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Radiofrequency Treatments for Neuropathic Pain: Review and New Approaches

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1. Introduction

There are 2 types of radiofrequency treatment (RF) for neuropathic pain: thermal (continuous) RF and pulsed RF (PRF).

Thermal RF (TRF) uses a constant high-frequency electric current (100,000-500,000 Hz) to produce tissue temperatures of 45 °C or more, resulting in neuroablative thermocoagulation. Thus, TRF is a neurolytic technique that uses heat for controlled destruction of nociceptive pathways. However, the use of TRF for the management of neuropathic pain is controversial because neuroablation can lead to lasting motor deficits, neuritis, and deafferentation pain.

PRF was developed as an alternative to TRF. In PRF, the current is delivered in short pulses, and the tip temperature of the probe is adjusted so that it does not increase above 42 °C, thus avoiding lesions. PRF has been applied to treat various chronic pain conditions (Chua et al., 2011) but, the mechanisms of the analgesic action have not been studied in detail, and the optimal electrical parameters (voltage and duration) have not been established.

This chapter discusses the use of both TRF and PRF for treating neuropathic pain. We excluded treatments administered for arthropathy or discogenic pain, such as RF of the medial branch that innervates the zygapophyseal joints or that of the intervertebral disc.

The review section of this chapter critically evaluates the efficacy of TRF and PRF by discussing several randomized clinical trials (RCTs) and well-designed observational studies. Therefore, case reports also have been excluded.

We then presented our results from 2 self-controlled studies on each method.

2. TRF for neuropathic pain

2.1 Mechanism of action

The passage of low-energy, high-frequency alternating current (100,000–500,000 Hz) causes intense oscillations of tissue ions. This oscillation heats charged macromolecules, most notably proteins (Organ, 1976−1977). In TRF, heating during RF causes many cells to die rapidly if tissue temperatures reach 45 °C. Neuroablation is produced whether the electrode is placed inside the dorsal root ganglion (DRG) or onto a peripheral nerve. Above 55 °C, there is indiscriminate destruction of both small- and large-diameter myelinated fibers,

accompanied by focal necrosis, hemorrhages, extensive edema, and features of Wallerian degeneration. Even with a voltage as low as 0.1 V, an electrode placed inside a DRG and heated to 67 °C results in total loss of myelinated fibers and hemorrhage (de Louw et al., 2001; Govind & Bogduk, 2010; Podhajsky et al., 2005; Smith et al., 1981).

The mode of action of RF was initially attributed to the thermocoagulation of nerve fibers, but contradictory observations (most notably that only transient sensory loss is observed in the associated dermatome, whereas the pain relief may last much longer) suggest that temperature is not the only mechanism responsible for the decrease in pain transmission (Racz & Ruiz-Lopez, 2006).

2.2 Treatment of neuropathic pain and its complications

2.2.1 Trigeminal neuralgia

Trigeminal neuralgia is a common, idiopathic form of neuropathic pain that presents with paroxysms of pain involving 1 or more divisions of the trigeminal nerve.

TRF of the trigeminal ganglion has been used for decades to treat trigeminal neuralgia, and several large retrospective series have been conducted to evaluate the efficacy of this procedure. Taha and Tew (Taha & Tew, 1996) reevaluated the effects of TRF on trigeminal ganglion and compared the effectiveness with other surgical procedures for the treatment of trigeminal neuralgia. In this study, among the successfully completed procedures (n = 6205), complete initial pain relief was highest after TRF and microvascular decompression (MVD) (98%), whereas, glycerol rhizotomy and balloon compression relieved pain in 91% and 93% of patients, respectively. TRF had the highest success rate (98%) when considering both completion of the procedure and achievement of pain relief, whereas lowest success rates were achieved by glycerol rhizotomy (85%) and MVD (83%). The rate of pain recurrence following these percutaneous techniques was lower with TRF (20% in 9 years) than with glycerol rhizotomy (54% in 4 years) or balloon compression (21% in 2 years).

The chief disadvantages of TRF of the trigeminal ganglion was that the deliberately produces sensory loss with an unavoidable incidence of neuropathic pain in some patients (Niv & Gofeld, 2009). The most common complications and adverse effects of TRF of the trigeminal ganglion included facial numbness (98%), dysesthesia (24%), anesthesia dolorosa (1.5%), corneal anesthesia (7%), keratitis (1%), and trigeminal motor dysfunction (24%) (Rathmell, 2009). The mechanism of injury during TRF for trigeminal neuralgia may be related to injury caused during placement of the cannula or injury caused by thermal destruction during the procedure.

2.2.2 DRG

TRF of DRG (TRF-DRG) is mainly used to treat persistent radicular pain. Although uncontrolled studies reported acceptable clinical efficacy, the controlled clinical data on TRF yielded variable results that depended on the pain syndrome treated and the specific mode of TRF-DRG employed (Malik & Benzon, 2008). To date, there is limited evidence for only short-term relief of cervicobrachial pain, no conclusive evidence that TRF-DRG is an effective treatment for cervicogenic headaches, and limited evidence against its use in the treatment of lumbar radicular pain.

Three prospective controlled trials have examined TRF-DRG for treating neuropathic pain stemming from cervical DRG.

Van Kleef et al. (van Kleef et al., 1996) divided the patients with intractable chronic cervicobrachial pain into 2 treatment groups: 9 patients underwent TRF of the cervical DRG at 67 ºC, whereas 11 underwent sham treatment. Patients were evaluated before the procedure and 8 weeks after it. Eight patients in the thermal RF group (88.8%) and 2 patients (18.1%) in the sham group reported pain relief. Regarding side effects of TRF, 7 patients treated with TRF noticed a faint burning sensation in the treated dermatome that subsided within 3 weeks after treatment.

Slappendel et al. (Slappendel et al., 1997) conducted second RCT involving TRF of the cervical DRG in patients with cervicobrachial pain. They compared 32 patients who received TRF-DRG at 67 ºC with 29 patients who received TRF-DRG at 40 ºC, which could not produce neuroablative thermocoagulation. No statistically significant difference in pain scores was found between the 2 groups. Neuritis was reported in the TRF-DRG at 67 ºC group (18.8%) and TRF-DRG at 40 ºC group (17.2%) 6 weeks after TRF-DRG. Moreover, a few patients reported motor disturbances with a decreased pinch force 3 months after treatment.

A trial by Haspeslagh et al. (Haspeslagh et al., 2006) included 30 patients with cervicogenic headache. Patients were randomized to 2 groups. One group (n = 15) was treated by TRF of cervical facet joints, followed by TRF of the cervical DRG at 67 ºC if necessary, whereas the second group (n = 15) was treated by injections of a steroid and a local anesthetic into the greater occipital nerve, followed by transcutaneous electrical nerve stimulation (TENS) if necessary. There was no significant difference in the success rate between the 2 treatments, and the authors concluded that sequential TRF of facet joints and DRG had similar efficacy to local steroid and anesthetic injection, followed by TENS.

There have been no prospective controlled trials on TRF of the thoracic DRG.

Stolker et al. (Stolker et al., 1994) conducted a prospective uncontrolled trial using TRF of the thoracic DRG at 67 ºC to treat 45 patients afflicted with thoracic segmental pain. They reported that 91% patients obtained > 50% pain relief at 2 months and that 78% continued to experience pain relief for 13 to 46 months. A smaller number of patients (13.3%) reported a transient burning pain in the corresponding dermatome that subsided within 3 weeks.

There is only 1 prospective controlled trial on the clinical efficacy of TRF of the lumbar DRG. A trial by Geurts et al. (Geurts et al., 2003) included 83 patients with chronic lumbosacral pain; 45 patients underwent TRF-DRG at 67 ºC, whereas 38 underwent sham treatment. After 3 months, 16% patients treated with TRF-DRG and 25% of sham-treated patients reported a decrease in lumbosacral pain (P = 0.43). Adverse events and complications, such as treatment-related pain, changes in sensation, or loss of motor function, did not differ between the treatment groups. They concluded that TRF was not an effective treatment for chronic lumbosacral radicular pain and stressed that such patients would attain little benefit from TRF-DRG.

Whereas the clinical efficacy of TRF was confirmed for some types of neuropathic pain, each of these studies has limitations, particularly small sample numbers and short-term follow-up. In

their review, Malik and Benzon (Malik & Benzon, 2008) concluded that larger-scale, longer-term, controlled clinical trials are required to clearly establish the efficacy of TRF-DRG for different types of neuropathic pain, particularly pain originating from thoracic DRG.

2.2.3 Sympathetic ganglia

Although systematic reviews have found no tangible evidence supporting the benefit of sympathectomy for the management of neuropathic pain, TRF of the stellate, thoracic, and lumbar sympathetic ganglia has been used for treatment of neuropathic pain arising from sympathetic ganglia dysfunction such as complex regional pain syndrome. However, evidence for the therapeutic efficacy of TRF, is limited to small case series. RCTs are needed to validate the efficacy of TRF for these syndromes and to define measurable and reproducible end points for it.

3. Neuropathic pain treatment by combined TRF and glucocorticoids

3.1 Background

TRF is controversial because of its neurodestructive nature (Bogduk, 2006; de Louw et al., 2001; Podhajsky et al., 2005; Smith et al., 1981; Uematsu et al., 1974). Heat lesions produced by TRF causing neural destruction have sequelae similar to other forms of neural injury. Even with proper technique, TRF is associated with sensory loss and the onset of neuropathic pain. Although the frequency of these complications is minimized by the proper use of sensory and motor stimulation trials to isolate somatosensory and motor axons before lesion, injury to adjacent nerves can easily occur (Rathmell, 2009). Glucocorticoids have been used to treat neuropathic pain for many years, and they do effectively alleviate acute and continued postoperative pain by suppressing inflammatory mediators and glial activation, resulting in decreased nociceptive activity, sympathetic sprouting, and central neuropathic changes such as central sensitization (Romundstad & Stubhaug, 2007). We suggest that the effect of glucocorticoids could be additive to that of TRF and that glucocorticoids might avert pain associated with neuroinflammation after RF lesioning.

3.2 Methods

3.2.1 Patients

Fourteen patients (7 females, 7 males) with refractory neuropathic pain from postherpetic neuralgia were included in this study. Median age was 70.5 years (interquartile range, 69.3–71.8 years). The median pain duration was 9.0 months (interquartile range, 7.0–13.5 months).

Patients were selected to undergo TRF of the thoracic paravertebral nerve (TRF-TPN) combined with glucocorticoid according to the following criteria: (1) the presence of radiating pain in the thoracic region following herpes zoster; (2) no response to conventional treatments such as anti-inflammatory drugs, antidepressants, anticonvulsants, opioid analgesics, and topical capsaicin; (3) at least 6 months of conventional treatment; (4) temporary positive response (100% pain relief) to TPN block using local anesthetics and glucocorticoids (conventional NB) at each painful dermatome; and (5) pain severe enough to disturb sleep.

Exclusion criteria were as follows: (1) MRI showing acute pathology; (2) history of adverse reactions to local anesthetics or glucocorticoids; or (3) coagulation disorders, or use of anticoagulants.

After we provided complete information on the RF technique and its possible benefits, risks, and side effects, the patients gave verbal informed consent for the procedure.

3.2.2 Conventional paravertebral nerve block

In the first part of this study, conventional nerve block (NB) was achieved using a local anesthetic and glucocorticoid, and the duration of pain relief was recorded.

The duration of pain relief was defined as the number of days after the treatment until the pain intensity returned to the level experienced before treatment.

The level at which conventional NB was administered was determined by the affected dermatome, the degree of tenderness under the rib using fluoroscopy with a C-arm, and the effect of the intercostal NB.

Conventional NB was performed using a 22-gauge, 80-mm needle under real-time fluoroscopy with a C-arm by the laterodorsal approach (Uchida, 2009). We administered 1.5 ml of 2% mepivacaine as the local anesthetic and 2 mg of betamethasone (Rinderon®, Shionogi, Osaka, Japan) as the glucocorticoid.

3.2.3 Radiofrequency procedures

Four to eight weeks after assessment of the effect of conventional NB, TRF-TPN was administered in the same manner as the previous conventional NB. In the TRF procedure, the electrode (22-gauge 99-mm needle with 4-mm bare tip, TFW 22G × 99 mm®, Hakko, Japan) was used instead of a 22-gauge, 80-mm needle. Once the electrode was positioned, the electrode stylet was replaced with a thermocouple electrode. We tested whether the thermocouple electrode was placed in the physiologically correct location by applying 100-Hz stimulation of the needle tip. We initially set the voltage at 0 V, and then gradually increased it until the patient felt a tingling sensation. If a tingling sensation in the corresponding dermatome was reported at a voltage of < 0.5 V, the electrode was assumed to be in the correct position. After verifying that the needle was in the correct position, 1.5 ml of 2% mepivacaine and 2 mg of betamethasone were administered.

Five minutes later, TRF-TPN was applied at 90 °C and duration of 90 seconds under control of a generator (Neuro Therm JK 3™ system, Croydon, Surrey, UK) with an automatic temperature control mode to avoid excessive elevation of temperature. After therapy, the number of days of pain relief and the complications resulting from TRF-TPN were recorded.

3.3 Results

3.3.1 Primary outcomes

The duration of pain relief after TRF was significantly longer than that after conventional NB ($P < 0.0001$, Kaplan–Meier analysis and the log–rank statistic) (Figure 1).

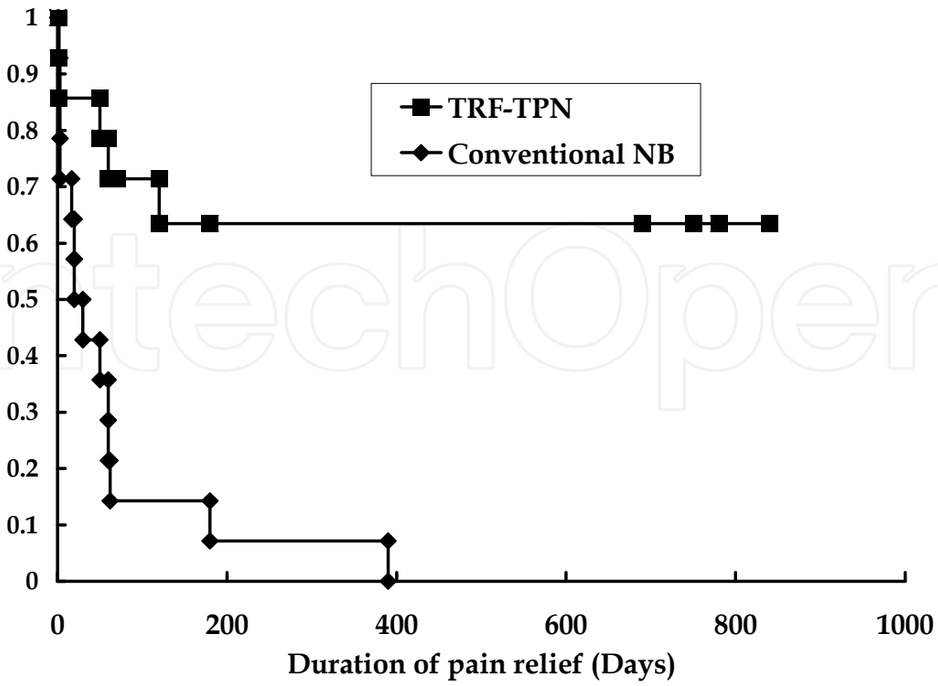

Fig. 1. Analgesic effect of conventional NB vs. TRF of TPN.

Kaplan-Meier graphs depicting the cumulative proportions of patients who reported pain relief following conventional NB or TRF-TPN. Censored values represent patients whose pain returned to pretreatment levels. The vertical axis indicates cumulative proportion of patients reporting pain relief.

3.3.2 Secondary outcome

The mean electrical sensory stimulation threshold before TRF-TPN was 0.20 ± 0.14 V (mean ± SD) at 100 Hz and 0.20 V at 3 Hz (median, interquartile range: 0.10–0.35 V). The impedance after therapy (local anesthetic and glucocorticoid injection + TRF) was significantly lower than that measured before TRF (before TRF: 637.9 ± 182.4 Ω; after therapy: 511.6 ± 79.3 Ω; mean ± SD, $P = 0.0045$ by paired t-test).

In all cases, hypoesthesia increased in the corresponding dermatome after TRF. No major complications, such as anesthesia dolorosa and burning pain, were reported after the procedure, and no patient claimed that their pain had increased after the procedure.

3.4 Discussion

Controversy has arisen over the use of TRF for the management of nonmalignant neuropathic pain because of its potential for neurodestruction, which could lead to motor deficits, neuritis, and deafferentation pain. Van Kleef et al. (Van Kleef et al., 1995) suggested that the potential hazard of nonspecific neural destruction after treatment with TRF-DRG might actually intensify symptoms by inducing deafferentation pain. Therefore, they insisted that TRF-DRG was not suitable for neuropathic pain syndromes with sensory loss due to nerve damage, such as postthoracotomy pain, postherpetic neuralgia, and postmastectomy syndrome, and that TRF-DRG should be restricted to purely nociceptive pain syndromes.

Peripheral nerve destruction caused by TRF has paradoxical effects on neuropathic pain. It is believed that the therapeutic effect of TRF is achieved by a partial nerve lesion to nociceptive afferents (Bogduk, 2006). On the other hand, minor nerve injury can sometimes produce devastating pain, whereas modest or diffuse deafferentation does not (Devor et al. 2006). The cause of this effect has not been elucidated. In a clinical study, it was suggested that even long-standing central sensitization can be reversed quickly when the peripheral input is removed (Gracely et al., 1992). Therefore we believe that TRF is an acceptable treatment modality for neuropathic pain.

We used TRF-TPN for postherpetic neuralgia instead of TRF-DRG in this case series. TRF-TPN has an simpler surgical approach than TRF-DRG and thus a lower probability of injuring the radicular artery, an event that may induce serious neurologic complications, including brain and spinal cord infarction and death (Uchida, 2009) .

We reported previously that repeated administration of TRF-TPN combined with glucocorticoid administration decreased pain and improved the quality of life in patients with the refractory neuropathic pain of postmastectomy syndrome (Uchida, 2009).

Although the use of glucocorticoids for NB is also controversial, glucocorticoids are usually coadministered with a local anesthetic. Pro-inflammatory cytokines secreted at or near the site of nerve injury are involved in the development and maintenance of central sensitization and neuropathic pain (Romundstad & Stubhaug, 2007).

The lesions produced by the RF energy are well-demarcated areas of coagulative necrosis surrounded by inflammatory cell infiltrate and hemorrhage. This inflammatory response can lead to increased tenderness, pain, and limited movement after TRF (Dobrogowski et al., 2005). Glucocorticoids are known to suppress pro-inflammatory cytokines (such as TNFα and IL-1β) and induce the expression of anti-inflammatory cytokines (such as IL-10). Moreover, there is convincing evidence for acute analgesic and antihyperalgesic effects of glucocorticoids after surgery in humans and experimental injuries in animal models (Romundstad & Stubhaug, 2007).

The duration of pain relief was significantly longer after TRF-TPN treatment than after conventional NB in this self-controlled study, and few serious side effects were reported despite the increased hypoesthesia. Van Kleef et al. (van Kleef et al., 1995) evaluated the effectiveness of TRF-DRG (67 °C, 60 s) on patients presenting with chronic thoracic pain and reported significantly better short-term and long-term pain relief. However, in their report, 14 (33%) out of 43 patients experienced a mild burning pain in the treated dermatome for some days following treatment. In our previous report, 3 patients experienced no transient burning pain after 21 successive TRF-TPN despite the high temperature and repetition (Uchida, 2009). Dobrogowski et al. (Dobrogowski et al., 2005) found that TRF with methylprednisolone administration to the lumbar medial branch tended to decrease the frequency of postoperative pain.

Although the site and extent of treatment were different as well as the degree of the effect of glucocorticoid remains unclear, these results suggests that glucocorticoids can decrease the pain related to neural injury after TRF.

4. Pulsed radiofrequency treatment for neuropathic pain

4.1 Mechanism of action

Two theories have been proposed to explain the analgesic effects of PRF.

One is that pain relief depends on the rapidly changing electric fields (Sluijter, 1998); the other is that PRF produces brief heat bursts at temperatures in the range associated with destructive heat lesions (Cosman & Cosman, 2005). It is not known, however, if these transient heat bursts do have an ablative effect (Chua et al., 2011).

Secondary effects on the nervous system after PRF application have been studied in animal models (Erdine et al., 2009; Erdine et al., 2005; Hamann et al., 2006; Higuchi et al., 2002; Podhajsky et al., 2005; Protasoni et al., 2009; Tun et al., 2009; Van Zundert et al., 2005). These studies reported increased c-Fos expression in the dorsal horn (Higuchi et al., 2002; Van Zundert et al., 2005), increased expression of activating transcription factor 3 (Hamann et al., 2006), and morphological changes in the DRG or the peripheral nerve (Erdine et al., 2009; Erdine et al., 2005; Podhajsky et al., 2005; Protasoni et al., 2009; Tun et al., 2009).

4.2 Treatment of neuropathic pain and treatment complications

4.2.1 Trigeminal neuralgia

For trigeminal neuralgia, the therapeutic efficacy of PRF has neither surpassed nor equaled TRF. Erdine et al. (Erdine et al., 2007) compared the efficacy of TRF with PRF of the trigeminal ganglion in patients with idiopathic trigeminal neuralgia. Significant pain reductions were reported in all patients treated with TRF (n = 20), whereas only 2 of 20 patients in the PRF treatment group reported pain reduction. Five of the 20 TRF patients and 3 of 20 PRF patients reported moderate headache for 24 h. There was mild hypoesthesia and paresthesia in all patients from the TRF group. Anesthesia dolorosa occurred in 1 patient from the TRF group and medical treatment was given. They concluded that PRF, unlike TRF, was not an effective treatment method for idiopathic trigeminal neuralgia.

4.2.2 DRG

Two RCTs have examined PRF of DRG for neuropathic pain (Simopoulos *et al.*, 2008; Van Zundert *et al.*, 2007). These studies presented limited evidence that PRF of the cervical DRG could produce short-term relief of cervical radicular pain; however, there is limited evidence against its use existed in treatment of lumbar radicular pain (Malik & Benzon, 2008).

Van Zundert et al. (Van Zundert et al., 2007) compared PRF of the cervical DRG to sham treatment at 3 months after treatment; PRF of the cervical DRG showed significantly better outcome on both the global perceived effect (> 50% improvement) index and visual analog scale (20-point pain reduction).

Simopoulos et al. (Simopoulos et al., 2008) randomly divided patients with lumbosacral radicular pain into 2 groups; 1 group was treated with PRF only, whereas the second group was treated first with PRF and then with TRF at the maximum tolerated temperature. There was no significant difference in the response rate or in the average decline in VAS between the 2 groups. Survival curves showed that for both treatment groups experienced a steep loss in the analgesic effect between 2 and 4 months after the procedure. By the 8th month, the vast majority of patients relapsed to baseline pain intensity.

Malik and Benzon (Malik & Benzon, 2008) reviewed published articles on PRF-DRG and concluded that none of the studies reported any significant side effects or complications.

However, Sluijter (Sluijter, 2001) divided the postoperative observational period after PRF procedure into four phases and found that the second phase was associated with the highest post-procedure discomfort, which lasted up to 3 weeks.

5. Low-voltage PRF treatment for radicular neuropathic pain

5.1 Background

The clinical effects of PRF have been examined for various regions and pain conditions using voltage outputs of 20–45 V. There are no standardized criteria for the voltage output of PRF, except that voltage should not be sufficient to increase temperature above 42 °C. However, rapid temperature spikes above 42 °C were observed during PRF bursts of 45 V, occasionally reaching the lethal temperature range of 45–50 °C or more (Cosman & Cosman, 2005). These rapid temperature spikes might induce microscopic tissue damage, leading to a period of discomfort after PRF, and induce antinociceptive action.

To avoid rapid temperature spikes, we used low-voltage PRF (L-PRF) where the voltage output is only 5 V. This section will describe the first reported effects of L-PRF for radicular neuropathic pain using a self-controlled design.

5.2 Materials and methods

5.2.1 Patients

This study was approved by the institutional review board of the institution where our study was performed, and patients provided written informed consent for participation. The basic demographic and clinical characteristics of the patients are listed in Table 1. Patients were subgrouped according to treatment sites as cervical (C), thoracic (T), and lumbar (L).

	Age (years)*	Female/Male	Duration of Pain (months)*	Etiology
C	49 (49-55)	10/2	14 (10-21)	Cervicobrachialgia
T	70 (68-72)	3/7	6 (5-6)	Postherpetic neuralgia
L	70 (65-79)	5/3	74 (14-80)	Degenerative spondylosis

*Median (Interquartile range)

Table 1. Characteristics of the Subjects

Patients were selected for this study according to the following criteria: (1) chronic unilateral radicular pain of at least 3 months' duration that could not be adequately controlled with oral medications; (2) average pain intensity higher than 30 mm as measured on a 100 mm VAS; (3) temporary positive response (100% reduction of pain) more than twice to C, T, or L DRG block with local anesthetics and glucocorticoids under fluoroscopy; and (4) return of pain intensity to baseline after temporary relief resulting from C, T, or L DRG block.

Exclusion criteria were as follows: (1) MRI showing acute pathology; (2) history of adverse reactions to local anesthetics or glucocorticoids; or (3) history of cancer, myelopathy,

diabetes mellitus, psychotherapeutic management, coagulation disorders, or use of anticoagulants.

5.2.2 Conventional NB procedures

Conventional NB and L-PRF of C, T, and L- DRG were performed using a 22-gauge needle under real-time fluoroscopy with a C-arm as described by Gauci (Gauci, 2004).

After fluoroscopy confirmed that the needle tip was positioned correctly, 0.2 ml of iohexol (Omnipaque 240®; Daiichi-Sankyo, Tokyo, Japan) was injected to guard against venous uptake and false-negative responses. If the contrast dye was washed out by blood flow, the needle was removed and reintroduced. Thereafter, 0.5 ml of 2% mepivacaine as the local anesthetic and 0.5 ml of 0.4% betamethasone (Rinderon®; Shionogi, Osaka, Japan) were administered.

Four to eight weeks after assessment of the effect of conventional NB, patients were treated by L-PRF.

5.2.3 L-PRF procedure

L-PRF was performed under fluoroscopy with a C-arm in the same manner as conventional NB. For L-PRF, an RF needle (22-gauge 99-mm needle with 4-mm bare tip, TFW 22G × 99 mm®, Hakko, Japan) was used instead of the 22-gauge injection needle used for conventional NB. After optimizing the position of the needle, we tested whether the thermocouple electrode was placed in the physiologically correct location by applying 100-Hz stimulation to the needle tip using a generator (Neuro Therm JK 3™ system; Neuro Therm, Croydon, Surrey, United Kingdom). If a tingling sensation was obtained at a voltage of < 0.5 V at 100-Hz stimulation, the electrode was assumed to be in the correct position. Each threshold was measured twice and the average was obtained. After the 100-Hz stimulation threshold was determined, we measured the stimulation threshold at 3 Hz that was required to induce throbbing and touch-like sensations in a similar manner and impedance.

Ten seconds after the measurement, L-PRF was initiated. The L-PRF protocol consisted of 20-ms radiofrequency current bursts at 2 Hz for 180 s with a generator (Neuro Therm JK 3™ system). The oscillation frequency of the alternating current was 500 kHz, which is generated by a voltage of 5 V. During 1 cycle, the active phase of 20 ms was followed by a silent period of 480 ms to allow dissipation of the generated heat.

Throughout the L-PRF, the current output, voltage, and tip temperature were recorded every 30 s.

Ten seconds after L-PRF, the electrical stimulation thresholds at 100 Hz and 3 Hz, as well as the impedance were reevaluated. Following completion of L-PRF, 0.5 ml of 2% mepivacaine and 0.5 ml of 0.4% betamethasone were administered through the RF needle into the nerve. The dosages of the local anesthetic and glucocorticoid were the same for both the conventional NB and L-PRF groups.

After conventional NB and L-PRF, the number of days of pain relief was recorded. The duration of pain relief was defined as the number of days after therapy until the pain intensity returned to the baseline level experienced before the therapy.

5.3 Results

5.3.1 Primary outcomes

The duration of pain relief after L-PRF was significantly longer than that after conventional NB for treating all target sites (C, T, and L DRG) ($P < 0.05$, Kaplan-Meier analysis and the log rank statistic) (Figure 2, 3, and 4).

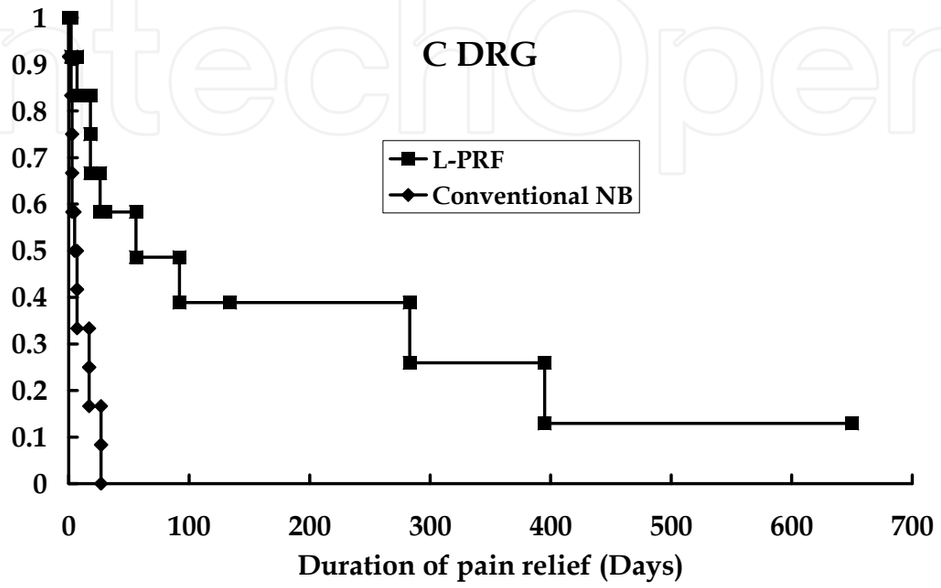

Fig. 2. Analgesic effect of conventional NB vs. L-PRF of C DRG

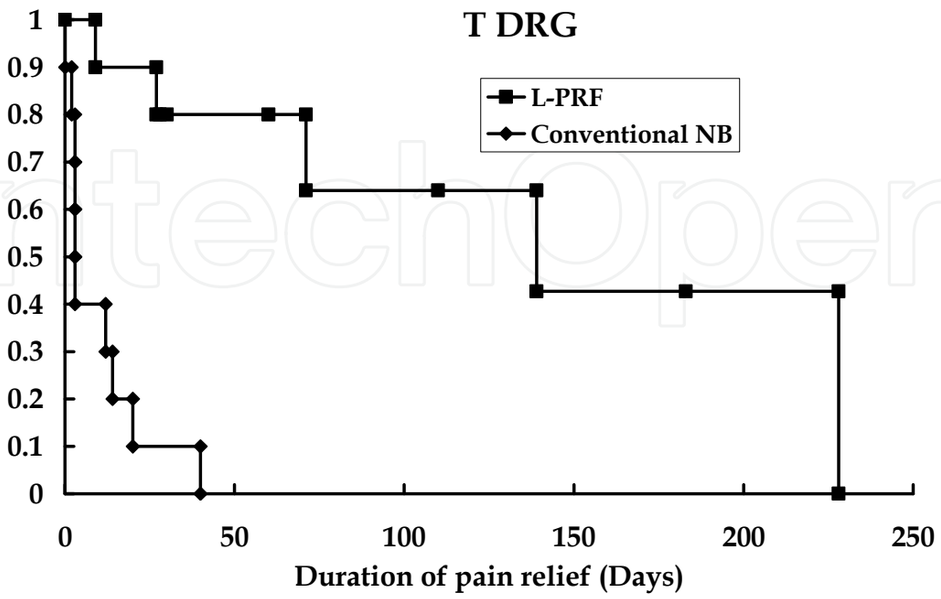

Fig. 3. Analgesic effect of conventional NB vs. L-PRF of T DRG

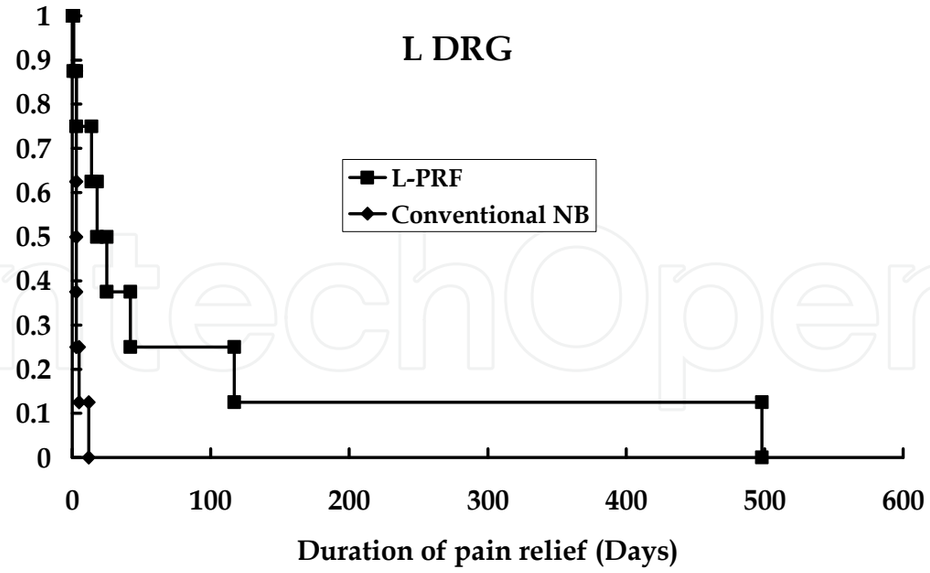

Fig. 4. Analgesic effect of conventional NB vs. L-PRF of L DRG

Kaplan-Meier graphs depicting the cumulative proportions of patients who experienced pain relief for a given period after conventional NB or L-PRF of C (Fig. 2), T (Fig. 3), and L (Fig. 4) DRG revealed that patients treated by L-PRF exhibited a much longer analgesic response. Censored values in these plots represent patients who experienced the same level of pain as before therapy. Vertical axes indicate the cumulative proportions of patients experiencing pain relief at that time.

5.3.2 Secondary outcome

The secondary outcomes measured included voltage, current, and temperature profiles during L-PRF (Table 2) as well as the measurements of electrical sensory stimulation thresholds at 100 Hz and 3 Hz and impedance values before and after L-PRF (Table 3) for patients treated by L-PRF of C, T, or L DRG.

	0	30	60	90	120	150	180
C							
Voltage [V]	5.0 (0.0)	5.0 (0.0)	5.0 (0.0)	5.0 (0.0)	5.0 (0.0)	5.0 (0.0)	5.0 (0.0)
Current [mA]	20.0 (5.0)	17.5(5.0)	17.5 (5.0)	17.5 (5.0)	17.5 (5.0)	17.5 (5.0)	17.5 (5.0)
Temperature [°C]	38.0 (0.8)	40.0 (1.8)	40.0 (1.8)	40.0 (1.8)	40.0 (1.5)	40.0 (1.3)	40.5 (2.3)
T							
Voltage [V]	5.0 (0.8)	5.0 (0.0)	5.0 (0.0)	5.0 (0.0)	5.0 (0.0)	5.0 (0.0)	5.0 (0.0)
Current [mA]	15.0 (3.8)	15.0 (3.8)	15.0 (3.8)	15.0 (3.8)	15.0 (3.8)	15.0 (3.8)	15.0 (3.8)
Temperature [°C]	38.5 (1.0)	40.0 (1.0)	41.0 (1.8)	41.0 (1.8)	41.0 (1.0)	41.0 (1.0)	41.5 (1.0)
L							
Voltage [V]	5.0 (0.0)	5.0 (0.0)	5.0 (0.0)	5.0 (0.0)	5.0 (0.0)	5.0 (0.0)	5.0 (0.0)
Current [mA]	20.0 (5.0)	20.0 (2.5)	20.0 (5.0)	20.0 (2.5)	20.0 (2.5)	20.0 (2.5)	20.0 (5.0)
Temperature [°C]	38.0 (1.5)	41.0 (2.0)	42.0 (0.5)	42.0 (1.0)	42.0 (0.0)	42.0 (0.0)	42.0 (0.0)

The median and interquartile ranges are presented in each cell of this table.

Table 2. Electrical and temperature profiles during 180-s L-PRF

The electrical sensory stimulation threshold at 100 Hz and 3 Hz after L-PRF was significantly higher than that before treatment (C and L DRG group: $P < 0.05$ by paired t-test, T DRG group: $P < 0.05$ by Wilcoxon's signed rank test). The impedance after L-PRF was significantly lower than that before treatment in all groups ($P < 0.05$, paired t-test, respectively) (Table 3).

	100 Hz [V]		3 Hz [V]		Impedance [Ω]	
	Baseline	**After**	**Baseline**	**After**	**Baseline**	**After**
C	0.26 ± 0.14	0.51 ± 0.21*	0.50 ± 0.47	0.62 ± 0.39*	505.8 ± 77.6	448.0 ± 63.6*
T	0.19 (0.13–0.35)	0.35 (0.12–0.49)*	0.21 (0.20–0.33)	0.34 (0.31–0.54)*	582.2 ± 88.2	492.0 ± 100.3*
L	0.15 ± 0.11	0.35 ± 0.18*	0.24 ± 0.19	0.35 ± 0.16*	586.1 ± 144.7	441.3 ± 74.5*

Values are expressed as mean ± SD or median (interquartile range). *$P < 0.05$, versus baseline values.

Table 3. Electrical sensory stimulation thresholds at 100 Hz and 3 Hz and impedance before and after L-PRF

5.4 Discussion

In this study, PRF was administered at low voltage (5 V) to avoid temperature spikes that might induce heat lesions and lead to a period of discomfort after treatment. The calculated and measured heat spikes during PRF should be proportional to $V(peak)^2/2R$ (resistance), where V (peak) is the peak RF voltage on the electrode (Cosman & Cosman, 2005). Therefore heat spikes in this study were about 1/16-81 in comparison with that at 20-45 V. Although the actual tissue temperature around the electrode could not be measured, it was assumed that the heat spikes by L-PRF treatment were suppressed enough.

In this study, the duration of pain relief after L-PRF treatment was significantly longer than that after conventional NB. Although it is difficult to compare our results with those following conventional PRF-DRG because the study protocols are different, this improved efficacy of L-PRF seems correlates with the results following conventional PRF-DRG (Chua et al., 2011).

Moreover, we applied 100-Hz and 3-Hz electrical stimulation before and immediately after L-PRF and recorded the changes in electrical sensory stimulation thresholds to detect the immediate effect of L-PRF on nerve excitability. Despite the significant decrease in the impedance after L-PRF, the electrical sensory stimulation thresholds at 100 Hz and 3 Hz were significantly higher immediately after L-PRF. We cannot explain the relationship between the elevation in sensory stimulation threshold and the prolonged pain relief after L-PRF. This observed decline in sensory perception may reflect the prompt analgesic effect of L-PRF, which raises the possibility that this phenomenon induces long-term changes in gene expression that underlie neuronal plasticity (Van Zundert et al., 2005).

There is no evidence to suggest that L-PRF and conventional PRF work through different mechanisms. Two parameters related to rapidly changing electric fields are keys to the change in neuronal transmission: temperature and electrical pattern.

The median tip temperature of the electrode ranged from 38 °C to 42 °C in our study. Heating a nerve to a relatively low temperature (40-45 °C) has been reported to block conduction along

the nerve, but only temporarily (Brodkey et al., 1964). These reports lend support to the possibility that L-PRF has a transient inhibitory effect on sensory transmission.

The electrical pattern of L-PRF consisted of 2 distinct phases: bursts of 2 Hz and oscillating current of 500 kHz.

Bursts of 2 Hz are at almost the same frequency as that used for TENS. Munglani (Munglani, 1999) suggested that PRF works in a manner similar to TENS, activating both spinal and supraspinal mechanisms that may decrease sensory perception. Nerve stimulation at 1-2 Hz was shown to induce long-term depression (LTD) of synaptic transmission in the spinal cord (Pockett, 1995, Sandkühler et al., 1997). De Col and Maihöfner (De Col & Maihöfner, 2008) reported that sensory decline was induced after transcutaneous electrical stimulation at 0.5 Hz or 20 Hz and that the underlying mechanisms might involve higher sensory integration centers such as the thalamus, primary somatosensory cortex (S1), secondary somatosensory cortex (S2), and surrounding somatosensory association cortices that process noxious and innocuous stimuli.

Cosman and Cosman (Cosman & Cosman, 2005) calculated that the rapid oscillation in transmembrane potential in response to a 500-kHz current would induce transmembrane rectification of neuronal currents, which might also cause LTD as well as depolarizing pulses at 1-2 Hz. In this case, both temporal phases of current oscillation might induce LTD and thereby decrease afferent pain transmission.

This pulsed stimulus pattern might also induce secondary effects in the nervous system, such as enhancement of the descending noradrenergic and serotonergic inhibitory pathways (Hagiwara et al., 2009), that modulate neuropathic pain. Furthermore, histological analyses revealed changes in neuronal morphology following PRF (Erdine et al., 2009; Erdine et al., 2005; Podhajsky et al., 2005; Protasoni et al., 2009; Tun et al., 2009), which may alter the electronic properties of sensory neurons and potentially interrupt normal afferent signaling to the spinal cords.

Although the applied site and the electric profiles of PRF were different, it is possible that our observation was related to these mechanisms.

To date, PRF has not achieved the clinical efficacy of TRF (Govind & Bogduk, 2010). However, PRF has a principal advantage over TRF. By minimizing structural damage to nontarget axons through heat dissipation, PRF is associated with fewer side effects. From this perspective, L-PRF might be an attractive alternative treatment, if L-PRF surpasses the clinical efficacy of conventional NB and does indeed induce fewer or less severe thermal lesions than conventional PRF or TRF.

In conclusion, L-PRF of the DRG resulted in significantly longer pain relief compared with conventional NB in patients with chronic radicular pain. To elucidate the mode of action of PRF, further research is needed. Furthermore, the optimal stimulus parameters must be determined to improve analgesic efficacy and safety.

6. Conclusion

This chapter presented evidence demonstrating the clinical efficacy of RF for the treatment of neuropathic pain. We also presented 2 preliminary studies showing that TRF combined

with glucocorticoids and L-PRF are useful, and possibly safer, treatments for neuropathic pain. These studies are preliminary and a lot of work needs to be done before the mechanism of action and most effective electric parameters are defined.

Although chronic neuropathic pain is a clinical challenge, radiofrequency treatments have several benefits including relative safety and technical simplicity. If pharmacological treatment and conventional NB have failed, RF might be a valuable alternative for patients with refractory neuropathic pain.

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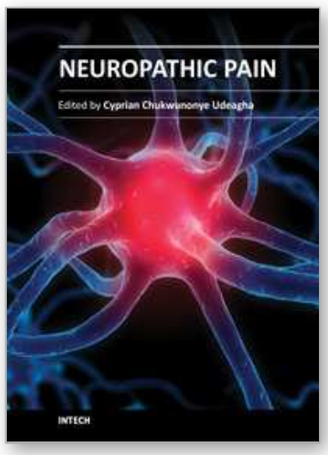

Neuropathic Pain

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Neuropathic pain is known to be pain with nerve involvement. The intensity of which depends on the severity, pain threshold and the ability of suffers to cope. Neuropathic pain may need mono-therapy or combination of therapies to be resolved. Neuropathic pain may not resolve completely, therefore patient's compliance and understanding is essential in its management. Awareness and patient's education on targets may be of help during therapies for neuropathic pain. All chapters treated introduction, characteristics, diagnosis and randomized interventions to certain management of neuropathic pain. We acknowledge all those involve in the making of this book.

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