterior epidural steroid injection (TFAESI) applied to the dorsal root ganglion (DRG) in herpes zoster pain.

Methods: The results of patients who underwent DRG PRF and TFAESI for herpes zoster-related pain in the algology clinic were evaluated retrospectively. Demographic and clinical examination findings (gender, age, involved dermatome, side, neurologic examination, medications used), VAS scores, and complications were recorded at 1, 6, and 12 months after the procedure.

Results: Data of 93 patients were evaluated. Sixty-six patients were in the acute/subacute pain phase, while 27 patients had postherpetic neuralgia (PHN) at presentation. Eleven patients (C2–4:1, C3–5:2, C4–6:2, C5–7:2, C6–8:2, C7–T1:2) underwent cervical DRG PRF and TFAESI. Seventy-five patients underwent thoracic DRG PRF and TFAESI (T1–3:2, T2–4:6, T3–5:4, T4–6:11, T5–7:9, T6–8:9, T7–9:6, T8–10:5, T9–11:9, T10–12:7, T11–L1:3, T12–L2:4). Seven patients underwent lumbar DRG PRF and TFAESI (L1–3:3, L2–4:1, L5–S2:3). VAS scores for all three regions were significantly lower than pre-procedure scores at 1, 6, and 12 months after the procedure ($p < 0.001$, $p < 0.001$, $p = 0.008$, respectively). While 2 patients developed nausea and dizziness due to subdural and intravenous leakage after the procedure, no fatal complications were recorded in any patient.

Conclusion: In herpes zoster-associated refractory neuropathic pain, fluoroscopy-guided combined DRG and TFAESI application methods provide long-term effective pain control and are safe both in the acute/subacute phase and in patients who develop PHN.

Keywords: Epidural injection; herpes zoster; postherpetic neuralgia; pulsed radiofrequency; varicella-zoster virus.

Introduction

Herpes zoster is the result of activation of the varicella-zoster virus (VZV) that remains latent in the ganglion.^[1] It causes severe stabbing, stinging, and burning pain on the skin of the affected site during and after the acute infection. Patients experience an acute/subacute phase and a period of severe neuropathic pain as postherpetic neuralgia (PHN).^[2] The pain usually resolves itself within a few weeks. PHN with severe, persistent pain that occurs after the rash resolves may be observed as a common complication in 5–30% of patients with herpes zoster.^[3] The pain caused by

herpes zoster adversely affects patients physically and mentally, significantly reducing their quality of life. PHN is difficult to treat and requires a multimodal pharmacologic and interventional approach. Early interventions in medically refractory patients were shown to reduce the incidence of PHN by reducing the duration and severity of herpes zoster neuralgia.^[4]

It was proved that methods including epidural injections, paravertebral blocks, ozone injection, pulsed radiofrequency (PRF) applied to the dorsal root ganglion (DRG), radiofrequency thermo-coagulation (RFT), and spinal cord stimulation

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are effective in the treatment.^[5,6] Radiofrequency treatment has recently been preferred for its effectiveness, rapid onset of action, and minimal invasiveness. PRF is widely used in the treatment of herpes zoster-related pain as it does not result in destructive effects. DRG PRF treatment for pain control in herpes zoster was reported to have quite favorable therapeutic effects.^[7] However, it is argued that PRF treatment provides short-term pain control for refractory pain treatment. The combination of various treatments to increase the therapeutic effect and prolong the duration of analgesia is considered to be a more effective method to manage herpes zoster-related pain through different mechanisms. Steroids, ozone, and local anesthetics are administered in combination with PRF treatment to DRG, which is the primary target. However, the safety, efficacy, and feasibility of these combined treatment programs require testing in clinical trials. The literature includes a limited number of studies designed for this objective. In the present study, we aimed to evaluate the long-term follow-up results of patients who underwent combined cervical, thoracic, and lumbar DRG PRF and transforaminal anterior epidural steroid injection (TFAESI) for pain in the acute/subacute and PHN period after herpes zoster, focusing on pain control and complications that may develop.

Materials and Methods

The present study adopted a retrospective design based on a retrospective chart review and data collection of patients who underwent combined PRF and transforaminal epidural steroid injection (TFAESI) after herpes zoster.

Approval for the study was obtained from the Adnan Menderes University, Faculty of Medicine Clinical Research Ethics Committee (2024/78). This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Inclusion Criteria

Patients aged ≥ 18 years with a diagnosis of acute zoster pain and postherpetic neuralgia who underwent combined DRG-PRF and TFAESI were included in the study.

Exclusion Criteria

Patients with known pregnancy, major psychiatric disease, bleeding diathesis, infection in the procedure area, local anesthetic allergy, and patients with cardiac pacemaker were excluded from the study.

The demographic and clinical examination results (gender, age, involved dermatome areas, side, neurological examination, medications used) and VAS scores of the patients who underwent combined PRF and TFAESI after herpes zoster in the Algology clinic between May 2016 and March 2023 were recorded. VAS pain scores, clinical and neurologic examination, and complication reports were recorded at 1-month postoperative follow-up. At the end of the 6th- and 12th-month follow-ups, patients were evaluated for VAS pain scores, duration of pain control, recurrence, complications, and the recorded results were analyzed.

Primary endpoint: Patients who underwent combined PRF and TFAESI for herpes zoster-related pain were evaluated with long-term follow-up for pain control and recurrence.

Secondary endpoint: Patients who underwent combined PRF and TFAESI for herpes zoster-related pain were evaluated with long-term follow-up for complications.

Interventional Procedure

The interventional treatment was performed in the operating room under sterile conditions, with the patient in the supine position, under the guidance of a C-arm fluoroscopy device. After determining the appropriate level range for cervical DRG and TFAESI, the cannula insertion site was identified by angling the C-arm fluoroscopy device 45–65 degrees until the neural foramina were visualized in a circle. The skin or subcutaneous tissue was infiltrated with 2% lidocaine. A 5 cm long RF cannula with a 5 mm active tip was advanced to the 6 o'clock position of the neural foramina (Fig. 1a). The needle was advanced until it contacted the superior facet joint, then directed into the foramen. After entering the foramen, the needle was advanced to the facet column. To avoid intrathecal or direct damage to the spinal cord, the epidural space was entered while taking an anteroposterior view with a contrast agent (Fig. 1b).

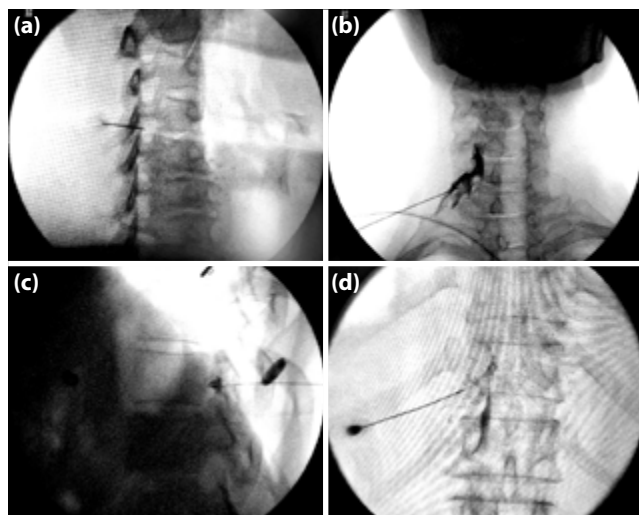


Figure 1. (a) Fluoroscopic 45-degree oblique position of the foramen and cannula for cervical DRG and TFAESI. (b) Fluoroscopic anterior posterior position of the opaque distribution in the anterior epidural space for cervical DRG and TFAESI. (c) Fluoroscopic lateral position of the cannula in the foramen and opaque distribution for thoracic DRG and TFAESI. (d) Fluoroscopic anteroposterior position for thoracic DRG and TFAESI image of cannula placement and opaque material distribution in the posterior position.

For the thoracic DRG and TFAESI procedure, an anteroposterior (A–P) view was taken, and then the C-arm was adjusted caudo-cephally to align the end plate of the vertebra of interest and bring the shadow of the costa over the shadow of the transverse process, followed by orientation of the C-arm approximately 20–25 degrees in an oblique view. The skin insertion point was just below the pedicle of the relevant level. The skin was infiltrated with 1 mL 2% lidocaine at the insertion point. A 10 cm, 22 G RF needle with an active tip of 10 mm was inserted just below the lateral edge of the pedicle (Fig. 1c). An A–P view was taken to verify the presence of contrast agent within the foramen and around the nerve root on fluoroscopy (Fig. 1d).

For lumbar DRG and TFAESI, the level was determined by placing the C-arm scope in the A–P position. It was then placed in a 15–20° oblique position to obtain an image of the intervertebral foramina. The skin and subcutaneous area were infiltrated with 1 mL 1% lidocaine. A 10 cm, 22 G RF needle with an active tip of 10 mm was directed into the intervertebral foramen, just below the lateral edge of the pedicle.

After the RF cannula was positioned in the appropriate range for cervical, thoracic, and lumbar applications, the catheter needle was considered to

be placed near the dorsal root ganglion when abnormal sensation, vibration, or pain was observed with less than 0.7 Volts of stimulation for sensory stimulation, and a motor pulse in the arm with less than 2.0 Volts of stimulation for motor stimulation. Once the tip of the needle was in the correct position, 0.5 mL of contrast medium was injected to confirm the typical anterior epidural spread. The image was also confirmed with A–P and lateral projections. The periradicular membrane image showed the diffusion of radiopaque material both within the foramen and around the nerve root on fluoroscopy.

Afterward, 4 mg (1 mL) dexamethasone and 20 mg (1 mL) lidocaine were administered for the cervical region, and 1 mL betamethasone and 1 mL bupivacaine for the thoracic and lumbar regions. The radiofrequency generator (Neurotherm NT1100/13001-12) was adjusted to keep the catheter needle tip temperature not exceeding 42°C and subjected to PRF treatment for 240 seconds.

Statistical Analysis

The research data were evaluated using the SPSS 21.0 statistical program. The conformity of continuous variables to normal distribution was investigated using visual (histogram and probability graphs) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk tests). Descriptive statistics of the study were summarized using number (n), percentage (%), mean, standard deviation (SD), median, minimum, and maximum. The Chi-square test was used to show whether there was a difference between categorical variables in the study. The Student-t test was used to compare the parametric properties of continuous variables in independent groups, the Mann–Whitney U test was used to compare the non-parametric properties of continuous variables in independent groups, and the Wilcoxon test or Friedman test was used to compare the non-parametric properties of continuous variables in dependent groups. For statistical significance, a p-value lower than 0.05 was set.

Results

Demographic and clinical characteristics of the patients are given in the table (Table 1).

Table 1. Demographic and clinical characteristics of the patients

	n (%)
Gender	
Male	48 (51.6)
Female	45 (48.4)
Age (mean±SD)	72±9.6
Symptom duration (mean±SD)	120±56.8
Segment	
Thoracic	75 (80.6)
T1-3	2 (2.1)
T2-4	6 (6.3)
T3-5	4 (4.2)
T4-6	11 (11.8)
T5-7	9 (9.6)
T6-8	9 (9.6)
T7-9	6 (6.3)
T8-10	5 (5.3)
T9-11	9 (9.6)
T10-12	7 (7.5)
T11-L1	3 (3.2)
T12-L2	4 (4.3)
Cervical	11 (11.8)
C2-4	1 (1)
C3-5	2 (2.1)
C4-6	2 (2.1)
C5-7	2 (2.1)
C6-8	2 (2.1)
C7-T1	2 (2.1)
Lumbar	7 (7.5)
L1-3	3 (3.2)
L2-4	1 (1)
L5-S2	3 (3.2)
Etiology	
COVID-19 infection/vaccine	7 (30.4)
Malignancy	7 (30.4)
Steroids/Immunosuppressant drug	6 (26.1)
Metabolic disease (renal failure)	3 (13)
Disease duration	
Acute/subacute herpes zoster	66 (71)
Postherpetic neuralgia	27 (29)
Medical treatment	
Combine	35 (37.6)
Gabapentinoid	22 (23.7)
Antidepressant	22 (23.7)
Opioid	14 (15.1)
Complication	
None	91 (97.8)
Nausea and dizziness	2 (2.2)

n: Sample size; SD: Standard deviation.

Ninety-three patients (45 females, 48 males) with a mean age of 72 years (range: 56–77 years) were evaluated. The mean symptom duration at presentation was 120 days (range: 10 days–2 years). Sixty-six patients were in the acute/subacute pain phase, and 27 patients had postherpetic neuralgia (PHN) at presentation. Eleven patients had cervical segment involvement, 75 patients had thoracic segment involvement, and 7 patients had lumbar segment involvement.

Eleven patients underwent cervical DRG PRF and TFAESI (C2–4 levels: 1 patient; C3–5 levels: 2 patients; C4–6 levels: 2 patients; C5–7 levels: 2 patients; C6–8 levels: 2 patients; C7–T1 levels: 2 patients). Seventy-five patients underwent thoracic DRG PRF and TFAESI (T1–3 levels: 2 patients; T2–4 levels: 6 patients; T3–5 levels: 4 patients; T4–6 levels: 11 patients; T5–7 levels: 9 patients; T6–8 levels: 9 patients; T7–9 levels: 6 patients; T8–10 levels: 5 patients; T9–11 levels: 9 patients; T10–12 levels: 7 patients; T11–L1 levels: 3 patients; T12–L2 levels: 4 patients). Seven patients underwent lumbar DRG PRF and TFAESI (L1–3 levels: 3 patients; L2–4 levels: 1 patient; L5–S2 levels: 3 patients).

At post-procedure follow-up at 1 month, 6 months, and 12 months, VAS scores for all three sites were significantly lower compared to the pre-procedure scores ($p<0.001$, $p<0.001$, $p=0.008$, respectively) (Table 2).

No significant difference was observed for PHN in patients in the acute/subacute phase and patients who developed PHN at 6-month and 12-month follow-up ($p=0.359$, $p=0.664$) (Table 3). In patients who underwent combined intervention in the acute/subacute phase, PHN development was observed in 7 patients (10.6%) at 6 months and in 9 patients (13.6%) at 12 months. Among patients admitted with PHN, regression of PHN was seen in 12 patients (44.5%) at both 6 and 12 months, whereas PHN persisted in 15 patients (55.5%).

Nausea and dizziness developed in 2 patients due to subdural and intravenous leakage recorded after the procedure. No fatal complications were recorded in any patient.

Table 2. Comparison of VAS scores before and 1, 6, 12 months after the procedure according to the involved segment

	VAS 0	VAS 1	VAS 6	VAS 12	p
Lumbar (n=7)					0.008
Mean±SD	8±1.3	4.57±2.64	4.4±3.2	4.3±3.35	
Median (min–max)	8 (6–10)	4 (2–9)	3 (2–10)	3 (1–10)	
Cervical (n=11)					<0.001^{1,2,3}
Mean±SD	7.8±0.9	3.8±2.8	3.9±3.3	3.8±3.3	
Median (min–max)	8 (6–9)	3 (0–9)	3 (0–9)	2 (0–9)	
Thoracal (n=75)					<0.001^{1,2,3}
Mean±SD	7.7±0.9	3.29±2.7	3±2.7	3.1±2.7	
Median (min–max)	8 (6–9)	3 (0–9)	2 (0–9)	2 (0–9)	

1: There is a statistically significant difference between VAS 0 and VAS 1; 2: There is a statistically significant difference between VAS 0 and VAS 6; 3: There is a statistically significant difference between VAS 0 and VAS 12; VAS: Visual Analog Scale; n: Sample size; SD: Standard deviation; Min: Minimum; Max: Maximum. P-value <0.05 was statistical significance.

Table 3. Comparison of the occurrence of PHN at 6 months and 12 months after the procedure performed in patients with acute/subacute period and PHN

	(-)	(+)	p
PHN 6 months			0.359
Acute/subacute herpes zoster (n=66)	59 (83.1)	7 (31.8)	
Postherpetic neuralgia (n=27)	12 (16.9)	15 (68.2)	
PHN 12 months			0.664
Acute/subacute herpes zoster (n=66)	57 (82.6)	9 (37.5)	
Postherpetic neuralgia (n=27)	12 (17.4)	15 (62.5)	

PHN: Postherpetic neuralgia; p-value <0.05 was statistical significance. The data has been represented as n. n: Sample size.

Discussion

Herpes zoster-related pain significantly affects quality of life both in the acute/subacute phase and when PHN develops. Radiofrequency therapy is known as an effective method for pain control. PRF exhibits a known neuromodulatory effect due to its non-destructive properties, and the final temperature of the active tip does not exceed 42°C.^[8] It functions through a low-intensity electric field that leads to a reduction in conduction in the pain pathways. Its primary effect is mediated through unmyelinated C-fibers and does not affect myelinated fibers. Studies show that PRF significantly modulates synaptic transmission, leading to prolonged analgesia and facilitating the inhibitory effect of serotonergic, noradrenergic, and endogenous opioid pain pathways.^[9] As shown in a rat study, PRF inhibits oxidative stress, restores antioxidant enzymes to control levels, and shows anti-

inflammatory activity by inhibiting the production of inflammatory markers in the muscles of animals exposed to trauma.^[10]

PRF is believed to exert antinociceptive activity through not only peripheral but also central modulation on pain pathways.^[11] Since PRF treatments do not cause deterioration, the affected segment can be treated regardless of the stage and severity of the disease. The dorsal root ganglion was chosen as a therapeutic target for PRF, which can affect the transmission of peripheral pain signals to the higher center, thereby inhibiting the release of excitatory neurotransmitters and regulating changes in central plasticity.

Factors such as advanced age, immunosuppression, presentation with severe acute pain and widespread rash, affected segment, and prolonged prodromal pain duration are risk factors affecting

the prognosis of pain after herpes zoster.^[12–14] Most patients in the acute/subacute phase achieve satisfactory results with PRF treatment. Nonetheless, for patients at risk of poor prognosis and refractory to treatment, combined therapy may be a better alternative. Combined treatment aims to alleviate the severity of pain after herpes zoster and reduce the risk of developing PHN.

The use of radiofrequency therapy in combination with other pain treatments is supported by previous studies reporting efficacy by targeting multiple mechanisms. Ma et al.^[15] investigated the efficacy of steroid and ozone injection combined with C3–8 DRG PRF applied by puncture of the posterior-superior foramen under computed tomography (CT) guidance in 104 patients with cervical herpes zoster involvement in the acute/subacute period. At 12-week follow-up, the results were found to be effective and safe. The success rate was 99.2%, and the incidence rate of PHN was 3.85%, which was found to be low. This success and the low rate of PHN development compared to other studies were attributed to early treatment.

In our study, we evaluated the results of combined interventional procedures in patients in both the acute/subacute phase and with PHN. No significant difference was found between the two groups regarding the development of PHN at 6 and 12 months. In patients who underwent combined intervention in the acute/subacute phase, PHN development was 10.6% at 6 months and 13.6% at 12 months. The higher rate of PHN development compared to the study by Ma et al.^[15] might be attributed to the fact that we included patients with all dermatomes instead of isolated cervical involvement. In our study, which was dominated by thoracic involvement, the difficulty of reaching the DRG with fluoroscopy in patients may have relatively decreased the efficacy because it would have been technically more difficult.

On the other hand, CT guidance was preferred in Ma et al.'s^[15] study as it was considered more reliable than fluoroscopy due to the high number of neurovascular structures in the cervical region. In our study, we preferred fluoroscopy guidance for DRG puncture, our target area, because of its considerably lower ionizing dose exposure compared to CT.

Despite the risk of vascular puncture and possible vascular injection, we used non-particulate steroids for the cervical region and particulate steroids for the thoracic and lumbar regions. We recorded 8 intravascular punctures and 2 subdural punctures without any mortal complications due to confirmation with contrast medium.

Li et al.^[16] compared the efficacy of combined PRF and nerve blocks applied to the affected area with single applications by measuring plasma cytokine and neuropeptide levels in 60 PHN patients. They concluded that the combined application is more effective and safer. The inflammatory cytokine IL-6, which is increased in the plasma of PHN patients, is highly correlated with central sensitization and hyperalgesia.^[17] Neuropeptide β -EP was significantly decreased in the cerebrospinal fluid of PHN patients.^[18] Neuropeptide β -EP directly inhibits pain transmission by activating brain and spinal posterior root opioid receptors.^[19] IL-6 levels were found to be lower, and Neuropeptide β -EP levels were found to be higher in the combined application, and the positive effect of the combined application was emphasized at the inflammatory level.

Despite the predominance of studies examining procedures performed in acute/subacute period patients in the literature, as in this study, we also included patients who developed PHN. In patients who developed PHN and underwent combined intervention, we noted regression of PHN in 44% of patients at 6 and 12 months after intervention. Combined interventions targeting multiple mechanisms become prominent in treatment-refractory patients, especially in those who develop PHN.

Fei et al.^[20] compared CT-guided combined PRF and paraspinal interferon α -2b injection with combined PRF and paraspinal saline injection with an efficacy period of 12 weeks in 62 acute herpes zoster patients. DRG pulsed radiofrequency combined with paravertebral injection of recombinant human interferon- α 2b was concluded to be a more effective treatment for acute-stage herpes zoster neuralgia. PHN development was also found to be low in the combined group. Combination procedures are effective by decreasing the incidence rate of PHN and reducing the severity of PHN even if it develops.

In a recent study, Rui et al.^[21] compared CT-guided combined DRG PRF and paravertebral injection therapy with repeated PRF in 150 acute/subacute herpes zoster patients. Repeated use of PRF resulted in better pain reduction at 1 month than combined PRF paravertebral injection. However, no significant difference in the incidence of PHN was observed between the two groups after 1 year. Based on this current study, repetitive PRF treatment, like combined application, can be applied as an effective method in clinical practice in resistant patients.

We evaluated the results of fluoroscopy-guided combined DRG PRF and TFAESI in 93 patients with acute/subacute herpes zoster and PHN involving the cervical, thoracic, or lumbar region. Our study aimed to evaluate the efficacy and safety results of the combined treatment. In our study, we found combined treatment to be effective in early and long-term follow-up. Distinct from previous studies, we evaluated patients who underwent combined intervention for both the acute phase and PHN. No fatal complications were found in our patients who underwent fluoroscopy-guided PRF to DRG, in contrast to previous studies reported in the literature. Unlike studies using CT for safer puncture due to close vascular neighborhood, fluoroscopy guidance with lower ionizing radiation provided both effective and safe results. In this respect, we think that our study contributes to the literature on herpes zoster-related pain with its technique, patient selection, and current results.

The limitations of our study are that it was retrospective in design and not a comparative study. Prospective controlled studies would shed light on our study.

Conclusion

In conclusion, herpes zoster is a highly resistant neuropathic pain syndrome that affects the patient's quality of life. Interventional approaches should be considered with a multiplanar strategy, especially in resistant patients. In cases of severe and persistent pain, interventional methods targeting multiple mechanisms may be applied early. In this respect, TFAESI combined with PRF treatment targeting the DRG, a well-known treatment for herpes zoster-related pain, provides effective results and is safe.

Ethics Committee Approval: The Adnan Menderes University Clinical Research Ethics Committee granted approval for this study (date: 29.04.2024, number: 2024/78).

Authorship Contributions: Concept – EE, ÖY; Design – EE, ÖY; Supervision – EE, ONA; Resource – EE, ÖY; Materials – ÖY; Data collection and/or processing – ÖY; Analysis and/or interpretation – EE, ÖY; Literature review – EE, ÖY; Writing – EE, ÖY; Critical review – EE, ONA.

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