Randomized Controlled Trial

Effect of Radiofrequency on Dorsal Root Ganglion Versus Transforaminal Steroids Injection on Tumor Necrosis Factor-Alpha Level in Lumbar Radicular Pain

Wael Fathy, MD[1], Mona Hussein, MD[2], Rehab Magdy, MD[3], Hatem Elmoutaz, MD[1], Heba Abdellatif, MD[4], Soha M Abd El Salam, MD[5], Mariana A Mansour, MD[1], Dina Y Kassim, MD[1], and Mohamed Abdelbadie, MD[1]

From: [1]Department of Anesthesiology, Surgical ICU and Pain Management, Beni-Suef University, Beni-Suef, Egypt; [2]Department of Neurology, Beni-Suef University, Beni-Suef, Egypt; [3]Department of Neurology, Faculty of Medicine, Cairo University, Cairo, Egypt; [4]Department of Clinical and Chemical Pathology, Beni-Suef University, Beni-Suef, Egypt; [5]Department of Medical Microbiology and Immunology, Suez University, Egypt

Address Correspondence:
Wael Fathy, MD
Surgical ICU and Pain Management, Department of Anesthesiology, Beni-Suef University
Salah Salem Street
Beni-Suef, Egypt 62511
E-mail:
drwaelfathy@med.bsu.edu.eg

Disclaimer: There was no external funding in the preparation of this manuscript.

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.

Manuscript received: 01-28-2023
Revised manuscript received: 05-05-2023
Accepted for publication: 05-16-2023

Free full manuscript:
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Background: The mechanism of pain control with pulsed radiofrequency (PRF) is unclear.

Objectives: We aimed to compare the efficacy of combined PRF on dorsal root ganglion (DRG) with transforaminal epidural steroid injection (TFESI) vs TFESI-alone on pain improvement and serum tumor necrosis factor-alpha (TNF-α) level in lumbar disc-related radicular pain.

Study Design: Prospective, randomized, controlled trial.

Settings: Neurology and Pain Management clinics.

Methods: A total of 80 patients with lumbar disc prolapse were divided into 2 groups: combined PRF on DRG with TFESI group and TFESI-alone group. The Numeric Rating Scale (NRS-11), Oswestry Disability Index (ODI), and Functional Rating Index (FRI) before intervention and at 2 weeks, 1 month, and 3 months after the intervention were observed. Serum TNF-α level was assessed pre- and post-intervention at 3 months.

Results: The scores of NRS-11, ODI, and FRI showed a significant improvement at 2 weeks, 1 month, and 3 months following intervention in both combined PRF & TFESI group and TFESI-alone group ($P < 0.001$ in all comparisons), with no significant difference between the 2 groups. Serum TNF-α levels showed a statistically significant reduction, 3 months following intervention in the combined PRF & TFESI group ($P < 0.001$), but not in the TFESI-alone group ($P = 0.297$) (P between groups < 0.001).

Limitations: The main limitation of this study is that TNF-α level was not assessed earlier to see how long the steroids might reduce TNF-α. On the other hand, further study with extended follow-up periods is needed to confirm the long-term lowering effect of TNF-α provided by PRF.

Conclusions: Combined PRF on DRG with TFESI showed similar outcomes to TFESI-alone in relieving pain in patients with lumbar disc prolapse. However, PRF on DRG caused a significant decrease in TNF-α serum levels at 3 months.

Key words: Pulsed radiofrequency, transforaminal steroids injection, tumor necrotic factor-alpha, lumbar disc prolapse

Pain Physician 2023: 26:E671-E677

Lumbar disc prolapse is one of the most prevalent causes of low back pain, significantly affecting the quality of life in young and middle-aged patients. Compressive and inflammatory mechanisms generally contribute to lumbar disc-related radicular pain (1).

When conservative management has failed, various interventional modalities are widely used as an alternative to surgical intervention with highly accepted efficacy and safety profiles (2). Pulsed radiofrequency (PRF) is a relatively newly developed neuromodulatory therapy in pain management with minimal thermal tissue damage (3). Observational studies (4-6) on PRF application on dorsal root ganglion (DRG) revealed its effectiveness and safety for treating cervical and lumbar radicular pain.

Comparative efficacy between PRF and transforaminal epidural steroid injection (TFESI) has been extensively investigated in cases with lumbar disc herniation (5,7-9). However, available data about the exact biochemical basis of the anti-inflammatory effect of PRF was still limited.

Tumor necrosis factor-alpha (TNF-α) is a pleiotropic inflammatory cytokine that substantially contributes to the pathogenesis of central and peripheral neuropathic pain. Therefore, it can be a targeted perspective for future drug development in neuropathic pain (10,11).

We aimed to compare the effect of combined PRF on DRG with TFESI vs TFESI-alone on pain severity, functional disability, and serum TNF-α levels in lumbar disc-related radicular pain.

Methods

Study Design and Patients

In this prospective, randomized, controlled trial, 80 patients diagnosed with symptomatic lumbar disc prolapse were randomly assigned into 1 of 2 groups using the opaque closed envelope technique. The first group received PRF on DRG combined with TFESI, and the second group received TFESI-alone (40 patients in each group). The patients were recruited from the Neurology and Pain Management clinics in Beni-Suef Pain Center from March 2022 to September 2022. The study was registered in ClinicalTrials.gov on March 21, 2022; this is the identification number NCT05288920. Written informed consent was signed by all patients. The study was performed in agreement with the Declaration of Helsinki. Ethical approval was obtained from the Research ethical committee of Beni-Suef University; the approval number was FMBSUREC/06042021/Fathy-2.

Eligibility Criteria

Patients with clinical and radiological evidence of lumbar disc prolapse of > 3 months and not responding to conservative treatment were eligible to participate. Exclusion criteria included: severe lumbar disc prolapse causing sphincteric troubles or unilateral or bilateral lower limb weakness, radiological evidence of sacroiliitis, hip osteoarthritis, or any inflammatory, tuberculous, or neoplastic lesion affecting the vertebrae or intervertebral discs, having contraindications for the interventional procedure (e.g., sepsis or coagulopathy), and pregnancy.

Regarding the flow of the patients through the trial, out of 135 patients assessed for eligibility, 55 patients were excluded (42 patients didn't meet the eligibility criteria, and 13 refused to participate). Forty patients in each group received the intervention. Seven patients in the combined PRF & TFESI group and 8 patients in the TFESI-alone group were lost to follow-up (Fig. 1).

Assessment of the Pain Severity and Functional Disability

The included patients were subjected to detailed history taking in addition to both neurological and radiological evaluation to confirm the diagnosis of lumbar disc prolapse.

Pain severity and functional disability were assessed using the following scales: Numeric Rating Scale (NRS-11), Oswestry Disability Index (ODI), and Functional Rating Index (FRI). The assessment was performed before and 2 weeks, 1 month, and 3 months following the intervention by a neurologist blind to the type of interventional procedure (Table 1).

NRS-11 is an 11-point numeric scale used to assess pain intensity, where 10 indicates maximum pain, and 0 indicates no pain (12).

ODI assessed the following items: level of disability, pain intensity, sitting, standing, walking, lifting, traveling, sleeping, social, and sexual life. Each question is scored on a scale from 0 (no limitation) to 5 (severe limitation). All scores were summed, then multiplied by 2 to achieve a score ranging from 0 to 100 (13).

FRI is a 10-item questionnaire; 8 focus on daily activities, and 2 focus on pain intensity. Each item has a score ranging from 0 (no pain) to 4 (severe pain). The total scores ranged between 0% (no detectable disability) and 100% (obvious severe disability) (14).

Assessment of Patients' Satisfaction

Patient satisfaction was assessed using the

Short Assessment of Patient Satisfaction (SAPS) scale 3 months after the intervention by a psychiatrist blinded to the patient's clinical data and the procedure. SAPS includes the following items: satisfaction with the prescribed treatment, respect by the physician, participation in medical decision-making, explanation of the outcome from treatment, satisfaction with the clinic and hospital, medical care, and time with the physician. The SAPS scores are either: 0-10 = very dissatisfied, 11-18 = dissatisfied, 19-26 = satisfied, or 27-28 = very satisfied (15).

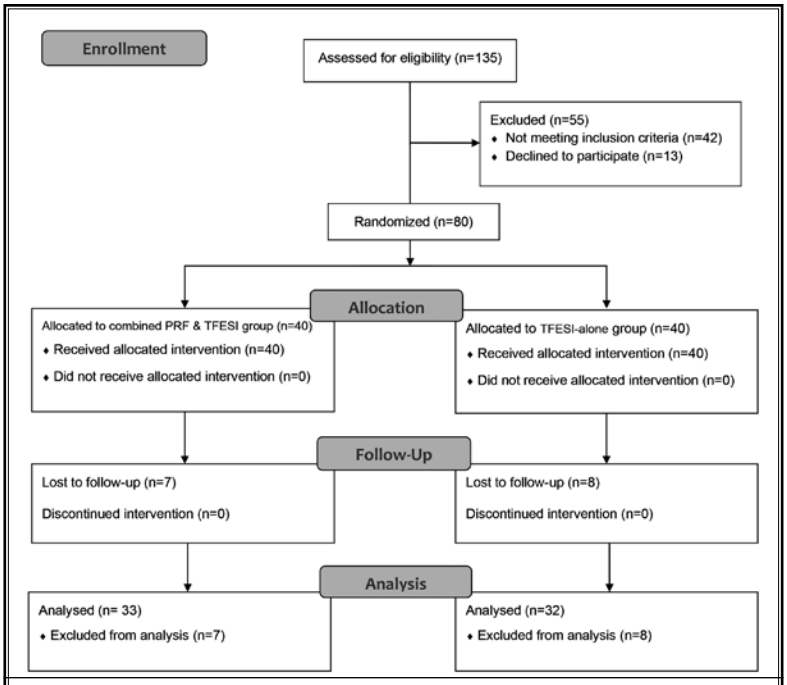

Fig. 1. *CONSORT 2010 flow diagram.*

Interventional Pain Procedure

The patients were requested to stop any medications for the lumbar disc prolapse 48 hours before the interventional pain procedure. At the time of intervention, an intravenous line was inserted, then the patient was placed in a prone position on the fluoroscopy table, connected to a monitor. Sedation was done using intravenous midazolam 0.02 mg/kg. Before each needle insertion, local anesthesia of 1 mL lidocaine 1% was injected intradermally. The patients were randomly assigned into 1 of 2 groups.

TFESI-alone Group

A 22-G, 3.5-inch needle was used in the steroid injection. The C-arm scope was placed in the anteroposterior position. Under fluoroscopic guidance, a spinal needle was advanced in an oblique view. After the classic Scottie dog view was obtained, the needle was directed toward the inferior-lateral boundary of the pedicle to access the safe triangle. Both lateral and anteroposterior views were obtained to confirm the appropriate location of the needle within the intervertebral foramen. The contrast medium was injected under real-time fluoroscopy to avoid subdural, intrathecal, or intravascular spread to achieve safety. At the target level, 1 mL of contrast medium was injected. In this group, patients received only transforaminal epidural injection of premixed steroids with local anesthetic (total dose of 7 mg betamethasone and 20 mg lidocaine 2%) diluted with hypertonic saline 3% to reach a total volume of 6 mL, and 3 mL was injected in each transforaminal level affected.

Combined PRF & TFESI Group

The RF was performed under fluoroscopic guidance following radiation safety standards. A 10 cm, 22-G needle with a 5-mm curved active tip was used. The DRG of lumbosacral roots were targeted. A radiculogram was done to confirm the proper location. The needle's location near the DRG was determined by sensory stimulation at 50 Hz, and motor stimulation at 2 Hz to avoid proximity to the anterior nerve root. A pulsed neuromodulation was generated by applying 45 V to the DRG for 6 minutes at 42 °C. In addition to the PRF, the patients received a transforaminal epidural injection of premixed steroids with local anesthetic (total dose of 7 mg betamethasone and 20 mg lidocaine 2%) diluted with hypertonic saline 3% to reach a total volume of 5 mL.

After the interventional pain procedure, the patients were transferred to the recovery room. They were assessed regarding possible procedural complications, such as nerve injury, spinal cord injury, direct vascular injury, or epidural hematoma.

Laboratory Assessment

The serum level of human (Hu) TNF-α was measured for the combined PRF & TFESI and TFESI-alone groups before and 3 months postinterventional procedure. The TNF-α level was detected by a Hu TNF-α enzyme-

Table 1. *NRS-11, ODI, FRI, and SAPS following intervention in both combined PRF & TFESI group and TFESI-alone group.*

		Combined PRF & TFESI Group	TFESI-alone Group
NRS-11	Before intervention	8 (7.25-10)	8 (7-9.75)
	After 2 weeks	5 (3-6.75)	5 (4-6)
	P value	< 0.001*	< 0.001*
	P value between groups	0.909	
	Before intervention	8 (7.25-10)	8 (7-9.75)
	After 1 month	4 (2-6)	4 (2-5.75)
	P value	< 0.001*	< 0.001*
	P value between groups	0.912	
	Before intervention	8 (7.25-10)	8 (7-9.75)
	After 3 months	4 (0-6)	3 (2-5)
	P value	< 0.001*	< 0.001*
	P value between groups	0.458	
ODI	Before intervention	54 (54-69)	62 (54-67.5)
	After 2 weeks	35 (25-55)	34 (30-50)
	P value	< 0.001*	< 0.001*
	P value between groups	0.974	
	Before intervention	54 (54-69)	62 (54-67.5)
	After 1 month	30 (20-44)	22 (20-27.5)
	P value	< 0.001*	< 0.001*
	P value between groups	0.124	
	Before intervention	54 (54-69)	62 (54-67.5)
	After 3 months	23 (18-31.5)	22 (18-28)
	P value	< 0.001*	< 0.001*
	P value between groups	0.676	
FRI	Before intervention	75 (52-83)	75 (55.75-82)
	After 2 weeks	46.5 (36-63.5)	51.5 (36.25-64.25)
	P value	< 0.001*	< 0.001*
	P value between groups	0.618	
	Before intervention	75 (52-83)	75 (55.75-82)
	After 1 month	38 (23-53.25)	44 (28-50.25)
	P value	< 0.001*	< 0.001*
	P value between groups	0.772	
	Before intervention	75 (52-83)	75 (55.75-82)
	After 3 months	28 (21-44)	28 (21.5-43.5)
	P value	< 0.001*	< 0.001*
	P value between groups	0.925	
SAPS	After 3 months	24 (22.25-25)	24 (22-25)
	P value	0.923	

Abbreviations: FRI: Functional Rating Index, NRS-11: Numeric Rating Scale, ODI: Oswestry Disability;
Index, PRF: Pulsed Radiofrequency, SAPS: Short Assessment of Patient Satisfaction, TFESI: Transforaminal Epidural Steroid Injection.
P value ≤ 0.05 is considered significant.

linked immunosorbent assay (ELISA) kit supplied by ALPCO (American Laboratory Products Company) Diagnostics (Salem, NH) (Catalog Numbers: 45-TNFHU-E01 & 45-TNFHU-E05) according to manufacturer instructions.

The TNF-kit is an ELISA in solid-phase sandwich form. The wells of the supplied microtiter strips have been covered with a monoclonal antibody specific for Hu TNF-α. These wells were pipetted with samples, including known Hu TNF-α content standards, control specimens, and unknowns.

Eighty serum samples were withdrawn from the included patients (lipemic and hemolyzed samples were excluded), stored in freezing conditions, and allowed to throw to room temperature prior to use.

The antigen of Hu TNF-α, during the initial incubation, was anchored to the immobilized (capture) antibody on a single spot. After rinsing, a biotinylated monoclonal antibody specific for Hu TNF-α was added. In the second incubation, this antibody was attached to the Hu TNF-α that was caught from the first incubation.

Streptavidin-peroxidase was added after the extra second antibody was removed. To finish the 4-member sandwich, this was bound to the biotinylated antibody. A substrate solution was added after a third incubation and washing to get rid of any unbound enzymes. The bound enzyme then acted on the substrate solution to create color, which was visible at 450 nm. The amount of Hu TNF-present in the initial specimen directly correlated with the intensity of this colored product.

Outcomes of the Study

The primary outcome was to compare the effect of combined PRF on DRG with TFESI vs TFESI-alone on TNF-α serum level 3 months following the interventional pain procedure.

The secondary outcome was to compare the effect of the 2 applied procedures on the improvement of pain intensity, functional disability, or patients' satisfaction 3 months following the intervention.

Sample Size

Our study was the first to investigate the therapeutic efficacy of combined PRF with TFESI vs TFESI-alone on TNF-α serum levels in patients with lumbar disc prolapse. So, the sample size for this study was calculated (using G*Power Version 3.1.9.7 Software [Heinrich-Heine-Universität, Düsseldorf, Germany]) based on the results of a pilot study we performed before starting our trial.

In this pilot study (10 patients in each group), pain

intensity, functional disability, and TNF-α serum levels were assessed in the 2 groups before and 3 months following the intervention. The 2 groups were matched in the preinterventional pain severity scores, functional disability, and TNF-α serum levels. We calculated the sample size based on the mean values of the postinterventional TNF-α serum levels in the 2 groups (because studying the comparative effect of the 2 interventional pain procedures on TNF-α serum levels was the primary outcome of this study). The mean value of postinterventional TNF-α serum levels in the combined PRF & TFESI group was 127.14 (65.02), and in the TFESI-alone group was 163.024 (40.3).

The effect size = 0.663, the probability of type I error (α) was 5%, degrees of freedom = 78, critical t = 1.665, and noncentrality parameter λ = 2.967; a total sample size of 40 patients in each group was required to obtain a statistical power (1–β) 90%.

Statistical Analysis

The data in this study were analyzed using IBM SPSS Version 25 (IBM Corporation, Armonk, NY). Categorical variables were expressed as numbers and percentages. Quantitative variables were expressed as median and IQR. Chi-squared test was used for comparing the combined PRF & TFESI group and TFESI-alone group in categorical variables, the Wilcoxon test was used for comparing pre- and postintervention quantitative variables in each group, and the Mann-Whitney U test was used for comparing the combined PRF & TFESI group and TFESI-alone group in quantitative variables. A mixed analysis of variance test was used to compare quantitative variables in both groups before and after the intervention. *P* value ≤ 0.05 was considered statistically significant. All tests were 2-tailed.

Results

General Characteristics of the Included Patients

Eighty patients diagnosed with symptomatic lumbar disc prolapse were evaluated. Forty of them received combined PRF on DRG with TFESI, and 40 patients received TFESI-alone. There were no statistically significant differences between both groups in either age or gender (*P* value = 0.227, 0.653, respectively) (Table 2).

The clinical and radiological characteristics of the included patients in the 2 groups are demonstrated in Table 2. There were no statistically significant differences between both groups in either the duration of pain, the number of prolapsed discs, or the preinterventional scores of NRS-11, ODI, or FRI. Regarding TNF-α serum levels before the intervention, there was no statistically significant difference between both groups (*P* value = 0.096) (Table 2).

Pain, Functional Disability, and Satisfaction Following Intervention in Both Combined PRF & TFESI Group and TFESI-alone Group

NRS-11, ODI, and FRI scores showed a statistically significant improvement 2 weeks, 1 month, and 3 months following intervention in both combined PRF & TFESI group and TFESI-alone group (*P* value < 0.001 in all comparisons), with no significant difference between the 2 groups. Also, SAPS scores showed no statistically significant difference between the 2 groups 3 months following the intervention (*P* value = 0.923) (Table 1).

Table 2. *Demographics, clinical, radiological, and laboratory characteristics of combined PRF & TFESI group and TFESI-alone group.*

		Combined PRF & TFESI Group (n = 40)	TFESI-alone Group (n = 40)	*P* value
Age [Median (IQR)]		64 (48.25-70.75)	54.5 (44-65)	0.227
Gender	Men [n (%)]	21 (52.5%)	23 (57.5%)	0.653
	Women [n (%)]	19 (47.5%)	17 (42.5%)	
Duration of Pain in Months [Median (IQR)]		24 (8-30)	22 (8.25-34.5)	0.783
Number of Prolapsed Discs [Median (IQR)]		3 (2-3.75)	3 (2-3.75)	0.960
NRS-11 Before Intervention [Median (IQR)]		8 (7.25-10)	8 (7-9.75)	0.695
ODI Before Intervention [Median (IQR)]		54 (54-69)	62 (54-67.5)	0.262
FRI Before Intervention [Median (IQR)]		75 (52-83)	75 (55.75-82)	0.931
TNF-α Serum Level Before Intervention [Median (IQR)]		151.8 (125.025-174.025)	164.7 (130.3-189.8)	0.096

Abbreviations: FRI: Functional Rating Index, NRS-11: Numeric Rating Scale, ODI: Oswestry Disability Index, PRF: Pulsed Radiofrequency, TFESI: Transforaminal Epidural Steroid Injection, TNF-α: Tumor Necrosis Factor-alpha.
P value > 0.05 is considered insignificant.

TNF-α Serum Level Before and Three Months Following Intervention in Both Combined PRF & TFESI Group and TFESI-alone Group

TNF-α serum levels were significantly reduced 3 months following intervention in the combined PRF & TFESI group (*P* value < 0.001), but not in the TFESI-alone group (*P* value = 0.297) (*P* value between groups < 0.001) (Table 3).

Discussion

Both RF neuromodulation and TFESI can improve pain in the short term. Still, PRF is superior to steroid injection in sustaining long-term pain relief effects. Although steroids have a strong anti-inflammatory effect, they are restricted to their short duration of action. Our study was designed to examine the anti-inflammatory effect of PRF on the inflammatory mediators, which is not well examined in previous studies for a better understanding of the underlying mechanism of the pain-relieving effect exerted by PRF.

The current study showed that PRF combined with TFESI could effectively and rapidly relieve lower back pain and lower extremity radicular pain in patients with lumbar disc prolapse, which was maintained for 3 months. However, at each evaluation time point (2 weeks, 1 month, and 3 months after the procedure), NRS-11, ODI, and FRI scores did not differ significantly in the group who received PRF combined with TFESI than those in the TFESI-alone group. Contrary to previous studies (7-9) that proved the superior efficacy of PRF combined with TFESI protocol over the single-method treatment.

There is a general agreement that the early pain-relieving effect might be attributed to the anti-inflammatory effect of steroid injection that can be observed even on day 1 postprocedure (7,16). On the other hand, PRF probably maintained the pain-relieving impact for a more prolonged period, as most previous reports (17,18) relied on it as an evaluation point. In light of these concepts, the superior efficacy of PRF combined with TFESI in pain reduction was not observed in our study at 3 month follow-ups compared to TFESI-alone, which may become evident if the follow-up was extended for 6 months.

The potential therapeutic mechanisms of pain relief by PRF include altering the transmission of pain signals by a rapidly changing electrical field, inhibiting excitatory C fibers, and long-term depression (3). However, characterizing the underlying biological mechanism by which PRF exerts a pain-relieving effect is a substantial challenge (19).

It is well established that herniated nucleus pulposus can enhance the release of pain-modulating substances, including TNF-α, by activated microglia that cause the associated chronic neuropathic pain (20).

This study showed that the postprocedure TNF-α level was significantly lower in the PRF combined with TFESI than the preprocedure levels (*P* < 0.001). In contrast, it was not statistically different when the TFESI has been applied alone (*P* = 0.297). Our results align with Cho et al (21) and Cho et al (22), who observed a down-regulation in the activity of microglia at the herniated lumbar disc level in rat models after PRF application. Moreover, Vallejo et al (23) found that the expression of genes encoding for proinflammatory factors, such as TNF-α and IL-6 decreased after PRF was applied in a rat model of spared nerve injury. We presume that the later study might explain the lowering effect of TNF-α by PRF, which was detected after 3 months in our study.

On the other hand, the present study showed that decreased TNF-α levels in the TFESI-alone group did not accompany improvement in pain and functional disability scores. It is broadly accepted that steroids exert their anti-inflammatory effects through glucocorticoid receptors (24), and stimulation of such signaling pathway results in suppression of microglia activation (25), the primary source of neuroinflammatory parameters, including TNF-α (20). However, it seems that this anti-inflammatory effect may last for fewer than 3 months, the time we investigated for TNF-α levels. On the other hand, the impact of PRF on the serum TNF-α may last longer, which may be explained by PRF-mediated gene repression, as we mentioned earlier. Nevertheless, steroids were used in both groups. Hence, the significant reduction in TNF-α serum levels at 3 months in the PRF combined with the TFESI group than in the TFESI-alone

Table 3. *TNF-α serum level before and three months following intervention in both combined PRF & TFESI group and TFESI-alone group.*

		Combined PRF & TFESI Group	TFESI-alone Group
TNF-α Serum Level	Before intervention	151.8 (125.025-174.025)	164.7 (130.3-189.8)
	After 3 months	101.35 (90.05-124)	165.25 (130.975-190.975)
	P value	< 0.001*	0.297
	P value between groups	< 0.001*	

Abbreviations: TNF-α: Tumor Necrosis Factor-alpha, PRF: Pulsed Radiofrequency, TFESI: Transforaminal Epidural Steroid Injection.
*P value ≤ 0.05 is considered significant.

group supports the additive role in reducing TNF-α provided by PRF.

The main limitation of this study is that the TNF-α level was not assessed earlier to see how long the steroids might reduce TNF-α. On the other hand, further study with extended follow-up periods is needed to confirm the long-term lowering effect of TNF-α provided by PRF.

Conclusions

Combined PRF on DRG with TFESI showed similar outcomes to TFESI-alone in improvement in pain and functional disability in patients with lumbar disc prolapse. However, PRF on DRG caused a significant reduction in TNF-α serum levels at 3 months.

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