Randomized Trial

# Pulsed Radiofrequency on Thoracic Dorsal Root Ganglion Versus Thoracic Paravertebral Nerve for Chronic Postmastectomy Pain, A Randomized Trial: 6-Month Results

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**Background:** Pharmacologic treatment is not successful in all cases of postmastectomy pain syndrome (PMPS). Some patients continue suffering pain while taking their medications, and others cannot tolerate the side effects of antineuropathic analgesics. Radiofrequency technology has provided promising results in the management of chronic neuropathic pain.

**Objectives:** Considering that affection of intercostobrachial nerves are the main reason behind PMPS, we aimed to evaluate and compare the analgesic efficacy of pulsed radiofrequency (PRF) when delivered either on thoracic dorsal root ganglion (DRG) of intercostobrachial nerves (thoracic DRG 2, 3, and 4) or their corresponding thoracic paravertebral nerves (PVNs).

**Study Design:** Prospective randomized-controlled clinical trial.

**Settings:** Interventional pain unit, tertiary center, university hospital.

**Methods:** Sixty-four patients complaining of PMPS were randomized to either group DRG (n = 32) that received PRF on thoracic DRG, or group PVN (n = 32) that received PRF on thoracic PVN. The outcome variables were that the patients showed > 50% reduction in their visual analog scale (VAS) pain score; the VAS pain score and global perceived effect (GPE) was evaluated during a 6-month follow-up period.

**Results:** The percentage of patients who showed > 50% reduction of their VAS pain score was significantly higher in group DRG compared with group PVN, assessed at 4 and 6 months postprocedure (23/29:79.3% vs. 13/29:44.8%; $P = 0.007$) and (22/29:75.9% vs. 7/29:24.1%; $P < 0.001$), respectively, however, the 2 groups did not significantly differ at 1, 2, and 3 months postprocedure (DRG vs. PVN), (21/29: 72.4% vs. 21/29: 72.4%; $P = 0.542$), (24/29: 82.8% vs. 23/29: 79.9%; $P = 0.778$), and (24/29: 82.8% vs. 19/29: 65.5%; $P = 0.136$), respectively. There was a statistically significant reduction of VAS pain score at 4 and 6 months (DRG vs. PVN, mean ± standard deviation, 2.9 ± 2 vs. 3.9 ± 1.5; mean difference (95% confidence interval), 1 (0.06:1.9); $P = 0.038$; 3 ± 1.94 vs. 5.1 ± 1.5; mean difference (95% confidence interval), 1.9 (1:2.9); $P < 0.001$, respectively), however, the 2 groups did not significantly differ at 1, 2, and 3 months postprocedure. With regard to the patient's satisfaction (i.e., GPE), assessed at 3 and 6 months postprocedure, there was a significantly higher satisfaction in group DRG compared with group PVN (median [interquartile range (IQR)], 6 (5:7) vs. 3 (2:4);$P < 0.001$), however, the patient's satisfaction was similar between groups at 3 months postprocedure: median (IQR), 6 (4:7) vs. 6 (5:6); $P = 0.327$.

**Limitations:** The study follow-up period is limited to 6 months only.

**Conclusions:** PRF of both the thoracic DRG and the thoracic PVN are effective treatments for PMPS; however, PRF of DRG provided a better long-term analgesic effect. Nevertheless, given the inherent risk of performing thoracic foraminal interventions and the technical difficulty of targeting thoracic DRG, we recommend that PRF of DRG should be reserved for cases that failed to gain adequate response to PRF of thoracic PVN in conjunction with medical treatment.

**Key words:** Postmastectomy pain syndrome, radiofrequency, dorsal root ganglion, paravertebral nerve

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Breast cancer is the most frequent cause of death in women worldwide (1). The majority of breast cancer is treated surgically according to its stage by either modified radical mastectomy that entails the removal of the breast, skin, adipose tissue, and ipsilateral axillary lymph nodes, or removal of the primary tumor with free margins with or without axillary evacuation according to the results of sentinel lymph node biopsy (conservative mastectomy) (2).

Approximately 20% to 68% of these patients experience postmastectomy pain, this is defined (3) by the International Association for Study of Pain as chronic pain in the anterior aspect of the thorax, axilla, and/or upper half of the arm beginning after mastectomy or quadrantectomy and persisting for > 3 months after the surgery (4).

Four subtypes of neuropathic pain developed after mastectomy have been depicted: (1) intercostobrachial neuralgia that represents 20% to 50% of patients (5) and is defined as pain and sensitive changes in the distribution of the intercostobrachial nerve. Fromm (6) suggested that the term intercostobrachial neuralgia would be more appropriate for this type of neuropathic pain instead of postmastectomy pain syndrome (PMPS); (2) pain secondary to a neuroma that presents in the surgical scar and is triggered by percussion (Tinel's sign); (3) pain because of damage to other nerves, which might result from damage or even traction of the pectoral, thoracodorsal, and long thoracic nerves; and (4) phantom breast pain, "painful sensation on the excised breast."

PMPS (intercostobrachial neuralgia) has been described as burning or tenderness with paroxysms of lancinating, shock-like pain, and has been occasionally experienced as dysesthesia with different degrees of discomfort in the pectoral region, axilla, and upper arm. It varies from mild to severe, intermittent or continuous, with periods of worsening and improvement (7). PMPS results in mood changes, difficulty at work, reduction of physical activities, and change in the quality of life (8).

Multimodal approaches that use N-methyl-d-aspartate receptor antagonists (9), gabapentinoids (10), venlafaxine (11), and afferent neural blockade (12) in the perioperative period have the potential to prevent central neuroplasticity and subsequent development of PMPS (13).

Because of its neuropathic nature, treatment of PMPS is a difficult task. Amitriptyline (14), venlafaxine (15), and levetiracetam (16) are the drugs of choice that are used for treatment of PMPS.

Unfortunately, pharmacologic treatment is not successful in all cases of PMPS. Some patients continue suffering pain while taking their medications, and others cannot tolerate the side effects of antineuropathic analgesics. Radiofrequency (RF) technology has provided promising results in the management of chronic neuropathic pain (17). Considering that affection of intercostobrachial nerves are the main reason behind PMPS, the investigators conducted this study to evaluate and compare the analgesic efficacy of pulsed radiofrequency (PRF) when delivered either on thoracic dorsal root ganglion (DRG) of intercostobrachial nerves (thoracic DRG 2, 3, and 4), or their corresponding thoracic paravertebral nerves (PVNs).

## Methods

After obtaining the ethical committee approval of our institutional review board and the signing of an informed, written consent from each patient, including explanation of the procedure, the benefits, the risks, and the alternatives, 60 patients suffering from chronic postmastectomy pain were willing to participate in this study. The study is a single center, registered at Clinical Trial.gov with unique ID: NCT03374423, and the CONSORT standard for clinical trial reporting was implemented.

Inclusion criteria were age ≥ 18 years, body mass index < 35 kg/m$^2$, duration of pain ≥ 6 months, visual analog scale (VAS) pain score ≥ 5 on a 0 to 10 scale despite treatment with pregabalin up to a dose of 150 mg daily and amitriptyline up to a dose of 50 mg daily, and the postmastectomy pain seemed to be of neuropathic origin based on the Douleur Neuropathique 4 questionnaire score ≥ 4, and the pain was located in the ipsilateral breast/chest wall, axilla, and/or arm, and occurred at least 50% of the time.

Exclusion criteria included any prior interventional pain procedure for chronic postmastectomy pain, the presence of local pathology such as recurrent cancer or chronic infection in the breast region that could account for persistent symptoms, abnormal anatomy of the thoracic vertebrae such as scoliosis or severe kyphosis, infection at the site of needle entry, pregnant women, uncorrected coagulopathy, and hypersensitivity of any drugs used throughout the study.

### Randomization and Assignment

The patients were randomly assigned into 2 equal groups using a computer-generated list of numbers that were masked in opaque, sealed envelopes and opened before the procedure: group DRG (n = 32) that

received PRF on thoracic DRG, and group PVN (n = 32) that received PRF on thoracic PVN.

## Procedure

The patient was brought to the pain interventional room that was equipped with an anesthesia machine, monitor, fluoroscopy, and RF apparatus. The patient was gently rested in prone position on the operating table, basic monitors (pulse oximeter, electrocardiogram, and noninvasive blood pressure) were connected on the patient, and a nasal canula delivering oxygen at a flow of 4 L/min was fixed. An intravenous canula was inserted and secured in place, and 10 mg of nalbuphine for sedation was administered. Disinfection and draping of the thoracic spine was accomplished. We proceeded from above downward; the first thoracic vertebra was identified by its characteristic upward directed and ballooned transverse process that distinguishes it from the last cervical vertebra (Fig. 1).

For the DRG procedure, an anteroposterior (A-P) image was taken, and then the C-arm was adjusted caudo-cephalic to align the lower endplate of the concerned vertebra, and to make the shadow of the rib over the shadow of the transverse process, then the C-arm was directed in oblique view, approximately 20 to 25 degrees. The skin entry point was just below the pedicle of the concerned level (Fig. 1). The skin was infiltrated with 2 mL of 2% lidocaine at the entry point, RF needle, 10 cm, 22 G, with active curved tip 1 cm was inserted (end-on) under the C-arm (Fig. 2). The lateral view was obtained to see the needle tip just behind the posterior boundary of the foramen (Fig. 3). At this position, 0.2 mL of radiopaque dye was injected to see it spreading under the pedicle laterally, and importantly the dye should delineate the medial boundary of the pedicle and spread upward (characteristic image of transforaminal epidural) (Fig. 4). In the lateral view the dye was seen as a vertical line at the back of the foramen (Fig. 3), at this point, the threshold of sensory stimulation was < 0.5 volts in all cases. Occasionally, it was difficult to enter the foramen with the aforementioned approach as the foramen was directed anteriorly and the transverse process behind it was obstructing the needle pathway, so we tried to enter the foramen by inserting the needles "under the A-P view" in a slightly medial-cephalad direction immediately below the transverse processes, incrementally walked into the thoracic intervertebral foramen, and the final position was confirmed using the lateral fluoroscopic imaging.

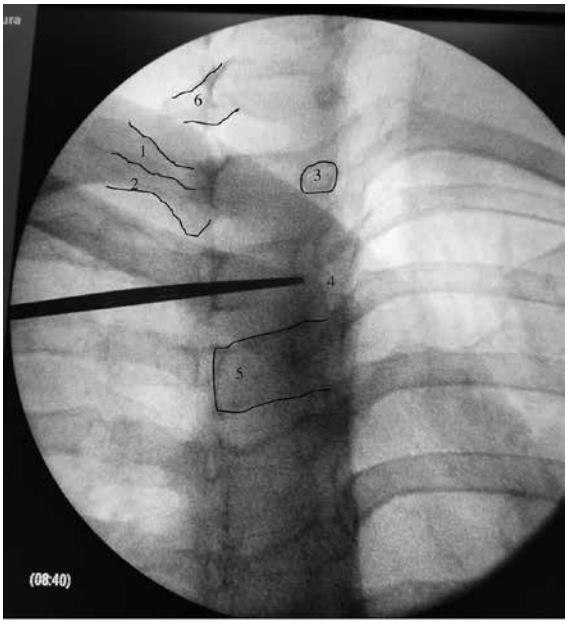


Fig. 1. *An oblique x-ray view of the spine depicting the radiologic anatomy of the upper thoracic region and needle entry point. 1 = the transverse process of first thoracic vertebra (slanting upward and ballooned). 2 = the first rib. 3 = the pedicle of the first thoracic vertebra. 4 = the arrow points to the subpedicular needle entry point. 5 = the third thoracic vertebra. 6 = the transverse process of the last cervical vertebra (slanting downward).*

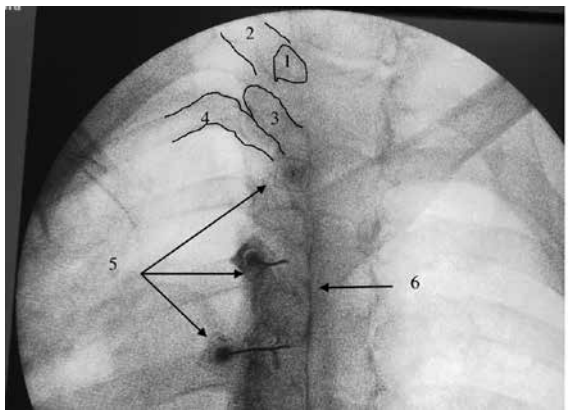


Fig. 2. *An oblique x-ray view of the upper thoracic spine depicting the DRG procedure. 1 = the pedicle of the first thoracic vertebra. 2 = the transverse process of the first thoracic spine (slanting upward and ballooned). 3 = the transverse process of the second thoracic spine. 4 = the second rib. 5 = the RF needles targeting the second, third, and fourth thoracic DRG (from above downward), the fluoroscopy is adjusted to see the RF needle targeting the second thoracic DRG (end on view). 6 = the arrow points to epidural spread of the dye.*

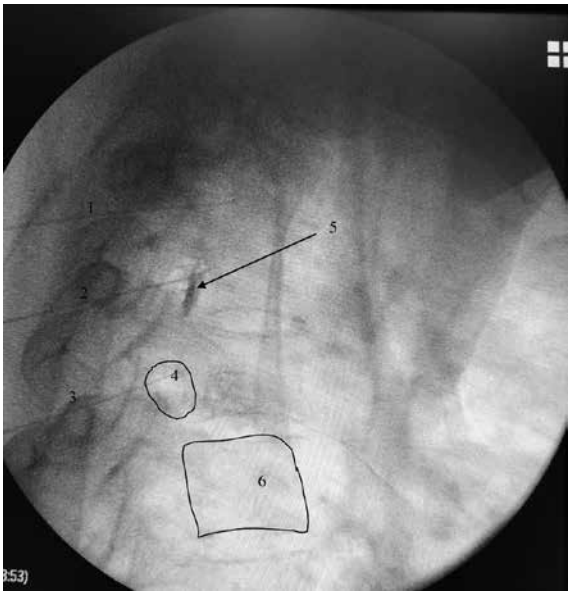


Fig. 3. *Lateral x-ray view of the upper thoracic spine depicting the DRG procedure. 1, 2, and 3 = the RF needles targeting the second, third, and fourth thoracic DRG (from above downward). 4 = the fourth intervertebral foramen. 5 = the dye delineating epidural spread. 6 = the fifth thoracic spine.*

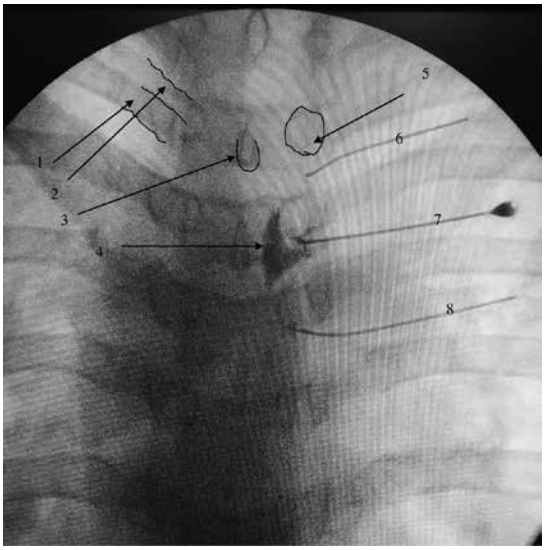


Fig. 4. *An A-P x-ray view of the upper thoracic spine depicting the DRG procedure. 1 = the transverse process of the second thoracic spine. 2 = the second rib. 3 = the spine of the second thoracic vertebra. 4 = dye delineating the transforaminal epidural. 5 = the pedicle of the second thoracic vertebra. 6, 7, and 8 = the RF needles targeting the second, third, and fourth thoracic DRG, respectively.*

For the PVN procedure, an A-P image was taken and caudo-cephalic orientation was done to bring the shadow of the transverse process over the shadow of the rib, the skin entry point was chosen at the lower border of the medial half of the transverse process. After infiltration of the skin with 2 mL of 2% lidocaine at the entry point, RF needle, 10 cm, 22 G, with active curved tip 1 cm was inserted (end-on) under the C-arm. The curved tip should be upward directed when it lands on the lower border of the transverse process (Fig. 5), then the needle was pulled back for half a centimeter and the curved tip was directed downward to walk off the bone and advanced for 1 cm, and the lateral view image was obtained to see the needle tip at the vicinity of the foramen. At that position, sensory stimulation was done and the needle manipulated, either rotated or advanced further, to pick the nerve at a stimulation threshold < 0.5 volts, the needle tip position should not pass the level of the posterior border of the foramen, for further confirmation dye was injected to see it spreading beneath the rib and lining the lateral boundary of the vertebra at the A-P view (Fig. 6).

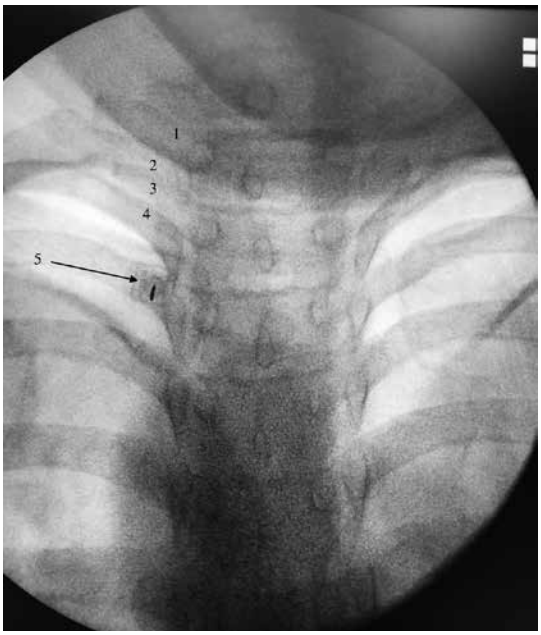


Fig. 5. *An A-P x-ray view of the upper thoracic spine depicting the thoracic PVN procedure. 1 = the transverse process of the first thoracic spine (slanting upward and ballooned). 2 = the first rib. 3 = the transverse process of the second thoracic vertebra. 4 = the second rib. 5 = the arrow points to the RF needle (end on view) landing on the lower border of the transverse process of the third thoracic vertebra.*

For both groups, we started at the level of the second thoracic vertebra and proceeded downward to the level of the fourth thoracic vertebra. After the 3 needles were in place at the desired target, the patients were given propofol 1.5 mg/kg to tolerate the procedure, 3 cycles of PRF 2 minutes each were delivered, PRF was applied in 20 ms pulses every 500 ms (20 ms of 500-kHz RF pulses, delivered at a rate of 2 Hz), maximum temperature voltage was automatically controlled to 42°C, then the needles were removed and the skin was covered by a sterile patch. Finally, the patient was transferred to the observation room and discharged after 4 hours.

## Blinding (Masking)

The PRF procedures were performed by the same investigator (senior staff pain clinician) and all follow-ups were carried out by another investigator who was not aware of the type of performed intervention. Also the patients were not aware of the type of implemented intervention.

## Postprocedural Follow-Up and Treatment

The patients were advised to continue their chronic analgesic drugs that they received prior to intervention (pregabalin and amitriptyline) until 1 month postprocedure. The intensity of pain was assessed by VAS, and the analgesic treatment was titrated according to response at 1, 2, 3, 4, and 6 months following the procedure.

The primary outcome variable was the percentage of patients who showed > 50% reduction of their VAS pain score (from baseline values), measured at 6 months postprocedure. The secondary outcome variables were the changes in level of pain intensity measured by a VAS at 1, 2, 3, 4, and 6 months following the procedure, the percentage of patients who did not require additional analgesics and the global perceived effect (GPE) was assessed at 3 and 6 months following the procedure. The GPE was assessed by a 7-point Likert-like verbal rating scale in which extremely dissatisfied = 1, dissatisfied = 2, somewhat dissatisfied = 3, undecided = 4, somewhat satisfied = 5, satisfied = 6, and extremely satisfied = 7.

## Statistical Analysis

The statistical analysis was carried out on a personal computer using SPSS Version 22.0 (IBM Corporation, Armonk, NY). Normality of continuous data distribution were tested with the Anderson–Darling test prior to further statistical analysis. Categorical data were described as number and percentage, and comparisons were made by the chi-square and the Fisher exact tests. Continuous data were described as mean ± standard deviation (SD) or 95% confidence interval (CI), and point-by-point comparison was done by unpaired Student t test. A linear general model for repeated measures was used for analysis of VAS pain scores over time 1, 2, 3, 4, and 6 months following the procedure, examining the following effects: group, time, and group-by-time interaction, followed by a posthoc test with Bonferroni correction for multiple comparisons. Medians and interquartile ranges (IQR) were used for skewed data (i.e., GPE), and comparisons were made using the Mann–Whitney U test. $P < 0.05$ was considered statistically significant.

Based on previous studies (18), we believed that a sample size containing 28 patients in each group would detect 25% difference in the proportion of patients showing > 50% reduction of their VAS pain score at 6 months postprocedure, assuming a confidence level 95% and study power 80%, type 1 error was set at 5% and $P$ value was considered significant at a level < 0.05. To account for dropouts, we enrolled 30 patients in each group.

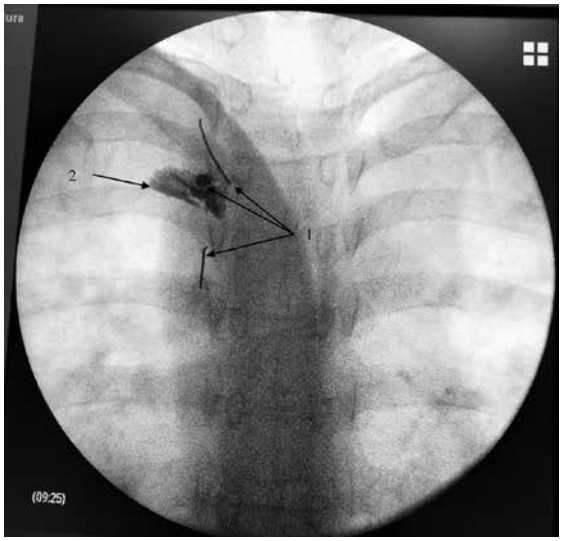


Fig. 6. *An A-P x-ray view of the upper thoracic spine depicting the thoracic PVN procedure after dye injection. 1 = 3 RF needles landing on the lower border of the second, third, and fourth transverse process of thoracic spine (the fluoroscopy is adjusted to see the RF needle targeting the transverse process of the third thoracic vertebra, end on view). 2 = the dye delineating the paravertebral space adjacent to the third thoracic vertebra.*

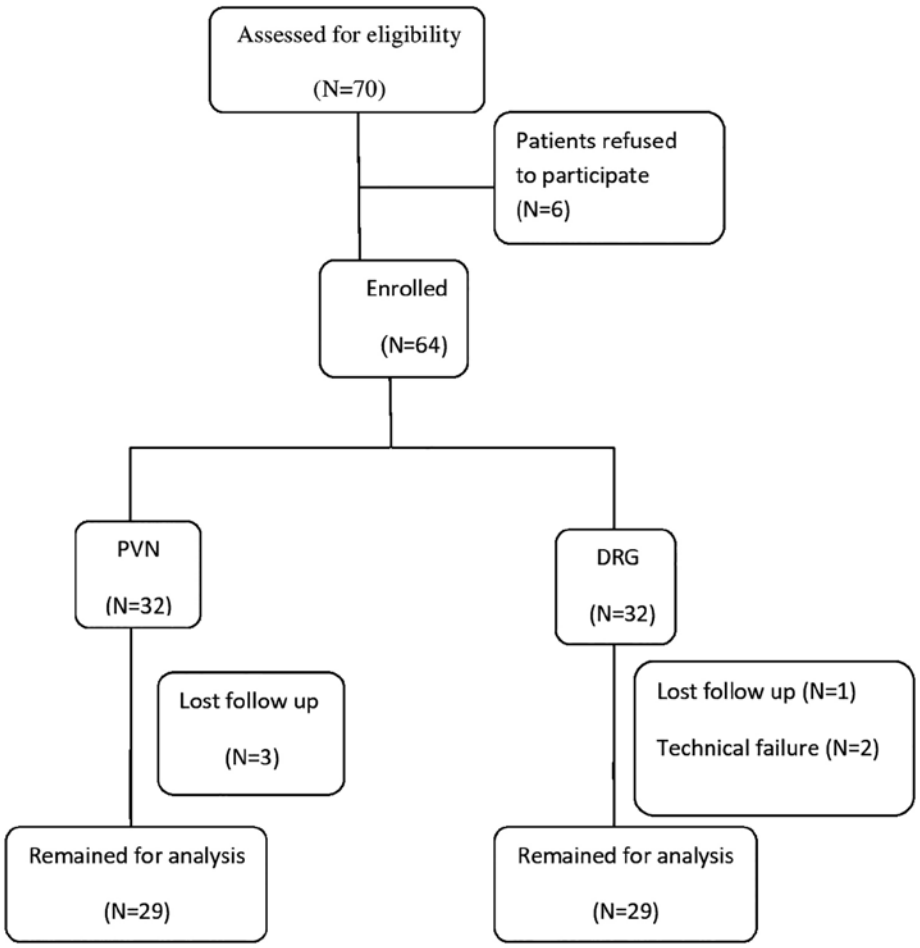


Fig. 7. *Flow chart of patients through the study.*

## Results

Seventy patients were assessed for eligibility, 6 patients refused to participate, 64 patients were allocated into 2 equal groups, 32 in each, 2 patients in group DRG were excluded due to technical failure (we could not position the needle tip on DRG due to bone crowdedness), 4 patients were lost to follow-up (one in DRG group and 3 in PVN group), and 29 in each group remained for analysis (Fig. 7).

There was not a statistically significant difference among the 2 groups with respect to demographic data and patient's characteristics (Table 1). However, the operative time for the procedure was quite longer for the DRG group than the PVN group (DRG vs. PVN; mean ± SD, 27.9 ± 6.4 minutes vs. 19.1 ± 3.7 minutes; $P < 0.001$).

The percentage of patients who showed > 50% reduction in their VAS pain score was significantly higher in group DRG compared with group PVN when assessed at 4 and 6 months postprocedure (23/29: 79.3% vs. 13/29: 44.8%; $P = 0.007$) and (22/29: 75.9% vs. 7/29: 24.1%; $P < 0.001$), respectively, however, the 2 groups did not significantly differ at 1, 2, and 3 months postprocedure (DRG vs. PVN, 21/29: 72.4% vs. 21/29: 72.4%; $P = 0.542$; 24/29:82.8% vs. 23/29:79.9%; $P = 0.778$; and 24/29: 82.8% vs. 19/29: 65.5%; $P = 0.136$), respectively (Table 1).

Analysis of VAS pain score over time 1, 2, 3, 4, and 6 months following the procedure using the general linear model revealed no statistically significant overall group difference (DRG vs. PVN, mean ± standard er-

Table 1. *Demographic data, patient's characteristics, operative time, the percentage of patients that showed more than 50% reduction of their initial pain and the GPE.*

| Variable | DRG (n=29) | PVN (n=29) | *P* value |
|---|---|---|---|
| Age (years) | 47.97 ± 6.33 | 48.67 ± 10.01 | 0.467 |
| BMI (kg/m2) | 29.1 ± 2.8 | 29.9 ± 3.7 | 0.381 |
| Operative time | 27.9 ± 6.4 | 19.1±3.7 | 0.001 |
| VVAS reduction > 50%, 1 MO | 21/29:72.4% | 21/29: 72.4% | 0.542 |
| VVAS reduction > 50%, 2 MO | 24/29:82.8% | 23/29:79.9% | 0.778 |
| VVAS reduction > 50%, 3 MO | 24/29:82.8% | 19/29:65.5% | 0.136 |
| VVAS reduction > 50%, 4 MO | 23/29:79.3% | 13/29:44.8% | 0.007 |
| VVAS reduction > 50%, 6 MO | 22/29:75.9% | 7/29:24.1% | 0.001 |
| GPE_6 MO | 6 (5:7) | 3 (2:4) | 0.001 |
| GPE_3 MO | 6 (4:7) | 6 (5:6) | 0.327 |

DRG = dorsal root ganglion. PVN = paravertebral nerve. BMI= body mass index. VAS = visual analogue scale. MO = Month. GPE = global perceived effect. Data are presented as means ± SD for (age, BMI and operative time), numbers and percentages for (VAS reduction) and median (IQR) for (GPE).

ror [95% CI], 3.47 ± 0.224 [2.98:3.96] vs. 3.93 ± 0.224 [3.45:4.43]; $P = 0.183$). However, there were significant time and group-by-time interaction effects (the VAS pain score decreases over time, 1, 2, 3, 4, and 6 months, in both groups, and this decrease is greater in the DRG group) when the tests of within-subject effects and within-subject contrasts had been applied ($P < 0.001$).

Further point-by-point comparisons of the means of VAS pain score at 1, 2, 3, 4, and 6 months after the procedure using the independent sample t test revealed a statistically significant reduction of VAS pain score at 4 and 6 months (DRG vs. PVN, mean ± SD, 2.9 ± 2 vs. 3.9 ± 1.5 [mean difference (95% CI)], [1 (0.06:1.9)], $P = 0.038$, (3 ± 1.94 vs. 5.1 ± 1.5) [mean difference (95% CI)], [1.9 (1:2.9)], $P$ value < 0.001, respectively). However, the 2 groups do not significantly differ at 1, 2, and 3 months postprocedure (Table 2).

During the 6-month follow-up period, the number of patients who discontinued their chronic, regular analgesics they received prior to the procedure were higher in group DRG compared with group PVN when evaluated at 3 and 6 months postprocedure (10/29, 34.5% vs. 5/29, 17.2%), (13/29, 51.9% vs. 2/29, 6.9%), respectively.

With regard to the patient's satisfaction (i.e., GPE) assessed at 3 and 6 months postprocedure, there was a significant higher satisfaction in group DRG compared with group PVN (median (IQR), 6 (5:7) vs. 3 (2:4); $P < 0.001$) at 6 months evaluation, however, the patient's satisfaction was similar between groups at 3 months postprocedure (median (IQR), 6 (4:7) vs. 6 (5:6); $P = 0.327$) (Table 1).

## Discussion

The current study showed that treatment of chronic postmastectomy pain with PRF modality, applied on either thoracic DRG of T2-T4 or their corresponding thoracic PVNs, has decreased pain intensity and analgesic requirements; however, PRF for thoracic DRG (T2-T4) has achieved a better long-term analgesic benefit.

To the best of our knowledge and from reviewing literature, this is the first prospective randomized trial to evaluate and compare the analgesic efficacy of PRF modality for chronic postmastectomy pain when applied on either thoracic DRG or thoracic PVN.

It is widely accepted in interventional management for chronic pain that a certain analgesic modality is considered effective when the patients received this modality gained > 50% reduction of their pain. Therefore, we considered it as the primary outcome variable of this study, and it was clear from our data analyses that a significantly higher percentage of patients showed > 50% reduction of their pain in group DRG in comparison to PVN group at 6 months follow-up period, (22/29: 75.9% vs. 7/29: 24.1%; $P = 0.001$) and consequently, less analgesic requirement and a better satisfaction were observed in the DRG group. However, a similar reduction of pain intensity between groups was noted until 3 months after the procedure (24/29: 82.8% vs. 19/29: 65.5%; $P = 0.136$).

PRF has been introduced by Sluijter et al (19) with the aim of dissociating the effects of electromagnetic waves from the thermal destruction that is known to be caused by continuous RF. Many clinical studies, mostly in neuropathic pain conditions, have reported pain relief for weeks or months after application of PRF, either

Table 2. *Intensity of pain measured by VAS pain score.*

| Variable | DRG (n=29) Mean ± SD | PVN (n=29) Mean ± SD | Mean difference | 95% CI | *P* value |
|---|---|---|---|---|---|
| VAS_Basal | 6.4 ± .73 | 6.3 ± .75 | - 0.1 | (-0.49:0.29) | 0.596 |
| VAS_1 MO | 3.3 ± 1.7 | 2.4 ± 1.5 | - 0.66 | (-1.5:0.19) | 0.128 |
| VAS_2 MO | 2.6 ± 1.98 | 2.7 ± 1.3 | 0.10 | (-0.78:0.99) | 0.816 |
| VAS_3 MO | 2.8 ± 1. 9 | 3.3 ± 1.4 | 0.52 | (-0.36:1.4) | 0.242 |
| VAS_4 MO | 2.9 ± 2 | 3.9 ± 1.5 | 1 | (0.06:1.9) | 0.038 |
| VAS_6 MO | 3 ± 1.94 | 5.1 ± 1.5 | 1.9 | (1:2.9) | 0.001 |

Data are expressed as mean (SD) and mean difference (95% CI). MO = Month

close to the DRG (20-22) or to the peripheral nerves (23-27).

In this context, Cohen et al (18) retrospectively evaluated a diversity of chronic postsurgical pain in the thoracic region, received either PRF on DRG, PRF on intercostal nerve (ICN), or medical therapy, and found that at 3-months follow-up, 53.8% in the DRG group continued to report ≥ 50% pain relief versus 19.9% in the medical therapy group, and 6.7% in the ICN group, respectively ($P$ = 0.02). However, in our study the PVN group achieved a similar improvement as the DRG group until the 3-month follow-up period, and this could be attributed to the severity of pain the patients have "most of the patients in Cohen et al (18) study were postthoracotomy and poststernotomy pain." Moreover, in our study, we targeted all the accused dermatomes (T2, T3, and T4) of postmastectomy intercosto-brachialgia, which was difficult in the Cohen et al study.

In agreement with the improved pain until 3 months postprocedure in group PVN in the current study, our previous work in which Hetta et al (27) applied PRF to the ilioinguinal nerve and the genital branch of the genitofemoral nerve for patients with chronic postgroin surgeries and orchialgia, and found that the percentage of patients showed > 50% reduction in their VAS pain score that was 80% (24/30) in the PRF group versus 23.33% (7/30) in the sham group.

Although the exact mechanisms of PRF remain unclear, researchers have been working to detect the underlying processes. Erdine et al (28) detected ultrastructural changes in the sensory nociceptive axons following exposure to PRF by using electron microscopy. They claimed that PRF produced selectively larger lesions in the smaller principal sensory nociceptors such as the C and Aδ fibers than in the larger nonpain-related sensory fibers. Hagiwara et al (29) showed that PRF potentiates the noradrenergic and serotonergic descending pain inhibitory pathways and inhibits excitatory nociceptive C-fibers. Cho et al (30) found decreased microglial activity in the spinal dorsal horn after applying PRF to the DRG. Because microglia are implicated in chronic neuropathic pain by releasing various cytokines and chemokines that are related to pain signaling, the authors proposed that downregulation of microglia may reduce chronic neuropathic pain. Moreover, Vallejo et al (31) found that proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-6, were reduced in neural tissues exposed to PRF. Recent trials have shown that PRF upregulates c-fos expression in laminae I and II of the dorsal horn (32) and increases synaptic changes transmission (33). These mechanisms may induce neuroplastic changes that could contribute to the long-term analgesic effect of PRF (34).

We believe that the prolonged and the greater analgesic effects of PRF on DRG are owing to suppression of the activation of microglia cells and p38 signaling pathway that occur after peripheral nerve injury. Microglia cells are the cells that form an envelope around the cell bodies of DRG neuron and are the first to be activated following peripheral nerve injury, and they remain active for several weeks (35,36). Microglia transform to reactive phenotype and display a progressive series of cellular and molecular changes, including morphological hypertrophy, rapid proliferation, upregulated expression of various genes, and increased expression of microglia characteristic markers, such as Iba1, and increased p38 phosphorylation in the spinal microglia cells (37).

It is noteworthy that we had more cases in the group DRG who discontinued their chronic, regular antineuropathic analgesics that "they were receiving prior to the implemented procedure."

### Technical Notes and Authors' Recommendations

For the PRF on thoracic PVN, the main concern is to avoid pneumothorax, which was reported in previous trials targeting the thoracic PVN or the ICN (18). First, you should land on a bone (transverse process) and never on a space with a curved tip needle, by rotating it allows easily walking off. Second, immediately after walking off the bone, start stimulation at 0.5 volts while advancing the needle to early pick the nerve, and the needle advancement should be under vision with lateral fluoroscopic view and never advance beyond the level of the posterior boundary of the foramen. Finally, the entry point should not be lateral to the tip of the transverse process in the A-P view, in this region the pleura is more superficial and is liable to injury (roughly, it has been advocated that the needle entry point should be within 4 cm from the spine).

For the PRF on thoracic DRG, the main concern is to position the needle tip exactly in the foramen. In the lower thoracic region, from thoracic vertebra number 9 and downward, it is easy to enter the foramen through a subpedicular approach, however, it is not the case in the upper thoracic region, and the C-arm should be caudally oriented in the A-P view about 15 degrees to navigate to the foramen and walk off any bone facing the needle trajectory, however, it does not work in all cases. Another approach is to land on the lateral vertebral margin in 20 degrees oblique view and direct the curved tip of the needle medially; in this case you will be very close to the DRG. Although entry to T3 DRG and T4 DRG can be achieved through oblique fluoroscopic angle at 20 to 25 degrees, entry to T2 DRG requires oblique fluoroscopic angle 30 degrees or more that place the needle entry point too lateral from the spine, and in this case, piercing the pleura is inevitable, therefore, we were restricted to oblique fluoroscopic angle < 25 degrees. So for T2 DRG, we placed the needle tip at the outer margin of the foramen and directed the needle tip medially "very close to T2 DRG."

Ultimately, we cannot ignore the risks of transforaminal procedures at the thoracic region. We reported one case in which the dye delineated injection through the paravertebral network of blood vessels (Fig. 8), the needle tip had been repositioned and the procedure was completed successfully without any side effects. The upper thoracic cord may be supplied by only one small radiculomedullary artery, injuring or injecting steroid prior to RF lesioning, as some authors advocated to reduce the incidence of neuritis may lead to spinal cord infarction (38).

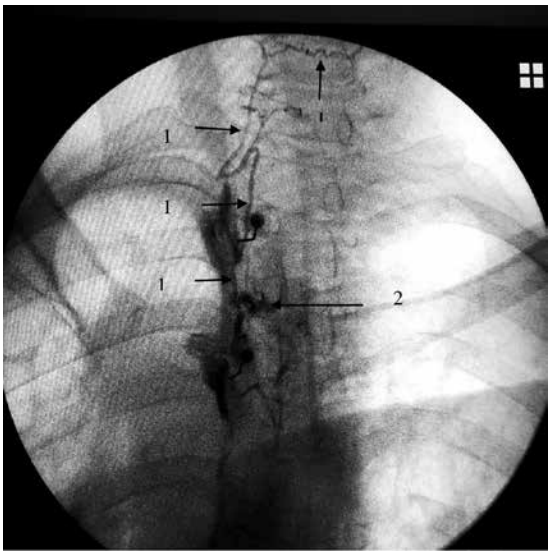


Fig. 8. *Inadvertent injection through the paravertebral networks of blood vessels. 1 = the arrows point to radiculomedullary vessels. 2 = the fluoroscopy is adjusted for the RF needle targeting the third DRG (end on view), the needle tip was inadvertently placed inside radicular blood vessels within the intervertebral foramen.*

### Study Limitations

The current study is limited by the relatively short postprocedure follow-up period. Moreover, we could not maintain a fixed analgesic protocol for all patients because of diversity of medications received by the patients prior to the intervention, such as amitriptyline, duloxetine, gabapentinoids, and tramadol. Also, some patients were receiving analgesics for another pain conditions such as metastatic bone pain, chemotherapy-induced neuropathy, and osteoarthritis. Furthermore, we did not inject any local steroids to ameliorate neuronal edema and subsequent postoperative soreness that could occur following PRF to be sure that the achieved analgesic effect is purely due to PRF.

Future trials are required to compare the analgesic effect of both techniques on diversity of thoracic pain syndromes and for an extended follow-up time period.

## Conclusions

Our findings suggest that PRF of both the thoracic DRG and the thoracic PVN are effective for alleviation of chronic postmastectomy pain. However, PRF of DRG provided a better long-term analgesic effect. Nevertheless, given the inherent risk of performing thoracic

foraminal interventions and the technical difficulty of targeting thoracic DRG, the authors recommend that PRF of DRG should be reserved for cases that failed to gain adequate response to PRF of thoracic PVN in conjunction with medical treatment. Ultimately, our impression is to consider PRF on DRG when you have a slim patient with a clear fluoroscopic image and an experienced pain interventionist for its better long-term analgesic benefit, otherwise PRF on thoracic PVNs is a safe alternative option.

## References


1. Forouzanfar MH, Foreman KJ, Delossantos AM, et al. Breast and cervical cancer in 187 countries between 1980 and 2010: A systematic analysis. *Lancet* 2011; 378:1461-1484.
2. Mamtani A, Morrow M. Why are there so many mastectomies in the United States? *Ann Rev Med* 2017; 68:6.1-6.13.
3. Vilholm OJ, Cold S, Rasmussen L, Sindrup SH. The postmastectomy pain syndrome: An epidemiological study on the prevalence of chronic pain after surgery for breast cancer. *Br J Cancer* 2008; 99:604-610.
4. International Association for the Study of Pain. *Task Force on Taxonomy–Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definition of Pain Terms, 2 ed.* Seattle, IASP Press, 1994.
5. Couceiro TC, Valença MM, Raposo MC, Orange FA, Amorim MM. Prevalence of post-mastectomy pain syndrome and associated risk factors: A cross-sectional cohort study. *Pain Manag Nurs* 2014; 15:731-737.
6. Fromm GH. The neuralgias. In: Joynt RJ, Griggs RC (eds). *Baker's Clinical Neurology*. Philadelphia, Lippincott Williams & Wilkins, 2000; 25:234-240.
7. Jung BF, Ahrendt GM, Oaklander AL, Dworkin RH. Neuropathic pain following breast cancer surgery: Proposed classification and research update. *Pain* 2003; 104:1-13.
8. Caffo O, Amichetti M, Ferro A, Lucenti A, Valduga F, Galligioni E. Pain and quality of life after surgery for breast cancer. *Breast Cancer Res Treat* 2003; 80:39-48.
9. McCartney CJL, Sinha A, Katz J. A qualitative systematic review of the role of N-methyl-D-aspartate receptor antagonists in preventive analgesia. *Anesth Analg* 2004; 98:1385-1400.
10. Fassoulaki A, Triga A, Melemeni A, Sarantopoulos C. Multimodal analgesia with gabapentin and local anesthetics prevents acute and chronic pain after breast surgery for cancer. *Anesth Analg* 2005; 101:1427-1432.
11. Reuben SS, Makari-Judson G, Lurie SD. Evaluation of efficacy of the perioperative administration of venlafaxine XR in the prevention of postmastectomy pain syndrome. *J Pain Symptom Manage* 2004; 27:133-139.
12. Hetta DF, Rezk KM. Pectoralis-serratus interfascial plane block vs thoracic paravertebral block for unilateral radical mastectomy with axillary evacuation. *J Clin Anesth* 2016; 34:91-97.
13. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: Risk factors and prevention. *Lancet* 2006; 367:1618-1625.
14. Kalso E, Tasmuth T, Neuvonen PJ. Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. *Pain* 1996; 64:293-302.
15. Tasmuth T, Hartel B, Kalso E. Venlafaxine in neuropathic pain following treatment of breast cancer. *Eur J Pain* 2002; 6:17-24.
16. Vilholm OJ, Cold S, Rasmussen L, Sindrup SH. Effect of levetiracetam on the postmastectomy pain syndrome. *Eur J Neurol* 2008; 15:851-857.
17. Van Boxem K, Huntoon M, Van Zundert J, Patijn J, van Kleef M, Joosten EA. Pulsed radiofrequency: A review of the basic science as applied to the pathophysiology of radicular pain: A call for clinical translation. *Reg Anesth Pain Med* 2014; 39:149-159.
18. Cohen SP, Sireci A, Wu CL, Larkin TM, Williams KA, Hurley RW. Pulsed radiofrequency of the dorsal root ganglia is superior to pharmacotherapy or pulsed radiofrequency of the intercostal nerves in the treatment of chronic postsurgical thoracic pain. *Pain Physician* 2006; 9:227-235.
19. Sluijter ME, Cosman ER, Rittmann WB, van Kleef M. The effects of pulsed radiofrequency fields applied to the dorsal root ganglion: A preliminary report. *Pain Clin* 1998; 11:109-117.
20. Van Zundert J, Brabant S, Van de Kelft E, Vercruyssen A, Van Buyten JP. Pulsed radiofrequency treatment of the Gasserian ganglion in patients with idiopathic trigeminal neuralgia. *Pain* 2003; 104:449-452.
21. Koh W, Choi SS, Karm MH, et al. Treatment of chronic lumbosacral radicular pain using adjuvant pulsed radiofrequency: A randomized controlled study. *Pain Med* 2015; 16:432-441.
22. Kim K, Jo D, Kim E. Pulsed radiofrequency to the dorsal root ganglion in acute herpes zoster and postherpetic neuralgia. *Pain Physician* 2017; 20:E411-E418.
23. Vanelderen P, Rouwette T, De Vooght P, et al. Pulsed radiofrequency for the treatment of occipital neuralgia: A prospective study with 6 months of follow up. *Reg Anesth Pain Med* 2010; 35:148-151.
24. Petrov-Kondratov V, Chhabra A, Jones S. Pulsed radiofrequency ablation of pudendal nerve for treatment of a case of refractory pelvic pain. *Pain Physician* 2017; 20:E451-E454.
25. Lee JJ, Sohn JH, Choi HJ, et al. Clinical efficacy of pulsed radiofrequency neuromodulation for intractable meralgia paresthetica. *Pain Physician* 2016; 19:173-179.
26. Gofeld M, Restrepo-Garces CE, Theodore BR, Faclier G. Pulsed radiofrequency of suprascapular nerve for chronic shoulder pain: A randomized

double-blind active placebo-controlled study. *Pain Pract* 2013; 13:96-103.

27. Hetta DF, Mahran AM, Kamal EE. Pulsed radiofrequency treatment for chronic post-surgical orchialgia: A double-blind, sham-controlled, randomized trial: Three-month results. *Pain Physician* 2018; 21:199-205.
28. Erdine S, Bilir A, Cosman ER, Cosman ER Jr. Ultrastructural changes in axons following exposure to pulsed radiofrequency fields. *Pain Pract* 2009; 9:407-417.
29. Hagiwara S, Iwasaka H, Takeshima N, Noguchi T. Mechanisms of analgesic action of pulsed radiofrequency on adjuvant-induced pain in the rat: Roles of descending adrenergic and serotonergic systems. *Eur J Pain* 2009; 13:249-252.
30. Cho HK, Cho YW, Kim EH, Sluijter ME, Hwang SJ, Ahn SH. Changes in pain behavior and glial activation in the spinal dorsal horn after pulsed radiofrequency current administration to the dorsal root ganglion in a rat model of lumbar disc herniation: Laboratory investigation. *J Neurosurg Spine* 2013; 19:256-263.
31. Vallejo R, Tilley DM, Williams J, Labak S, Aliaga L, Benyamin RM. Pulsed radiofrequency modulates pain regulatory gene expression along the nociceptive pathway. *Pain Physician* 2013; 16:E601-E613.
32. Haguichi Y, Nashold BS, Sluijter M, Cosman E, Pearlstein RD. Exposure of the dorsal root ganglion in rats to pulsed radiofrequency currents activities dorsal horn lamina I and II neurons. *Neurosurgery* 2002; 50:850-855.
33. van Zundert J, de Louw AJ, Joosten EA, et al. Pulsed and continuous radiofrequency current adjacent to the cervical dorsal root ganglion of the rat induces late cellular activity in the dorsal horn. *Anesthesiology* 2005; 102:125-131.
34. Cahana A, Vutskits L, Muller D. Acute differential modulation of synaptic transmission and cell survival during exposure to pulsed and continuous radiofrequency energy. *J Pain* 2003; 4:197-202.
35. Ikeda H, Kiritoshi T, Murase K. Contribution of microglia and astrocytes to the central sensitization, inflammatory and neuropathic pain in the juvenile rat. *Mol Pain* 2012; 8:43.
36. Tenorio G, Kulkarni A, Kerr BJ. Resident glial cell activation in response to perispinal inflammation leads to acute changes in nociceptive sensitivity: Implications for the generation of neuropathic pain. *Pain* 2013; 154:71-81.
37. Liu R, Xu X, Xu Y, Fang X, Lin X. Pulsed radiofrequency on dorsal root ganglion relieved neuropathic pain associated with downregulation of the spinal interferon regulatory factor 8, microglia, p38MAPK expression in a CCI rat model. *Pain Physician* 2018; 21:E307-E322
38. Baker R, Dreyfuss P, Mercer S, Bogduk N. Cervical transforaminal injection of corticosteroids into a radicular artery: A possible mechanism for spinal cord injury. *Pain* 2003; 103:211-215.