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Coordinator: Prof. Filippo Drago

"NEUROMODULATION THERAPY IN CHRONIC PAIN"

Ph.D. Thesis

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ABSTRACT

The International Association for the Study of Pain (IASP) defines chronic pain as pain that persists or recurs for longer than three months. This type of pain can be caused by a variety of factors, including injury, disease, or nerve damage, and it can affect various parts of the body. Chronic pain can often become the primary focus of medical treatment for some patients, and it can have a significant impact on their quality of life, mood, and overall well-being. Effective management of chronic pain requires a comprehensive approach that may include a combination of medication, physical therapy, psychological interventions, and neuromodulation therapies. When conservative treatment fails to relieve pain, interventional procedures may be an alternative option in selected patients.

Neuromodulation refers to the use of non-invasive, minimally invasive, or surgical electrical therapies to modify the function of the nervous system. Neuromodulation therapies have gained increasing popularity in the management of chronic pain in recent years, as they can provide effective pain relief with fewer side effects compared to traditional pain medications. Overall, neuromodulation therapies offer a promising approach to the treatment of chronic pain and are expanding rapidly in pain therapy.

This thesis looks at neuromodulation therapies such as spinal cord stimulation (SCS) considered alongside other invasive, minimally invasive such as radiofrequency, and non-invasive neuromodulation therapies, such as peripheral nerve stimulation, deep brain and motor cortex stimulation, and non-invasive treatments which include transcutaneous electrical nerve stimulation.

The aim of this research project is to understand the mechanism behind different neuromodulation therapy for treating chronic pain, focusing on exploring the principles and processes involved in these therapies, including clinical outcomes of common pain disorders.

INTRODUCTION

Chronic pain is defined by the International Association for the Study of Pain (IASP) such as “pain that persists or recurs for longer than 3 months. Such pain often becomes the sole or predominant clinical problem in some patients”.

Neuropathic pain is a type of pain that arises as a result of injury or disease to the somatosensory system, as opposed to nociceptive pain, which in caused by actual or potential damage to non-neural tissues and the activation of normally functioning sensory nerves. [1] Although the understanding of the pathophysiology of chronic neuropathic pain continues to evolve, many consider etiologies as split into peripheral and central causes of sensitization. [2,3]

Peripheral etiologies, alternatively termed peripheral sensitization, are thought to be nervous injuries that lead to spontaneous ectopic discharges and ectopic hyperexcitability.[2] Hyperactivity of the peripheral nervous system, in addition to resulting in increased painful stimuli itself, is postulated to enhance nociceptive signalling and increase the production and release of a myriad of proinflammatory mediators and proinflammatory cytokines. [2]

The creation of this hyper-excitability and inflammatory milieu primes c-fibers in the central nervous system (CNS) and leads to increased CNS signalling, termed “Central Sensitization”. [3]

Conventional treatments are aimed toward blocking individual pathways and include the judicious use of simple analgesics and neuropathic pain medications, such as, gabapentinoids, tricyclic antidepressants, and serotonin norepinephrine reuptake inhibitors, in conjunction with nerve blocks, ‘orthobiologic’ injections, and spinal cord stimulation, as indicated. [4,5]

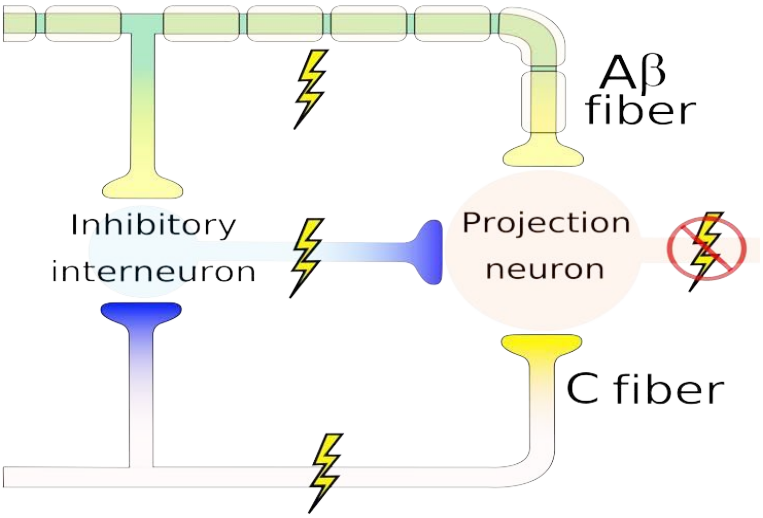
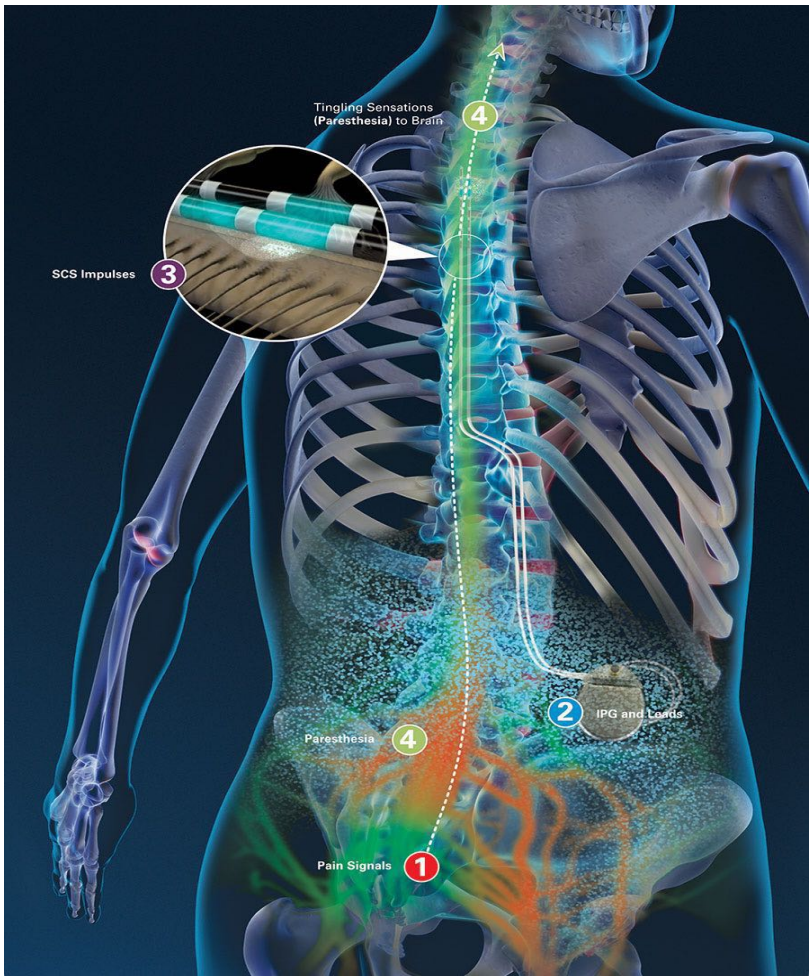


Figure 1 Gate Control Theory

When conservative treatment fails to relieve pain, interventional procedures may be an alternative option in selected patients. Neuromodulation is the use of non-invasive, minimally invasive, and surgical electrical therapies in fast expansion in pain therapy.

Figure 2 Spinal Cord Stimulation

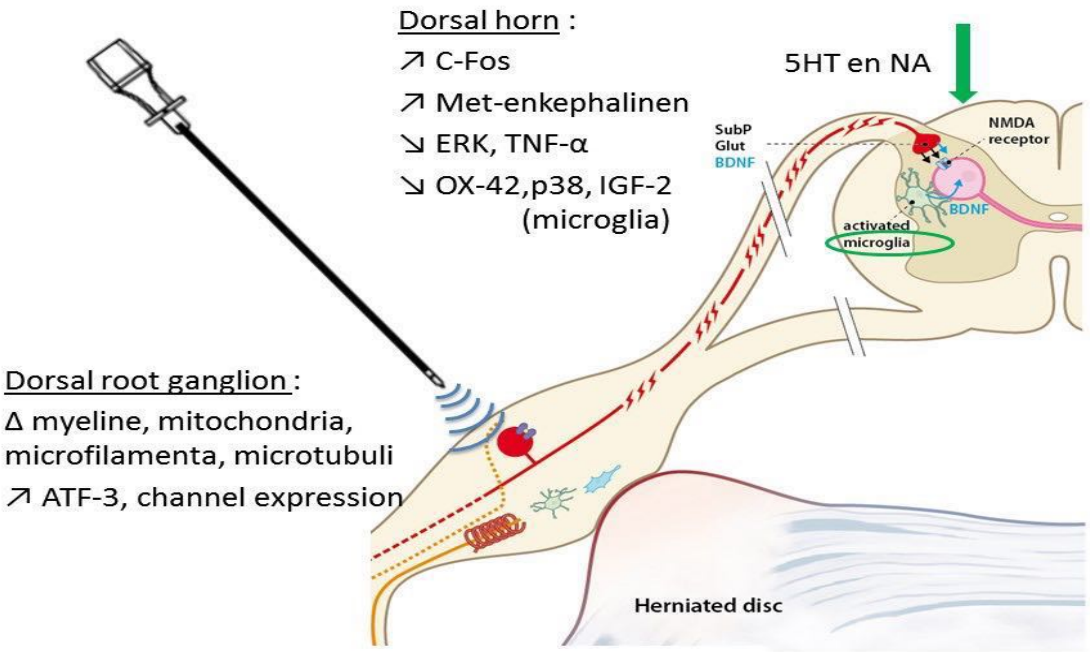


The International Neuromodulation Society defines neuromodulation as "the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body." [6] Modern pain management began to explore the potential of electrical stimulation in 1967 with *Melzack and Wall*'s gate control theory (Figure 1).[7] Subsequently, *Shealy and colleagues* noted a certain degree of pain relief using epidural spinal cord stimulation (SCS) (Figure 2), based on the assumption that stimulating high-velocity mechanoreceptive Aβ fibers can hinder the transmission of lower velocity nociceptive signals (transmitted by Aδ and C fibers) from reaching higher centers of the brain, leading to analgesia as a consequence.[8]

There are a range of invasive and non-invasive approaches in neuromodulation which we can categorized by modality (waveform or anatomical target). Here, the focus will be placed on those modalities which use either technologies with strong potential or for which there is good evidence of their success, concentrating on SCS, a therapy which has enjoyed enormous development over recent years, analysed in comparison to other neuromodulation techniques, such as pulsed radiofrequency (PRF) (Figure 3).

Where conservative therapies (including injections, where indicated) or non-invasive neuromodulation therapies have not provided a satisfactory response, patients would be referred for invasive therapies, inserted into an interdisciplinary care approach and after appropriate psychosocial evaluation, in accordance with clinical care directives.

Figure 3. Dorsal root ganglion pulsed Radiofrequency



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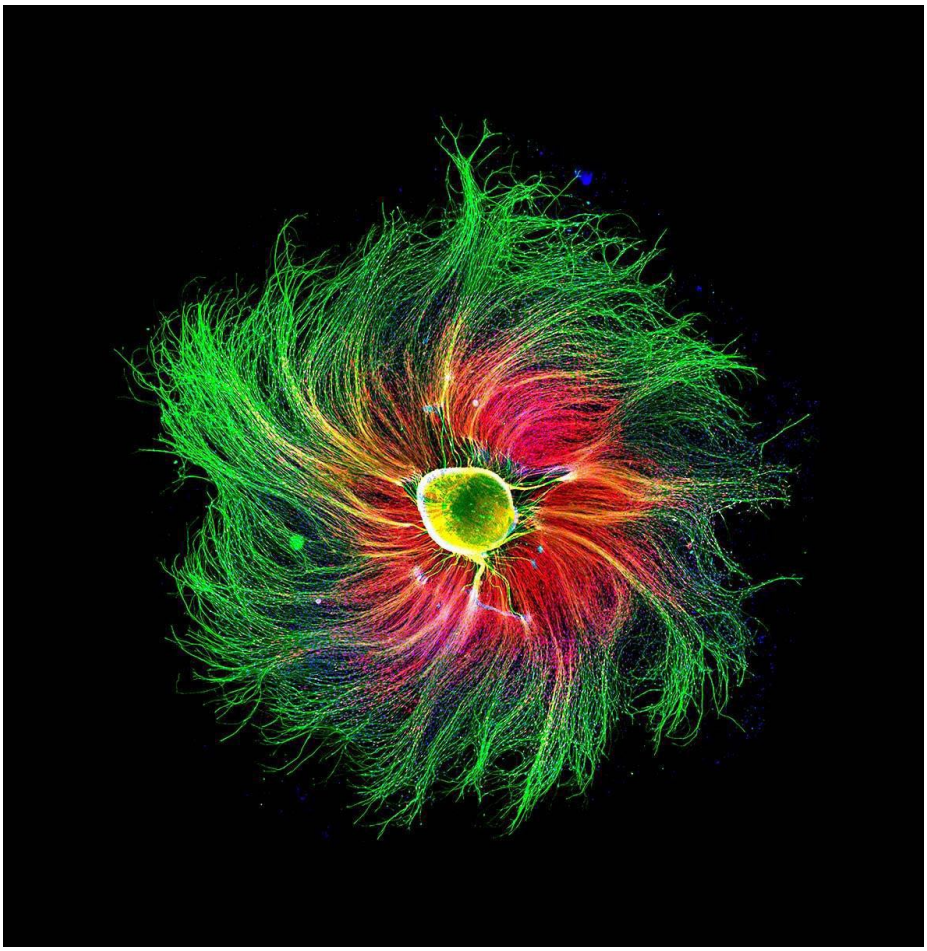
This thesis looks at neuromodulation therapies, such as spinal cord stimulation (SCS) considered alongside other invasive, minimally invasive such as radiofrequency, and non-invasive neuromodulation therapies, such as peripheral nerve stimulation, deep brain and motor cortex stimulation, and non-invasive treatments which include transcutaneous electrical nerve stimulation.

SCS methods with differing electrical variables compared to traditional SCS have been agreed upon. In theory, placebo-controlled trials should be possible for methods which avoid paraesthesias (subperception SCS as high frequency), however, few have been carried out to date. The quality of evidence to support SCS as being superior to conventional medical management or reoperation for failed back surgery syndrome is moderate to low, and evidence to support the advantage of traditional SCS over sham stimulation or between various SCS modalities is conflicting (SCS Implant Figure 4).

Another minimally invasive neuromodulation interventional pain management technique is PRF, which is commonly used for treating chronic neuropathic pain. There are several studies that evaluated and proved the efficacy of PRF in treating different pain conditions. PRF was developed to reduce or even avoid neuronal damage, making it potentially suitable for patients with neuropathic pain. [9]



Dorsal root ganglion microscope image

A computer modeling study based on data obtained in ex vivo tissue showed that PRF does, however, produce heat bursts with temperature peaks that may induce neurodestruction. Furthermore, PRF produces strong electromagnetic fields that may be capable of disrupting the neuronal membranes, thereby interfering with the generation of action potentials and ectopic firing. [10]

In radicular pain, ectopic discharges can be generated at different locations of the nervous system. On the basis of a selected experimental lesion model, [11] the primary lesion (L5 spinal nerve section) resulted in generation of discharges originating not only at the site of nerve injury but also in the somata of cell bodies of the axotomized DRG neurons. [12]

The rationale of performing a PRF treatment adjacent to the DRG at the involved level is based on conventional RF treatment with the reduction of nociceptive input of the primary sensory neuron by coagulation and Wallerian degeneration of a small part of the DRG. [13]

Reducing the nociceptive input at the concerned level is not enough, probably due to the spreading of the afferent nociceptive signal over different adjacent levels. Therefore, performing (pulsed) RF treatment at multiple adjacent levels might be required to improve efficacy.

Peripheral nerve stimulation technologies have developed at a fast pace, becoming less invasive and many even positioned using percutaneous procedures. The quality of evidence regarding peripheral nerve stimulation as an effective method to contrast neuropathic pain in an extremity is low to moderate, it is low regarding effectiveness for back pain with or

without leg pain and conflicting regarding prevention of migraines. Although not approved for chronic pain treatment in many European countries and the USA, motor cortex stimulation and deep brain stimulation are used for refractory cases. In general, brain stimulation has not produced satisfactorily clear evidence, with most sham-controlled trials yielding negative findings.

Regarding non-invasive modalities, evidence quality to support the fact that repetitive transcranial magnetic stimulation does not offer significant relief for chronic pain in general is moderate, however, it is conflicting regarding treatment for neuropathic pain and headaches. As regards transcranial direct current stimulation, the quality of evidence is low in favour of chronic pain relief and becomes conflicting when considering a low-level effect against headaches and neuropathic pain. There is low-quality evidence supporting transcutaneous electrical nerve stimulation as proving more beneficial than sham or absence of treatment for neuropathic pain, however, it becomes contradictory when applied to non-neuropathic pain.

Further research is needed to better determine the short-term and long-term efficacy of neuromodulation modalities in general and their impact on reducing the use of health-care, and to better define selection criteria and treatment variables.

Figure 4 Spinal Cord Stimulation Implant

The aim of this research project is to understand the mechanism behind different neuromodulation therapy for treating chronic pain, focusing on exploring the principles and processes involved in these therapies, including clinical outcomes of common pain disorders (knee osteoarthritis and neuropathic painful conditions).

Specifically, the research will delve into the mechanism and clinical data of dorsal root ganglion stimulation to relieve untreatable post-thoracotomy chronic pain. By examining the mechanisms underlying these therapies, the aim is to enhance our understanding of their effectiveness and identify potential areas for improvement in the treatment of chronic pain.

CHAPTER I

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Dorsal Root Ganglion Stimulation for Chronic Postoperative Pain Following Thoracic Surgery: A Pilot Study

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ABSTRACT

Objectives: Post-thoracotomy pain syndrome (PTPS) is defined as persistent pain following a thoracotomy and has an incidence of 21–61%. Dorsal root ganglion stimulation (DRG-S) is a form of neuromodulation that modulates pain signal transmission to the spinal cord. The aims of this study were to investigate the efficacy of DRG-S for the management of PTPS and to assess the role of thoracic paravertebral blocks (t-PVB) as a tool for prediction of success of DRG-S.

Materials and Methods: In this prospective study, we included all patients undergoing thoracic surgery, with PTPS not responding to pharmacotherapy and treated with DRG-S from September 2018 to February 2019. t-PVB followed by a percutaneous DRG-S trial was performed on all patients. Pain intensity was assessed through a numeric rating scale (NRS) and Douleur Neuropathique en 4 Questions (DN4) at baseline, post-trial, at 14 days, 90 days, and at one year after DRG-S implantation. Data summarized as continuous variables were expressed as means and standard deviations (SDs), and categorical variables were expressed as raw numbers and percentages.

Results: Four patients out of 51 who underwent thoracic surgery at our institution surveyed were included (mean age ± SD, 56 ± 16 years old). Mean NRS and DN4 were, respectively, 7.2 ± 0.96 SD and 8.2 ± 0.5 SD at baseline, 2.5 ± 0.6 SD and 3.2 ± 0.5 SD after t-PVB, 2.2 ± 0.5 SD and 2.2 ± 0.5 SD at 14 days, 90 days, and at one year after DRG-S implantation. No complications or side effects were reported.

Conclusions: Our preliminary results show that DRG-S is an effective therapy for PTPS after thoracic surgery. In addition, thoracic paravertebral blocks performed prior to DRG-S correlated with a positive outcome with treatment.

Keywords: Chronic pain, nerve block, postoperative pain, spinal ganglia, thoracic surgery

Conflict of Interest: Dr. Schatman serves as a research consultant to Modoscript. Dr. Schatman serves as a research consultant to Firstox. Federica Vernuccio serves as a speaker for Guerbet. The other authors declare that they have no conflict of interests for this study.

INTRODUCTION

Post-thoracotomy pain syndrome (PTPS) is defined by the International Association for the Study of Pain (IASP) as "pain that recurs or persists along a thoracotomy incision at least two months following the surgical procedure" (1). Primary causes of PTPS include acute postoperative pain, surgery-related nerve damage, and neuroplasticity changes in the central nervous system (2–5).

The management of PTPS is challenging and several modalities may prevent its development including epidural analgesia, preemptive gabapentinoids, or intravenous ketamine (6,7).The current standard-of-care treatment for PTPS includes antineuropathic drugs and lidocaine or 8% capsaicin patches (8,9). However, pharmacotherapy may be insufficient, thereby necessitating interventional pain procedures, ranging from nerve blocks to nerve ablation and neuromodulation (10–12). Among these, thoracic paravertebral blocks (t-PVB), involving the injection of a local anesthetic adjacent to the thoracic vertebra close to site at which

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the spinal nerves emerge from the intervertebral foramina, has proven to be affective for the management of PTPS. Mechanistically, t-PVB results in an ipsilateral somatic and sympathetic nerve blockade of multiple contiguous thoracic dermatomes above and below the site of injection (13).

Dorsal root ganglion stimulation (DRG-S) is a form of neuromodulation targeting the DRG through the prevention of pain signals being transmitted to the brain, inhibiting DRG hyperexcitability, and ectopic firing; these two processes are considered the primary causes of central sensitization and allodynia (14–16). DRG-S, like spinal cord stimulation, traditionally requires the patient to go through a trial period (usually three weeks) with a temporary external device to evaluate the effectiveness and identify potential adverse side effects. However, globally the trial period is becoming less common due to pharmacoeconomic reasons and greater knowledge of the mechanisms that have led to improved prediction of implant success (17).

Our research hypothesis is that the identification of the correct sensory level and testing patient responsiveness to the possible impact of DRG-S on the pain pathway through a single injection of t-PVB at the corresponding sensory level prior to the DRG-S-trial period may achieve positive results in terms of control of PTPS. However, to the best of our knowledge, no prior studies have investigated the role of t-PVB supporting the responsiveness to DRG-S in the management of PTPS following thoracic surgery. Therefore, the primary objective of this study was to investigate the efficacy of DRG-S for the management of neuropathic PTPS. Second, we investigated the susceptibility of patients to DRG-S treatment, based on the identification of the correct metamere through t-PVB.

MATERIAL AND METHODS

Study Cohort

This prospective study was approved by *Ospedale dei Colli*, *Naples* ethics committee. We included all patients undergoing surgery at the Thoracic Surgery Center of *Ospedale dei Colli* with PTPS with neuropathic features and treated with DRG-S at our pain therapy unit from September 2018 to February 2019. Of the 89 patients operated at our Thoracic Surgery Center, 51 were joined through a phone call at one-year telephone follow-up. The remaining patients were either deceased or did not respond to our calls.

Patients were then excluded if they lacked PTPS (n = 43), or if neuropathic pain regressed subsequent to standard-of-care medical therapy (n = 4) based combination treatment including physiotherapy, psychology, neuropathic pain medications, and interventional procedures.

The final study population included four patients with PTPS, not responsive to first line treatments, who were assigned to DRG-S (n = 4) (Abbott, Chicago, IL, USA) due to inadequate analgesia. Patients were informed about the study and consented to participate. We collected demographics and clinical information, including age, gender, and body mass index (BMI).

Pain Assessment and Treatment

The diagnosis of PTPS was made by a pain physician based on presence of persistent neuropathic pain for more than two months confirmed on physical examination with testing, including responses to fine touch and Von Frey stimuli. During the physical examination, pain characteristics were analyzed, including its intensity using the Numeric Rating Scale (NRS), and probability of being neuropathic through Douleur Neuropathique en 4 Questions (DN4) (18).

NRS and DN4 were assessed prior to the t-PVB procedure and 30 minutes following its completion. t-PVB were performed using an ultrasound linear probe (Sonosite, Amsterdam, The Netherlands) with a longitudinal oblique, "in-plane" technique at all sensory levels affected by pain. Six milliliters of levobupivacaine 0.5 mg/mL were administered to each sensory level treated (Fig. 1). A 100 mm and 21 G needle were used (Pajunk, Geisingen, Germany). Patients were considered responsive to t-PVB if their NRS score decreased by at least 50%.

After determining if the patients responded to t-PVB, a percutaneous staged DRG-S trial was performed (i.e., leads were placed, then tunneled, connected to adaptors and the adaptors were run outside of the body), and the leads were connected to an external pulse generator. All procedures were performed by two pain physicians (G.G. for t-PVB; A.P. for DRG-S), both with training and 20 years of expertise in pain management using interventional techniques.

A baseline NRS and DN4 was documented prior to the first stage trial of DRG-S and at 14 days postlead placement. If the

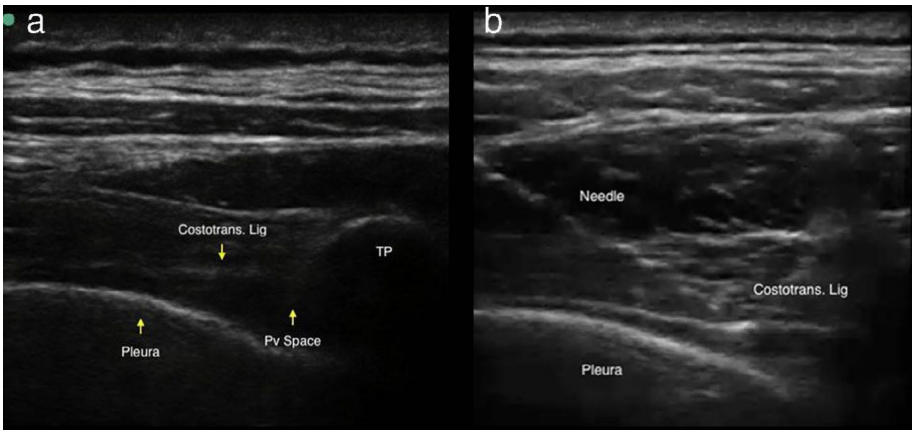

Figure 1. a. Ultrasound performed with a linear probe with longitudinal oblique, "in plane" technique demonstrating the paravertebral space. b. Demonstration of needle trajectory for t-PVB. [Color figure can be viewed at wileyonlinelibrary.com]

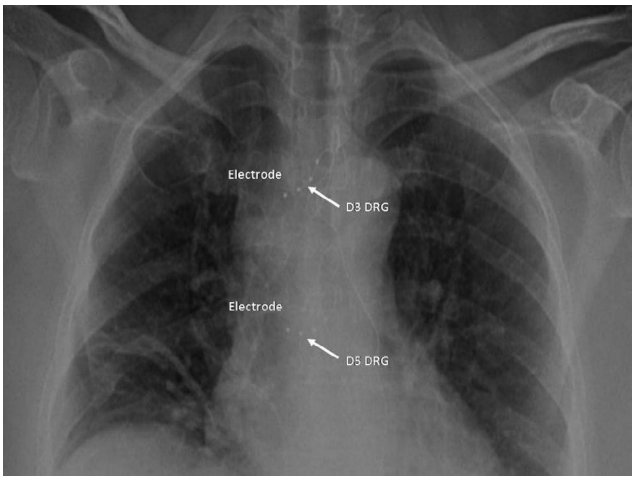

Figure 2. Thoracic radiograph with anterior–posterior view demonstrating DRG-S lead placement at the third and fifth dorsal (thoracic) levels.

treatment was effective (i.e., more than 50% of pain relief as measured by the NRS and DN4), a permanent system was implanted and a thoracic radiograph was performed routinely postimplantation (Fig. 2). All four patients had >50% relief with both the t-PVB and DRG-S trial and proceeded to implantation of the implantable pulse generator. NRS and DN4 were then evaluated 90 days postimplantation. The patients were treated according to standard operating procedures and followed-up telephonically one year following DRG-S implantation in February 2020.

Statistical Analysis

Descriptive statistics were used for sociodemographic data and pain characteristics using the NRS and DN4. Data summarized as continuous variables were expressed as means and standard deviations (SDs), and categorical variables were expressed as raw numbers and percentages.

RESULTS

Study Cohort

The incidence of PTPS following thoracic surgery at our institution was 15.6% (8 of 51 patients contacted telephonically), with 7.8% (4 of 51) treated with DRG-S. Four patients qualified for this study (mean age 56 ± 15.8 SD, years old; range, 37–70 years old) who were implanted with DRG-S, included two males and two females who had a mean BMI of 27 ± 3 SD; range 24–30 BMI (Table 1).

Pain Assessment and Treatment

At the time of the physical examination, all patients (4 of 4, 100%) presented with PTPS with moderate–severe pain, with a mean pain score of 7.2 ± 0.96 SD, range 6–8 using the NRS and 8.2 ± 0.5 SD, range 8–9 using the DN4 questionnaire (Table 1).

All four patients responded to t-PVB, with improvements in NRS (mean score 2.5 ± 0.6 SD, range 2–3 NRS) and DN4 (mean DN4 score 3.2 ± 0.5 SD, range 3–4 DN4) for several hours following the block.

All four patients implanted with DRG-S reported pain relief as measured on the NRS (mean score 2.2 ± 0.5 SD, range 2–3 NRS) and on the DN4 (mean score 2.2 ± 0.5 SD, range 2–3 DN4) scores, with maintained improvements at 14 days, 90 days, and one year postimplantation (Figs. 3 and 4). No complications or side effects were reported (0 of 4, 0%) for either t-PVB or DRG-S trials and definitive implants. All who experienced pain relief following t-PVB were responsive to the definitive DRG-S implantation (Table 1).

DISCUSSION

To our knowledge, this is the first prospective collection of data regarding the effectiveness and safety of DRG-S for the treatment of PTPS (15,19). Antony and colleagues' review provided a solid rationale for the use of the DRG in PTPS following thoracic surgery (20). Due to its location within the spinal intervertebral foramina, the DRG is anatomically accessible percutaneously and has been a target for therapies (21,22). Treatments such as pulsed radiofrequency of the DRG may be a solution for treating chronic pain and has generated mixed results (23,24).

The electrical field produced by the DRG-S leads can directly modulate nociceptive neural traffic at the T-junction of the primary sensory neuron and reduce DRG hyperexcitability and ectopic firing (14,25). In our study, DRG-S proved to be safe and effective in the treatment of PTPS.

Other pain interventional techniques such as radiofrequency or cryoanalgesia have resulted in complete relief lasting up to six months (26,27).

Table 1. Clinical Characteristics of the Study Population and Therapeutic Strategy.

	Patient 1	Patient 2	Patient 3	Patient 4
Age	68	49	37	70
Body mass index	29	26	24	30
Gender	F	F	M	M
Surgery	Lobectomy	Thymectomy	Lobectomy	Costal chondrosarcoma
Therapy, before DRG-S	Pregabalin 150 BDS Carbamazepine 400 mg BDS Ketorolac 30 mg TDS Oxycodone 30 mg BDS	Gabapentin 400 mg TDS Fentanyl patch 50 mcg/h	Pregabalin 150 BDS Tapentadol 150 mg BDS	Gabapentin 300 mg TDS Oxycodone 20 mg BDS Diclofenac 75 mg BDS
Therapy, after DRG-S	Pregabalin 150 BDS	Gabapentin 200 mg TDS	None	None
t-PVB level	Left T6, T7, and T8	Left T6, T7, and T8	Left T4, T5, and T6	Right T3, T4, and T5
DRG-S implant level	Left T6 and T8	Left T6 and T8	Left T4 and T6	Right T3 and T5

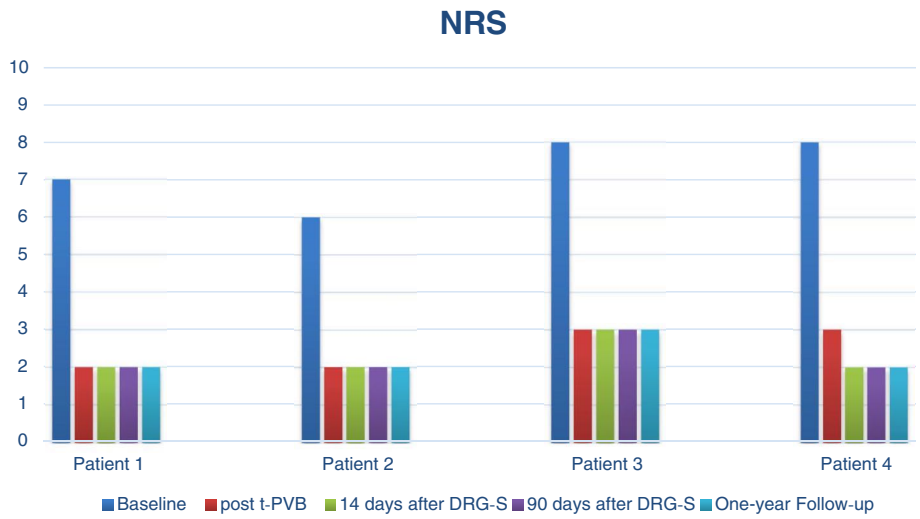

Figure 3. NRS at baseline and follow-ups per each patient. [Color figure can be viewed at wileyonlinelibrary.com]

Investigation of spinal cord stimulation use for PTPS has been limited to case studies (12). Our four patients who improved with DRG-S also experienced concordant improvements with a preprocedure t-PVB. While our four patients experienced neuropathic pain following thoracic surgery, Steegers et al. (28) highlighted that approximately 50% of PTPS experience neuropathic pain.

An interesting finding of our study is that t-PVB preliminarily appears to be an effective tool prior to DRG-S trials. The decision to perform t-PVB to test the patients' DRG-S responsiveness was suggested by the anatomic proximity of DRG to the superior costotransverse ligaments (28). However, according to the descriptive anatomy, while the paravertebral space itself does not include the DRG, there is communication between the PVS and the DRG (29,30). This contiguous space allows for the spread of local anesthetic to multiple vertebral levels, and thus it is not specific enough to use as a diagnostic measure for DRG-S (13,31).

Given the relative risks and costs of performing a t-PVB, consideration can be given for its utility as a tool to rule out patients who may not benefit from DRG-S. This small prospective series highlights the potential benefit of the DRG-S for the treatment of PTPS. Limitations of this study are the small sample size, potential for selection bias, and lack a control group. Our patient cohort experienced neuropathic pain following surgery and it has been noted that up to 50% of patients suffering from PTPS may be solely nociceptive in nature (32). Thus, this subgroup of PTPS patients may not necessarily be reflective of a true PTPS population. A larger prospective multicenter study is warranted to demonstrate the safety and efficacy of DRG-S for the treatment for PTSP. Additionally, the role of t-PVB as a screening tool requires further study to determine whether it may be a useful mean to determine success of DRG-S in the treatment of PTPS.

Our data demonstrate the potential for efficacy of DRG-S in the management of PTPS. In addition, we provide a degree of insight into thoracic paravertebral block responsiveness as a predictor of

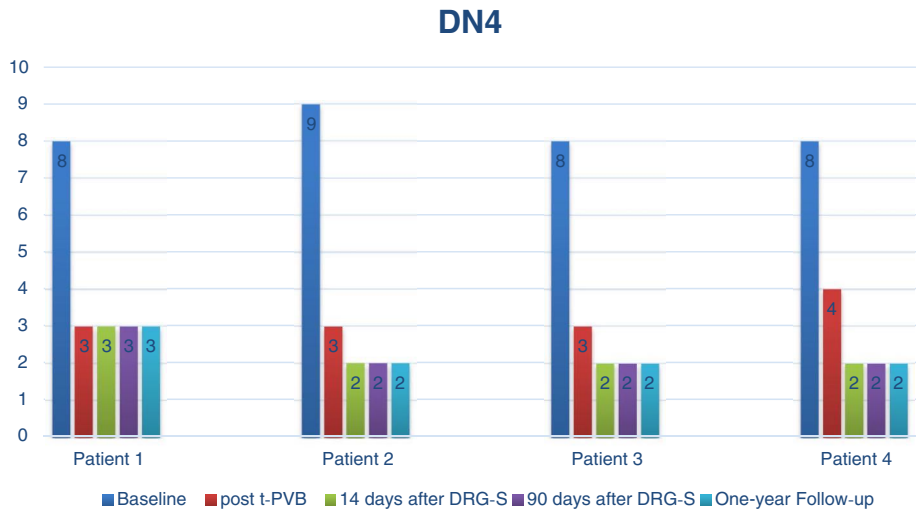

Figure 4. DN4 at baseline and follow-ups per each patient. [Color figure can be viewed at wileyonlinelibrary.com]

DRG-S effectiveness. The response of a targeted thoracic paravertebral block correlated with success of the DRG-S in these patients, although the relevance of this response is yet to be fully determined. Furthermore, the positive outcome of a targeted procedure can help guide the appropriate referral and selection of patients with chronic pain for DRG-S.

Authorship Statement

Giuliano Lo Bianco, Maria Teresa Di Dato, and Dario Tammaro performed the literature review. Giuliano Lo Bianco, Marco Rispoli, Alfonso Papa, and Giuseppe Gazzerro collected the data. Giuliano Lo Bianco and Federica Vernuccio performed the statistical analysis. Giuliano Lo Bianco, Federica Vernuccio, and Alfonso Papa drafted the manuscript. Michael Schatman and Giuseppe Gazzerro reviewed the manuscript. All authors approved the final version of the manuscript.

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COMMENT

The authors present a well written manuscript detailing mid-term outcomes of DRGs for a novel, off-label indication.

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CHAPTER II

Journal of Pain Research

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ORIGINAL RESEARCH

Genicular Nerve Pulsed Dose Radiofrequency (PDRF) Compared to Intra-Articular and Genicular Nerve PDRF in Knee Osteoarthritis Pain: A Propensity Score-Matched Analysis

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Background: Chronic knee osteoarthritic (OA) pain is a common and debilitating complaint in elderly patients. Despite numerous pharmaceutical options, the majority of patients still experience long-term pain. Genicular nerve (GN) radiofrequency has become increasingly popular as a treatment for knee pain. This retrospective study aimed to evaluate the effects of pulse dose radiofrequency (PDRF) in patients with chronic knee OA pain.

Patients and Methods: Propensity score matching analysis was performed in a retrospective cohort of 78 patients with moderate-severe knee OA pain unresponsive to conservative treatment who underwent PDRF GN or intra-articular (IA) and PDRF GN. Pain relief was measured using the numeric rating scale (NRS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Patient Global Impression of Change (PGIC) at 3 and 6 months post-intervention.

Results: A significant reduction in NRS scores was reported at 3 ($p<0.001$) and 6 months ($p<0.001$) after PDRF in both groups. NRS was lower in PDRF IA + GN than PDRF GN ($p<0.0001$). WOMAC pain was significantly reduced at 3 months in PDRF IA + GN group (baseline: 10.12±3.14, 3 months: 6.25±2.44, $p=0.0001$). WOMAC stiffness and function were improved only at 3 months in PDRF IA + GN compared to baseline ($p=0.007$ and $p=0.006$, respectively). A longer period of pain relief was reported after PDRF IA + GN (6.75±2.42 months) compared to PDRF GN (4.31±2.85 months, $p<0.001$) in association with higher PGIC scores.

Conclusion: This is the first study that compared two different PDRF techniques. PDRF GN and PDRF IA + GN were both effective in reducing pain at 3 and 6 months follow-up. However, only PDRF IA + GN was able to improve WOMAC scores at 3 months after the treatment with a longer period of efficacy compared to PDRF GN alone.

Keywords: knee pain, pulse dose radiofrequency; PDRF, radiofrequency; genicular nerve, osteoarthritis, chronic pain, WOMAC, interventional pain management

Introduction

Symptomatic knee osteoarthritis (OA) is very common among older people.[1] Its prevalence in subjects over 60 years-old is 12.2% and is notably higher in women (14.9%) than in men (8.7%). It increases with age, obesity and mechanical stress and leads to considerable social costs.[2] Common causes of OA include a disruption of homeostatic state of balanced anabolism and catabolism of the cartilage

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extracellular matrix with a shift toward a catabolic environment. This eventually leads to macroscopic hyaline cartilage degeneration and synovial overgrowth associated with inflammatory changes and bony hypertrophy (osteophyte formation). According to the OARSI guidelines, the first-line treatment of knee osteoarthritis includes non-pharmacological strategies (exercise programs, dietary weight management and education about OA) and secondly, topical or oral anti-inflammatory drugs, intra-articular hyaluronic acid and steroid injections.[3] Unfortunately, these therapies have demonstrated little effect in many patients, as well as undesirable side effects. Moreover, the resulting increase in opioid prescription has likely contributed to a dramatic increase in the number of accidental falls in the elderly with increased morbidity.[4] Arthroscopy or knee arthroplasty are often considered when other medical therapies fail to relieve symptoms.[5]

Pulsed dose radiofrequency (PDRF) is an evolution of conventional radiofrequency with less or no correlation with neural damage.[6] Considerable efficacy in reducing symptoms of knee OA has been established when this technique was applied to genicular[7] (GN) or intra-articular (IA) nerves.[8,9] In long-standing OA, it results in consistent improvement of reported pain, swelling, and stiffness. PRF creates a neuromodulatory effect, suppressing both excitatory C-fibers activation and the spread of pain impulse at the synaptic junction, in addition to a modulatory effect on pro-inflammatory cytokines.[10,11]

The purpose of this retrospective study was to evaluate the effects of PDRF applied to GN or to IA + GN in patients with OA knee pain refractory to conservative treatments. Propensity score matching was used to reduce patients' selection bias and to produce two groups that were comparable in terms of demographic profile and disease characteristics.

Methods

This is a single-center clinical cohort study based on a retrospective analysis of prospectively collected data on 78 consecutive patients with moderate-severe knee OA pain unresponsive to conservative treatment who underwent PDRF. The study was conducted at the Pain Unit of ICS Maugeri Hospital, Pavia, Italy, from January 2018 to December 2018. All participants signed a written informed consent. The study was approved by the hospital's Institutional Ethics Committee and was conducted in accordance with the Declaration of Helsinki. All patients were evaluated before PDRF with a knee x-ray and physical examination to ascertain their eligibility. The diagnosis and classification of knee osteoarthritis' severity were conducted through the Kellgren–Lawrence method.[12] Patients with knee pain unresponsive to conservative treatment (physiotherapy, oral analgesics) and intra-articular injection with steroids or hyaluronic acid were included in this study. Radicular pain (mainly L3-L4), pain post-total knee replacement, rheumatoid arthritis, complex regional pain syndrome or history of intra-articular injection with steroid or hyaluronic acid within the previous 3 months were considered as exclusion criteria. All enrolled patients underwent a successful diagnostic genicular nerve block with local anesthetic (Lidocaine 1%, 2 mL) prior to PDRF.[13]

Patients

Patients were assigned to PDRF GN or PDRF IA + GN according to physicians' preference and experience with the technique used.

An outcome investigation was performed in both groups at 3 and 6 months following the procedures. Pain intensity (NRS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Patient Global Impression of Change (PGIC) scores were obtained before PDRF and at each follow-up.

Technique

PDRF GN and PDRF IA + GN were performed with a 22G × 100 mm needle (NeuroTherm™, Medipoint GmbH, Hamburg, Germany) with 10 mm active tip. Fluoroscopic confirmation of the needle position was used for PDRF IA, while both fluoroscopic and ultrasound assessment of topographical localization of superior lateral, superior medial and inferior medial genicular nerve branches were used for PDRF GN. The superior medial genicular nerve curves around the femoral shaft pass on the femoral medial epicondyle to descend 1 cm anterior to the adductor tubercle, where the needle was placed. The inferior medial genicular nerve is situated around the tibial medial epicondyle and was found at the tibial insertion of the medial collateral ligament. The superior lateral genicular nerve was found at the junction between the femoral shaft and the femoral lateral epicondyle. Nerve localization was confirmed with stimulation at ≤0.4mV, 50 Hz. PDRF was performed using the following parameters: 1200 pulses at high voltage (45 V), with 20 ms duration followed by 480 ms silent phases.

Statistical Analyses

Propensity score matching analysis was used with the nearest matching algorithm (1:1 ratio, caliper value= 0.2). Patients' characteristics selected for the matching analysis were: age, body mass index (BMI), basal NRS, basal WOMAC total score and Kellgren–Laurence knee OA grade.

Comparisons between the two groups were carried out with a Mann–Whitney test (*U*-test), after evaluating the normality of the distribution with the Kolmogorov–Smirnov test.

The differences of the quantitative variables at different time points were analyzed with ANOVA for repeated measures with Bonferroni adjustment for multiple comparisons. A p-value <0.05 was considered statistically significant. Data are expressed as mean ±SD. STATA V.15 (STATA Corp., Texas, USA) was used for the analyses.

Results

112 patients with knee OA pain were screened and 34 did not meet the inclusion criteria. The reason for exclusion included: histories of steroid or hyaluronic acid intra-articular injections within 3 months (13 patients), L3-L4 radiculopathy (7 patients), pain following total knee replacement (7 patients), rheumatoid arthritis (6 patients) and complex regional pain syndrome type 1 (1 patient). Therefore, 78 patients met the inclusion criteria. Propensity score matching analysis resulted in 27 PDRF GN and 27 PDRF IA + GN matched cases, which comprise the study population used for comparisons. Age, BMI, basal NRS, basal WOMAC total score and radiographic disease severity were compared within the matched PDRF GN and PDRF IA + GN groups to evaluate the accuracy of the matching process. No statistically significant difference was observed in any of the above parameters, as demonstrated in Table 1. Female patients accounted for the majority of the sample (72%).

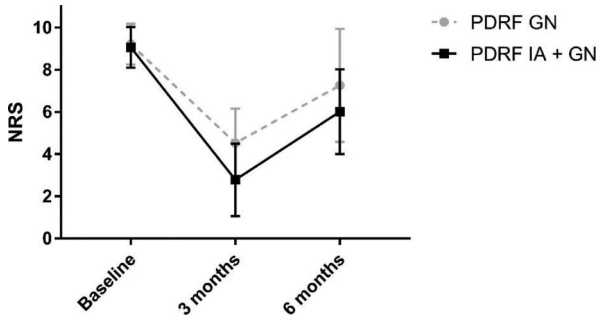

Figure 1 Pain intensity measured with a numerical rating scale (NRS) at 3 and 6 months after PDRF GN or PDRF IA + GN. The significant reduction observed at 3 months (p<0.0001) was maintained, although weakened, at 6 months (p=0.006).

Table 1 Population Variables. Comparison of Clinical Characteristic Between the PDRF GN and PDRF IA + GN Groups after the matching process

Population Variables	PDRF GN (n=27)	PDRF IA + GN (n=27)	p
Age	75.3±7.9	76.8±9.45	0.44
BMI	27.1±5.6	26.5±4.9	0.61
NRS basal	9.2±0.97	9.1± 0.96	0.73
WOMAC total score (basal)	71.8±14.6	72.27± 13.5	0.91
Radiographic knee OA severity			
Grade 2	8	7	0.76
Grade 3	14	13	0.59
Grade 4	5	7	0.51

A significant reduction in NRS score was reported in both groups at 3 months (p<0.001) and 6 months (p<0.001) compared to the baseline (PDRF GN: baseline NRS 9.2±0.97, 3 months NRS 4.5±1.63, 6 months NRS 7.2±2.68; PDRF IA + GN: baseline NRS 9.1±0.96, 3 months NRS 2.7±1.71, 6 months NRS 6±2.0). At 3 months, the PDRF IA + GN group's NRS was significantly lower than PDRF GN group's NRS (p<0.0001). At 6 months, the same results were confirmed although weakened (p=0.006) (Figure 1).

No change in WOMAC pain was found in the PDRF GN group at 3 months (p=0.40) and 6 months after the treatment (p=0.52). Otherwise, WOMAC pain was significantly reduced at 3 months in the PDRF IA + GN group (WOMAC pain baseline 10.12±3.14, WOMAC pain three months 6.25±2.44, p=0.0001). Moreover, WOMAC pain was reduced in PDRF IA + GN group compared to PDRF GN at 3 months (p=0.005) (Figure 2).

WOMAC stiffness was improved only at 3 months in the PDRF IA + GN group compared to baseline (WOMAC stiffness baseline 4.96±1.83, WOMAC stiffness three months 3.71±1.23, p=0.007) and no changes were found at different time points for PDRF GN. WOMAC stiffness was reduced in PDRF IA + GN group compared to PDRF GN only at 3 months (p=0.02) (Figure 2).

WOMAC function was improved only in the PDRF IA + GN group at 3 months after the treatment (WOMAC function baseline 55.08±14.52, WOMAC function three months 41.04±11.70, p=0.0006). No differences in WOMAC function were found between the two treatments at different time points (Figure 2). The WOMAC total score was significantly improved only in the PDRF IA + GN group at 3 months (p<0.001).

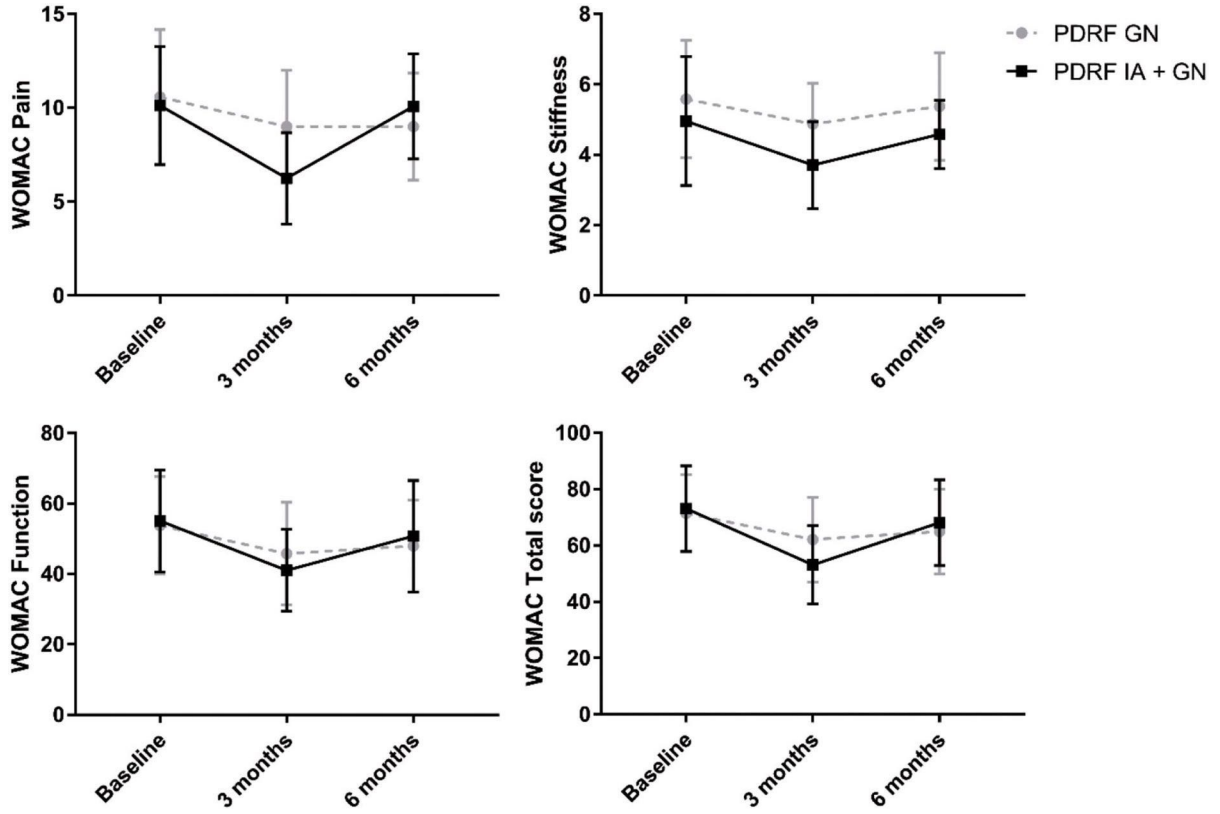

Figure 2 Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)showed an improvement in pain, stiffness, and function at 3 months post-procedure in the PDRF IA + GN group. WOMAC pain and WOMAC stiffness were significantly improved in the PDRF IA + GN group compared to PDRF GN (see the text). No differences were found for WOMAC function. The WOMAC total score was significantly improved only in the PDRF IA + GN group at 3 months.

Patients reported a longer period of pain relief following PDRF IA + GN (6.75±2.42 months) compared to PDRF GN (4.31±2.85 months, $p<0.001$). PGIC score was also better in PDRF IA + GN (PDRF GN 1.8±0.93 vs PDRF IA + GN 2.5±0.81, $p=0.005$).

Ten patients suffering from knee OA pain mainly located at the femoropatellar joint and confirmed by radiological degenerative findings did not experience any significant pain relief following PDRF. No patients developed significant complications after PDRF during the follow-up period.

Discussion

This study compares the efficacy of PDRF GN versus PDRF IA + GN in patients with moderate-severe knee OA pain unresponsive to conservative treatment. Pain intensity and knee function were analyzed at 1 and 3 months postprocedure follow-up.

PDRF has no neurodestructive effects since it maintains tissue temperature under 42°C, which is below the irreversible tissue damage threshold.[14] However, histological studies demonstrated ultrastructural changes in the C and Aδ nociceptive fibers after PDRF.[15,16]

On the contrary, intra-articular application of PDRF reduces the response of C fiber along with a reduction of the pro-inflammatory cytokines such as interleukin-1β and interleukin-6.[17] As suggested by Sluijter et al, the therapeutic effect of PDRF IA is related to the action of electric fields on immune cells. In fact, in joints with an "open" geometry such as the knee the deflection of the current by bony surfaces forcing the electric filed to remain inside the joint space is very limited.[11]

Serdar and colleagues investigated the use of ultrasound-guided PDRF GN and demonstrated a 50% pain reduction after 12 weeks with an improvement of WOMAC scores.[7] Similarly, Masala et al investigated the effectiveness of intra-articular knee PDRF in patients with chronic knee pain unresponsive to conservative therapies and reported an improvement in pain intensity and WOMAC up to 1 year after the procedure.[8] El-Hakeim

et al recently reported in a randomized controlled trial that genicular nerve radiofrequency is not only effective for pain reduction and knee function improvement, but is superior to conventional medical therapy.[18]

Our data addressed the results of two different PDRF procedures at 3 and 6 months follow-up. PDRF GN and PDRF IA + GN were both able to significantly reduce NRS scores at 3 months ($p<0.001$) and 6 months ($p<0.001$) compared to the baseline. WOMAC pain, WOMAC function, WOMAC stiffness and WOMAC total score were significantly improved only in the PDRF IA + GN group at 3 months following the treatment. Moreover, the PDRF IA + GN group demonstrated a better outcome in terms of pain reduction and WOMAC at 3 months compared to the PDRF GN group. The PDRF IA + GN group had a longer period of pain relief and better patient global impression of change at 6 months following treatment compared to the group receiving PDRF GN alone.

This is the first study that describes the association of the two techniques, although further investigations through randomized controlled trials are needed to confirm our findings.

A possible explanation for the increased efficacy of PDRF IA + GN in our patients could be related to the increased electromagnetic field that can act on capsular and genicular nerves, both of which are involved in knee pain nociception.[19] Moreover, the total amount of energy delivered to knees' anatomical structures with PDRF IA + GN is greater than PDRF GN as a monotherapy. As recently published, a bipolar PDRF IA seems to be more advantageous in reducing chronic knee pain and functional recovery compared with the unipolar approach.[9] Eyigor et al reported knee pain reduction but unmodified functional affects (no change in WOMAC, 20 m walking and 6-min walk test) after PDRF IA.[20] Karaman and his group confirmed the global effect of knee pain reduction after PDRF IA but they did not investigate the impact of this technique on knee function.[21] An improvement in knee's function after PDRF associated with viscosupplementation was reported by Filippiadis et al.[17] Unfortunately, the authors analyzed the knee function and mobility only with patients' verbal reports without standardized scales. Based on these findings, it is reasonable to hypothesize that PDRF IA can reduce pain but it is probably not effective alone in improving knee function.

PDRF techniques are effective treatments for knee OA pain non-responsive to conservative measures. Nevertheless, a standardization of the technique is needed to allow definitive acceptance of PDRF as a treatment available for knee OA. Due to the complex origin of knee joint pain, it is generally recommended to perform a nerve block with local anesthetics before PDRF as confirmed by McCormick et al.[22] Surprisingly, a recently published study by the same authors showed that the anesthetic block did not improve the patient selection and the rate of radiofrequency treatment success.[23]

Although a propensity score matching analysis could be considered comparable to a randomized trial,[24] this study still has limitations. The first is the absence of true randomization between the two PDRF treatment groups. In our study, physicians were permitted to treat patients with PDRF GN or PDRF IA + GN at their own desire. This can cause a possible degree of investigator bias. However, the utilization of a propensity matching technique was useful to reduce the likelihood of such bias. Hence, if we consider Table 1, we can see that the two matched groups presented the same preoperative characteristics. Second, our Center did not program any short term follow-up (at 4 and 8 weeks) for these patients. Consequently, data on the immediate post-treatment period are lacking, and the retrospective nature of this study does not allow us to obtain the data needed to ascertain immediate post-treatment effects. Another possible limitation of this study is that the patients' outcomes have been evaluated only according to the WOMAC scale, the NRS and the PGIC scores. As reported in the literature, additional measures such as the Chair Stand test or the time 20 m walk test could have been used to even better characterize the functional improvement of these patients.[25]

This study is retrospective in nature. Accordingly, a future prospective investigation will be required to substantiate the superiority of one technique compared to the other. Nonetheless, the differences identified between the two groups seem to indicate an additive effect of PDRF IA+ GN compared to PDRF GN.

It is noteworthy that patients from both groups who experienced no benefit after PDRF treatment originally manifested pain mainly concentrated at the femoropatellar joint, and simultaneously demonstrated radiographic indicators of patellofemoral joint OA (osteophyte formation, joint space narrowing, subluxation or dislocation, bone destruction). Additional investigations are needed to better understand the ideal PDRF treatment for femoropatellar OA pain.

Conclusions

In the current study, PDRF GN and PDRF IA + GN were both able to significantly reduce the NRS score at 3 months and 6 months compared to baseline. WOMAC pain,

WOMAC function, and WOMAC stiffness were significantly improved only in the PDRF IA + GN group at 3 months following the treatment. The PDRF IA + GN group demonstrated a significant WOMAC improvement compared to the PDRF GN group. PDRF IA + GN had a longer period of efficacy compared to PDRF GN and a better PGIC. A prospective analysis is still needed to improve our understanding of the relative benefits of the two PDRF techniques.

Disclosure

Dr Michael E Schatman reports consultancy for Kaleo Pharma, Salix Pharmaceuticals, and Quest Diagnostics, outside the submitted work. Drs Laura Demartini reports personal fees from Boston Scientific, personal fees from Abbott, personal fees from Grunenthal Italia, outside the submitted work. The authors report no other conflicts of interest in this work.

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CHAPTER III

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ORIGINAL RESEARCH

Intraarticular STP Radiofrequency for Painful Osteoarthritis in the Knee: A Retrospective Single Center Analysis

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Objective: Osteoarthritis (OA) is the most common cause of chronic knee pain, often a debilitating condition that can cause a significant reduction in functional capacity. Radiofrequency is a form of neuromodulation that modulates pain signal transmission and has become progressively more common as a treatment for knee pain. This retrospective study aims to evaluate the efficacy of intraarticular radiofrequency in patients with chronic knee OA pain.

Materials and Methods: In this retrospective study, we included 129 patients undergoing intraarticular pulsed radiofrequency using the Poisson curve for energy distribution (Sluijter-Teixeira Poisson radiofrequency) (STP) from March 2018 to November 2019. Knee osteoarthritis severity was assessed prior to the procedure using the Lequesne Index, classifying patients into six groups based on level of severity. Pain intensity was assessed through a 10-cm visual analog scale (VAS), and level of patient satisfaction was assessed through a questionnaire.

Results: In the sample, pain reduction as measured by VAS compared to baseline prior to the procedure was statistically significant immediately following the procedure, at 30 days and at 90 days ($p<0.001$); this difference was less significant at 180 days ($p<0.005$). Efficacy in patients with moderate to severe disability was considerably greater than in patients with very severe to extremely severe disability. 57.36% reported that they were very satisfied, 29.46% satisfied, 9.3% neither satisfied nor dissatisfied, 2.33% dissatisfied, and 1.55% very dissatisfied.

Conclusion: Our results suggest that STP radiofrequency may be a safe and effective procedure for knee OA, able to significantly reduce VAS scores at 1 month and 3 months compared to baseline. Based on our results, a key factor to consider when treating knee OA with STP radiofrequency is that it is more effective among patients with a lower level of disability. Due to the retrospective observational study design, prospective longitudinal investigation is required to further support the recommendation of STP radiofrequency for knee OA.

Keywords: pulsed radiofrequency treatment, knee joint, osteoarthritis, knee, chronic pain

Introduction

Osteoarthritis (OA) is the most common cause of chronic knee pain; it is a debilitating condition that often causes a significant reduction in functional capacity. OA incidence is directly proportional to age, as well as presenting well-known risk factors such as gender, obesity, knee trauma, and family history.[1–9] Among the pathophysiological mechanisms underlying OA, there is an imbalance

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between the synthesis and degradation of chondrocytes. The key to increased degradation of the chondrocytes lies in alterations of the extracellular cartilage matrix (ECM), which supports the biomechanical properties of this tissue. It has been demonstrated that factors such as IL-1, TNF, IL-6 and IL-17 are involved in the degradation process, which is fundamental in the regulation of cartilage metalloproteinases.[10–12] An increase in these substances can interfere with cartilage repair mechanisms by inhibiting the response of insulin-like growth factor-1 and growth factor-β. Therefore, "anti-cytokine" therapies could potentially be successfully integrated into OA management.[13–15]

Standard treatments of OA include physical therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), tramadol, opioids, intraarticular hyaluronic acid or steroids, as well as genicular nerve ablation.[16–19] In more severe cases, surgical knee arthroplasty should be considered.[16] Pharmacotherapy cannot always guarantee benefits, especially in light of the high incidence of side effects. Furthermore, NSAIDs should not be administered for long periods of time due to increased risks of gastric bleeding,[20] adverse cardiovascular events,[21] and renal failure,[22] iatrogeneses that are not favorable in the treatment of a chronic pathology. Opioids are often used, but are associated with numerous side effects, especially in the elderly. Knee surgery is not always feasible and can cause complications, such as hematomas, infections and damage to the surrounding tissue.

Pulsed and/or continuous radiofrequency are neuromodulatory and/or neurolytic techniques that represent an alternative to these therapies.[23–26,39]

Radiofrequency does not involve the use of drugs; it is not particularly invasive and may be repeatable.[27,28] In 2011, in a double-blind randomized controlled trial, Choi et al proposed continuous radiofrequency treatment from 70 ° C to 80 ° C for 90–180 seconds on the superior lateral (SLGN), upper medial (SMGN) and lower medial (IMGN) genicular nerves (IMGN).[29] The medial retinacular nerve and the infrapatellar branch of the saphenous nerve were also identified as target points.[30] Similarly, in 2008, Sluijter and Teixeira reported on the successful intraarticular use of pulsed radiofrequency (PRF) using the Poisson curve for energy distribution (Sluijter-Teixeira Poisson radiofrequency) (STP).[31,32] More recently, we reported on both intraarticular and genicular nerve simultaneous use with a longer period of efficacy.[33,34] In that study, we carried out a retrospective analysis of patients treated with STP intra-articular knee radiofrequency over a 20-month period in a single center.

Methods

This investigation was a retrospective analysis of patient records of STP unipolar intra-articular knee radiofrequency from March 2018 to November 2019. The study was conducted at Ospedale dei Colli, Naples, and approved by the hospital's Institutional Ethics Committee. One hundred and seventy-two consecutive patients treated with this method were included. Data from 43 patients were discarded as they were incomplete or because follow-ups did not meet the minimal number of observations. For the remaining 129 patients, data were available regarding the Lequesne Index of severity for knee osteoarthritis prior to the procedure[35] and the intensity of pain using a 10-cm visual analog scale (VAS). Zero identifies no pain whatsoever and 10 identifies the most severe pain imaginable. VAS values were collected prior to the procedure (baseline), immediately following the procedure, and at 30-, 90- and 180-days post-procedure. Based on the Lequesne Index, patients were classified into six groups of differing severity of osteoarthritis.[36] Medication intake before and after the procedure was evaluated, followed by further assessment after each follow-up visit. A satisfaction questionnaire was administered to all patients at 180 days, on which patients could choose between "very satisfied", "satisfied", "neither satisfied nor dissatisfied", "dissatisfied" and "very dissatisfied". An informed-consent form for non-sensitive data utilization was signed prior the procedure. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki of 1996.

Technical Procedure

Under aseptic operating room conditions, a NeuroTherm NT-1100 lesion generator was used. Following cutaneous local anesthesia with 1% lidocaine, a PRF needle (SMK C-10, 22G, active tip 10 mm; NeuroTherm, Wilmington, MA) was inserted into the joint. Insertion was performed under fluoroscopic guidance in two planes for 56 patients and under in-plane sonographic guidance for the remaining 73 patients. A superior, medial or lateral retro-patellar approach was used to enable insertion of the radiofrequency cannula as close as possible to the painful area within the joint. A "tunnel-vision" fluoroscopic technique was also adopted, taking care to visualize the intra-articular space. The lateral view is necessary to determine the depth of the needle in the joint.

Statistical Analysis

A one-way analysis of variance (ANOVA) using Microsoft Excel was used to test the statistical power of pain

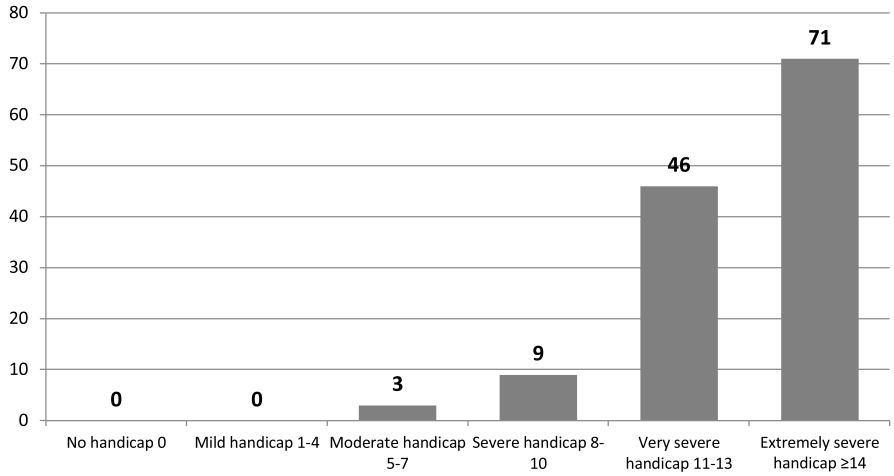

Figure 1 Patient distribution based on the Lequesne Index of severity for osteoarthritis.

reduction between the different timeframes (from baseline to 180 days after treatment). In addition, *t*-tests were performed using Microsoft Excel between every two consecutive timeframes. A Shapiro Wilk normality test was used to detect any departure from normality for each group. P-values were corrected using the Bonferroni method and the level of significance was set at 0.05. The bar plots and linear charts were prepared using Microsoft Excel.

Results

With respect to the demographic data, the 129 patients were divided as follows: 34 males, 95 females; mean age 74±10.7 years. Based on the results of the Lequesne Index of severity for osteoarthritis, the majority of patients were classified as having very severe disability in 46/129 subjects (35.66%) or extremely severe disability in 71/129 subjects (55.04%) (Figure 1). Pain reduction in terms of VAS was found to be statistically significant immediately post procedure, at 30 days and at 90 days ($p<0.001$); this difference was less significant at 180 days ($p<0.005$) (Figure 2). VAS values for first quartile, median and third quartile for all observed times are presented in Table 1. By assessing pain relief for the various disability classes obtained with the Lequesne classification, it is clear that efficacy in patients with moderate disability and severe disability was considerably more

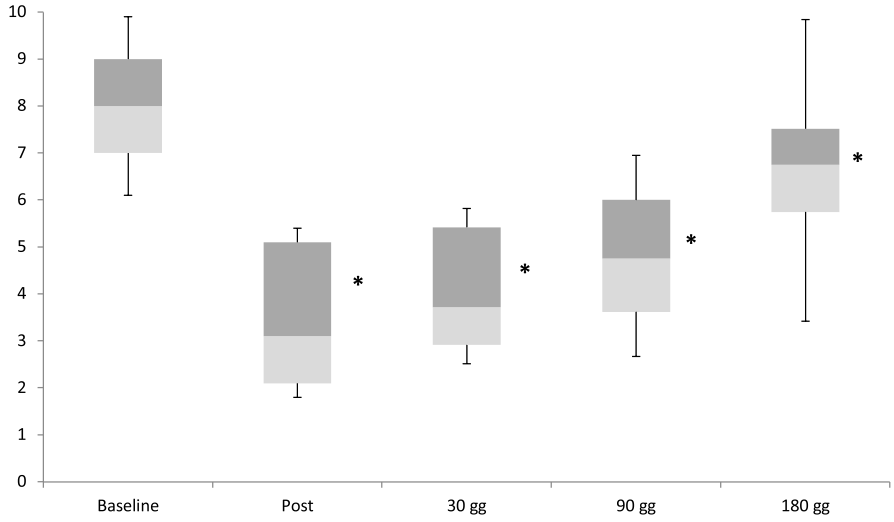

Figure 2 Box plot of median, first and third quartile of VAS values at different observation points.

Table 1 VAS Values of Median, First and Third Quartiles for Different Observation Points

	Baseline	After Procedure	30d	90d	180d
First quartile (min)	7	2	2.91	3.62	5.75
Median	8	3	3.72	4.75	6.75
Third quartile (max)	9	5	5.42	6	7.51

significant than in patients with very severe disability or extremely severe disability (Figure 3).

More specifically, 2 of 3 patients in the moderate Disability group, 7 of 8 in the severe Disability group, 31 of 45 in the very Severe Disability group, and 33 of 73 in the extremely severe Disability group reported greater than 50% pain relief.

None of the 3 patients in the Moderate Disability group, none of the 8 in the Severe Disability group, 6 of 45 in the Very Severe Disability group and 21 of 73 in the Extremely Severe Disability group reported less than 30% pain relief. No difference was found in pain relief between patients treated with fluoroscopic guidance compared to those treated with ultrasound guidance (Figure 4). Likewise, regarding the degree of satisfaction at 180 days, patients declared themselves very satisfied 74/129 (57.36%), satisfied 38/129 (29.46%), neither satisfied nor dissatisfied 12/129 (9.3%), dissatisfied 3/129 (2.33%) or very dissatisfied 2/129 (1.55%) (Figure 5). At least 118/129 patients (91.47%) opined that they would repeat the procedure if necessary. No major adverse events occurred, and only three patients experienced post-procedural pain, which, in each case lasted less than 24 hours.

Discussion

Our retrospective study arose from the need to evaluate our clinical experience originating from clinical data reported in the scientific literature by Sluijter et al,[30,31] and continued from an empirical evaluation of patient satisfaction data collected in our 2020 case series. Although the mechanism of action of PRF is not yet entirely clear, our data support the assertion of Schianchi et al, who postulated that intra-articular PRF may have a dual effect.[37] PRF is characterized by short bursts of energy application (10–20 milliseconds), between which were interspersed long silent phases (480 milliseconds), which contribute to maintaining tissue temperature below the irreversible tissue damage threshold of 42°C. This approach suppresses excitatory C-fiber activation and the spread of pain impulse at the synaptic junction, thus creating a neuromodulatory effect. In the STP mode, radiofrequency provides

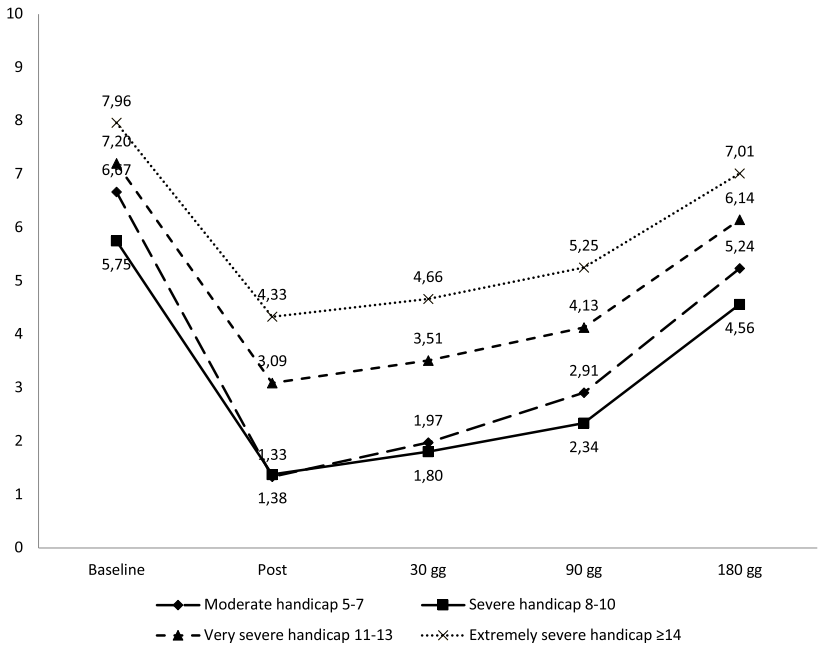

Figure 3 Pain relief related to the various disabled classes obtained using Lequesne classification.

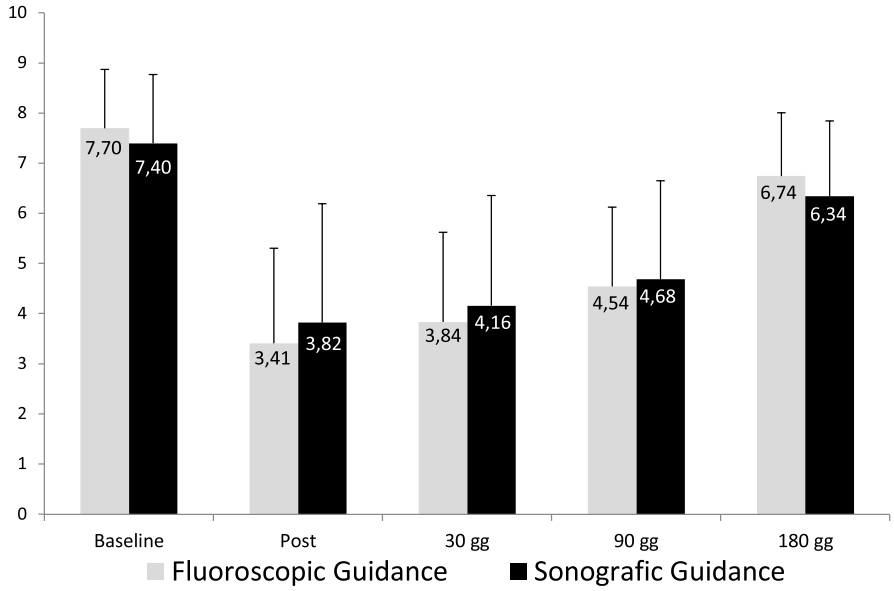

Figure 4 VAS values compared between patients treated under fluoroscopic guidance vs sonographic guidance.

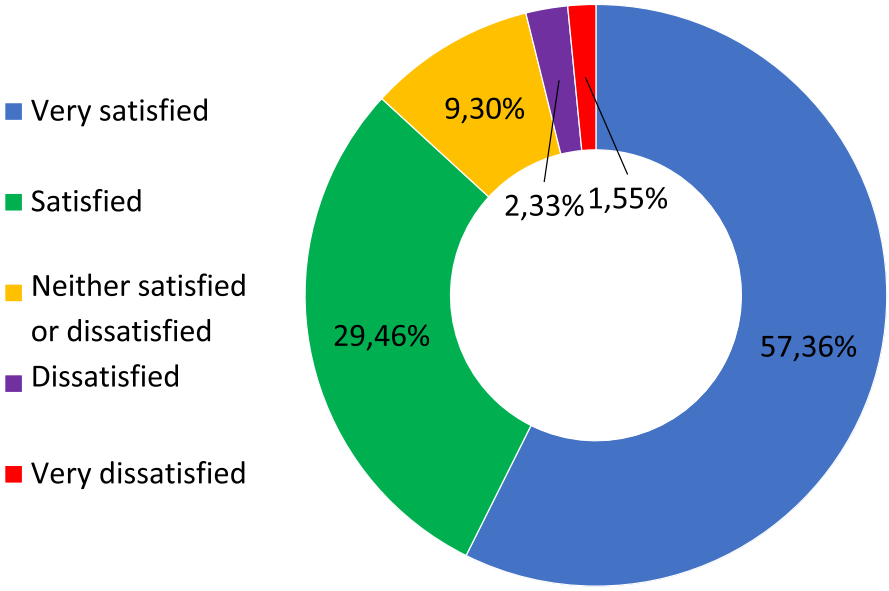

Figure 5 Patients satisfaction recorded 180 days after procedure.

a short pulse width for minimal destructive effect and a higher coefficient of variance for greater efficacy of treatment.

This pulsed method has been administered inside the intervertebral discs for discogenic pain, and with intra-articular application for arthrogenic pain, resulting in significant efficacy rates in terms of pain reduction and mobility improvement.[34]

The initial effect of this treatment is on nerve fibers and is thought to be due to amplification of the electric field that occurs within a closed joint. The second and most probable effect occurs due to modulation of the inflammatory response. Further to this, in a case study reported by Schianchi et al,[35] the authors concluded that the biological effects of low-range electrical fields consist of a remodulation of inflammatory cytokine production.

This hypothesis has been supported through in vitro investigations.[37,38]

The primary weakness of this study relates to its retrospective design. Even though the results were highly significant, prospective studies including control arms will be necessary in order to confirm our findings. Further, our study was performed at a single site, and generalizability of results will improve once we conduct a multi-site investigation. The minimally invasive nature and high safety levels of this procedure, in addition to the marked success rate anecdotally observed in common clinical practice, amplify the need for appropriate studies in order to clarify the efficacy of intra-articular knee PRF in OA patients.

Conclusion

In the current study, for Moderate and Severe Disability groups, intraarticular STP Pulsed Radiofrequency resulted in significantly reduced VAS scores at 1, 3 and 6 months compared to baseline in osteoarthritis pain. However, in the Extremely Severe Disability group, despite high levels of patient satisfaction, approximately one-third of patients reported less than 30% pain relief. In light of our experience, this technique should be reserved for the Moderate and Severe Disability groups as those are the groups which currently reported higher levels of satisfaction and good pain relief. In the Extremely Severe Disability group, this technique may be considered only in selected cases, when an adequate therapeutic and/or surgical alternative is not contemplated. Although this study's results are quite encouraging, a prospective analysis will be needed in order to substantiate the relative benefits of this technique.

Disclosure

Dr Michael E. Schatman is research consultant for Firstox and Modoscript, outside the submitted work. The authors report no other conflicts of interest in this work.

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CHAPTER IV

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Review

Practical Advices for Treating Chronic Pain in the Time of COVID-19: A Narrative Review Focusing on Interventional Techniques

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Abstract: Background: Since the management of chronic pain has become even more challenging secondary to the occurrence of SARS-CoV-2 outbreaks, we developed an exhaustive narrative review of the scientific literature, providing practical advices regarding the management of chronic pain in patients with suspected, presumed, or confirmed SARS-CoV-2 infection. We focused particularly on interventional procedures, where physicians are in closer contact with patients. Methods: Narrative Review of the most relevant articles published between June and December of 2020 that focused on the treatment of chronic pain in COVID-19 patients. Results: Careful triage of patients is mandatory in order to avoid overcrowding of hospital spaces. Telemedicine could represent a promising tool to replace in-person visits and as a screening tool prior to admitting patients to hospitals. Opioid medications can affect the immune response, and therefore, care should be taken prior to initiating new treatments and increasing dosages. Epidural steroids should be avoided or limited to the lowest effective dose. Non urgent interventional procedures such as spinal cord stimulation and intrathecal pumps should be postponed. The use of personal protective equipment and disinfectants represent an important component of the strategy to prevent viral spread to operators and cross-infection between patients due to the SARS-CoV-2 outbreaks.

Keywords: COVID-19; chronic pain; pain management; severe acute respiratory syndrome coronavirus 2; telemedicine; analgesics; opioid; spinal cord stimulation; disinfectants

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1. Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2 which can lead to COVID-19 disease) was declared a Public Health Emergency of International Concern on

30 January 2020 and, and as of March 2021, more than 120 million people worldwide have been infected, with more than two million deaths [1].

Pain physicians are treating an ever-increasing number of patients suffering from chronic pain [2]

The most recent data indicate that in Europe, moderate or severe chronic pain affects 22% of the population [3]. In the UK, results of a 2016 community-based population study estimated that 10.4% to 14.3% of the population reported suffering from moderate to severely disabling chronic pain and more than half of the elderly population claimed that chronic pain is the factor which most affects their quality of life [4,5]. Hence, satisfactory and tailored chronic pain management is a priority both morally and ethically, helping maintain patients' quality of life and protecting against subsequent psychological and physical complications [6–8]. During the SARS-CoV-2 pandemic, due to the reallocation of public health resources and the emergence of a series of complex needs and urgent requirements [9–11], the need for comprehensive chronic pain management has become even more challenging.

In countries in which the authors work (Italy, UK, USA), hospital-based chronic pain management activities were almost completely suspended from March until June 2020 and have then gradually been resumed. Physicians face the need to deliver high-quality treatments while ensuring safety for patients and health care workers while preventing infection spreading and contamination.

The high transmission rate of SARS-CoV-2 implies a rigorous platform of safety surveillance and meticulous organization in order to avoid further spreading of the disease and hospital outbreaks of infection while allowing for care of chronic pain patients.

Accordingly, the aim of this manuscript is to provide practical advice on the management of chronic pain in patients with suspected, presumed, or confirmed diagnoses of SARS-CoV-2 infection. Additionally, recommendations for hygienic maintenance of the clinic and its equipment during this challenging time are provided. Particular points of focus include: (A) interventional pain specific techniques under fluoroscopy/ultrasound guidance; (B) opioid use among COVID-19 patients; (C) telemedicine provision to chronic pain sufferers; (D) preventive measures to adopt for SARS-CoV-2 infected patients, both in acute and chronic pain settings; and (E) the psychological impact of COVID-19 among both patients and physicians involved in pain management.

2. Materials and Methods

The first author (GLB) identified and invited pain physicians and psychologists to join an expert panel to develop practical advice. All panel members were engaged in caring for patients with chronic pain and had experience and training in clinical research in secondary and tertiary care settings. Panel members were interviewed and asked to summarize the most relevant articles published between June and September of 2020 that focused on the treatment of chronic pain in COVID-19 patients. The literature search was conducted using the PubMed, MEDLINE/OVID, and SCOPUS databases. Each author selected relevant articles in their area of major expertise (as detailed in authors' contribution) Based on the present pathophysiological understanding of COVID-19 and potential practice implications according to the complex management of chronic pain, the panel developed its practical advice in this comprehensive narrative review with the purpose of summarizing the most relevant point of focus regarding chronic pain management during SARS-CoV-2 outbreaks.

3. Results

3.1. Infection Prevention and Control

SARS-CoV-2 [12], a small lipid-based enveloped virus that belongs to the coronavirus family.

Coronaviruses such as SARS and Middle East Respiratory Syndrome (MERS) can survive on dry inanimate surfaces such as metal, glass and plastic (and ultrasound systems) for between 48 and 96 h [13,14]. SARS coronavirus, MERS coronavirus or endemic human

coronaviruses have been shown to persist on fomites for up to 9 days, and therefore, this is an important consideration for ultrasound and other equipment used in all clinical settings [14]. The survival time of the virus depends on material, temperature, humidity and viral concentration. Temperature plays a fundamental role in decreasing viral survival time, as raising temperatures above 56 °C significantly decreases viral concentrations in 10 min, and above 70 °C, viral material is undetectable in just 5 min [14]. However, these data refer to viral RNA detection which is not necessarily strongly correlated with actual infectiousness; therefore, the mere detection of viral genomic material does not necessarily imply the risk of transmitting the disease. Results of a 2003 study on coronavirus strains from a SARS outbreak suggest that the risk of infection by contact with a droplet contaminated paper is small [15]. Hand washing after touching potential materials is therefore considered an effective safeguard against SARS-CoV-2 transmission [15].

There is a paucity of data regarding SARS-CoV-2 inactivation by disinfectants [16]. The United States Centers for Disease Control and Prevention (CDC) recommends social distancing, community mask-wearing, and practicing appropriate hand hygiene as the most effective strategy at this juncture to reduce COVID-19 infectivity rates [17]. The CDC advocates for the use of alcohol-based hand sanitizers (ABHS) while, in their last update on 17 May 2020, they providing warnings against products containing benzalkonium chloride (BAC), stating: "BAC, along with both ethanol and isopropanol, is deemed eligible by the FDA for use in the formulation of healthcare personnel hand rubs. However, available evidence indicates BAC has less reliable activity against coronavirus than either of the alcohols" [17].

Protecting equipment such as ultrasound machines and intrathecal pump (ITP) programmers against contamination should be undertaken through appropriate use of covers. In addition, it is important to ensure that any medications (e.g., ITP refills) and equipment should be transported fully covered in plastic bags. Furthermore, it is essential that these bags and their contents are handled with sterile gloves in a sterile area. Since ultrasound gel is easily contaminable, the use of single-use gel packets is preferred. If these are not available, gel bottles can be used, ensuring that they are not refilled and that their lids are closed throughout exams [13,14].

3.2. Screening

We recommend performing a telephone screening the day prior to non-urgent procedures (as illustrated in Table 1) to assess possible risk factors for SARS-CoV-2 infection (i.e., respiratory symptoms, fever, cough, anosmia, dysgeusia in the last three weeks or possible contacts with infected subjects) and postponing treatment of patients with CoV-2-risk factors until viral testing results are obtained, confirming negativity [18]. A standardized triage regarding symptoms and potential contacts with infected subjects should be completed during the telephone screening and signed by the patient during his/her consultation [18]. Patients with known positivity or strongly suspected of active SARS-CoV-2 infection should be treated only for urgent, non-deferrable procedures (as specified in Table 1) and scheduled at the end of the day in order to minimize risk of contamination to other patients.

3.3. General Precautions and Personal Protective Equipment (PPE) Requirements

As a suspected or confirmed COVID-19 patient enters the hospital or clinic, prevention of spread of infection must be a priority. The use of Personal Protective Equipment (PPE) is crucial for healthcare personnel (HCP) and should be done in conjunction with general hygiene rules, with particular emphasis on hand sanitizing [19–21].

Table 1. Interventional Pain Procedures.

Urgent Examples	Emergent Examples
Neurolytic procedures for refractory cancer pain	Implanted patients with wound complications
ESI for acute disk herniation	Epidural blood patch for refractory spinal headache
Replacement of neurostimulation devices if therapy cessation leads to abrupt decompensation	Migration of SCS or DRG leads with neurological deficits
Sympathetic blocks for early CRPS in refractory patients	Intrathecal pump refill of malfunction
	Epidural or paravertebral catheter for rib fractures

ESI, epidural steroid injections; CRPS, complex regional pain syndrome; SCS, spinal cord stimulation; DRG, dorsal root ganglion.

Conscientious use of PPE reduces exposure to body fluids and infectious agents [22]. Preventive measures should include:

- All patients must wear a surgical mask for the duration of the intervention; [23]
- Only the patient and treatment team should be allowed into the examination room;
- A maximum of 1 accompanying person can be admitted in special circumstances (e.g., elderly or patients with impaired mobility);
- Limiting the number of health care personnel in the examination room;
- Students and trainees should not be permitted to enter.

Interventional pain procedures can be categorized along 3 main dimensions: short or prolonged neuraxial entry, percutaneous or incisional/surgical procedures, and aerosol-generating or non-aerosol-generating procedures. Standard precautions using sterile techniques are appropriate for interventional pain procedures and surgeries, provided that adequate testing can be performed [13,24]. When aerosol-generating procedures are performed, airborne precautions are also suggested [25–27]. In patients with SARS-CoV-2, all of these precautions should remain in place; however, the addition of an eye shield or face shield is also essential in order to observe droplet precautions. Furthermore, during the present crisis, it is recommended that the remaining operating room (OR) staff enter the OR approximately 15–30 min after intubation, depending on the available air-exchange rate.

3.4. Care and Cleaning of Rooms and Equipment

As commonly recommended, during the outbreaks secondary to SARS-CoV-2, examination rooms should be free from all non-essential objects. Additional precautions such as cleaning of all furniture, ultrasound probes, keyboards, touch-screens and gel bottles with a low-level disinfectant (LLD) after each examination should be implemented. When covering ultrasound equipment, using a single-use probe cover is recommended.

3.5. Interventional Fluoroscopy Procedures

The global COVID-19 pandemic has significantly modified interventional pain management of chronic pain patients. Indeed, during the early phase of the pandemic, elective surgery to relieve pain was temporarily postponed, and the use of telemedicine was suggested. The American and European Societies of Regional Anesthesia and Pain Medicine (ASRA, ESRA) had recommended performing only urgent procedures such as ITP refills and device malfunction or infection management (Table 1 and Table 2) [28].

Table 2. Interventional Pain Procedures.

Elective Procedures	Postpone
Urgent procedures	decide on case-by-case basis
Emergent procedures	proceed with caution, and, if possible, at the end of surgery list

Adherence to this guidance eased as infection rates decreased, but given the recent dramatic surge in cases worldwide, this recommendation once again becomes quite salient. The evaluation of semi-urgent procedures (as specified in Table 1) is made by a pain physician, with conditions such as intractable cancer pain, acute or subacute herpes zoster or intractable postherpetic neuralgia, acute disc herniation with radiculopathy, intractable trigeminal neuralgia, complex regional pain syndrome and acute cluster headaches falling into this category according to current guidelines [29].

With regard to alternative strategies, such as various forms of neuromodulation [30–32] Deer and colleagues [29] recently reported that Australia has allowed radiofrequency ablations without prior diagnostic blocks and spinal cord stimulator implantation without the need for an external trial. Moreover, as recently noted [33–35], choosing a non-rechargeable implanted pulse generator (IPG) directly implanted without a trial phase resulted in effective spinal cord stimulation for the management of neuropathic pain in a pilot study. The use of telemedicine for most neurostimulation device troubleshooting was highly recommended, when possible, to solve device malfunction, modify stimulation patterns and manage technical problems or hardware malfunctions.

According to the approach developed by Thomson and colleagues [34], physicians can consider a pre-implant score to select clinical conditions or targeted procedures [35] with high probability of a successful spinal cord stimulation (SCS) trial. In cases of loss of neurostimulator function due to lead migration, lead fracture and IPG malfunction, the International Neuromodulation Society (INS) suggested avoiding surgically revising neurostimulator implants until planned elective surgeries are re-initiated [36,37]. The same authors recommend against the implant of any new ITP system with the exception of judiciously selected cancer pain cases in which the benefit is considered to outweigh the risk of acquiring a COVID-19 pneumonia by using adequate personal protective equipment (PPE). ITP refills should be ensured in order to prevent drug withdrawal as well as unnecessary severe pain exacerbations. Programmable ITP should be surgically replaced every 6–10 years depending on battery consumption, and careful planning of elective ITP replacement has been suggested, reserving surgery for devices whose battery exhaustion is imminent. [36]. Moreover, since ITP refills are procedures that require the operator to come within a distance of less than 1 m from the patient, the PPE used should be commensurate with local guidelines. In selected cases or in high-risk patients in which ITP infusions are solely of opioids, oral equivalents can be substituted. The possible onset of withdrawal symptoms should be considered and adequately managed, since opioid equivalence is not an exact estimation [38]. To the contrary, the oral substitution of baclofen or clonidine is not suggested due to potential life-threatening withdrawal effects.

Corticosteroids are commonly used in interventional pain management for their anti-inflammatory properties. The frequently used routes of administration are via epidurals, joint blocks, peripheral nerves and soft tissue injections. The major anti-inflammatory effect is the result of phospholipase inhibition with a subsequent reduction of cytokine expression, a reduction in the chemotactic or chemoattractant properties of lymphocytes and membrane stabilization [39]. Although the rationale for epidural steroid injections relate to their anti-inflammatory properties, it has been suggested that their perceived effect is also based on blocking conduction in nociceptive nerve fibers [40]. Regarding viral infections, joint corticosteroid injections were associated with a significant increase in the risk of infection, even among flu-vaccinated patients [41]. Since Rabinovitch and colleagues [42] reported a strong correlation between epidural volume and pain relief

irrespective of steroid dose for up to one year, it can be argued that epidural steroid injections (ESI) are not the only important component of the sound treatment of epidural inflammation. Moreover, as recently demonstrated by Bise and colleagues, platelet-rich plasma is not inferior to ESI in terms of pain reduction and Oswestry Disability Index (ODI) improvement for patients with persistent radicular pain (>6 weeks) [43]. In early March of 2020, the Royal College of Anaesthetists [44] recommended against the use of systemic corticosteroids in patients suffering from or at high risk of COVID-19, since the immunological impacts of ESI and the effects of steroids use in interventional pain management for patients with this new virus are still unknown. To the contrary, in early June of 2020, the preliminary results of the RECOVERY trial demonstrated a 3% mortality reduction in patients on mechanical ventilation and treated with dexamethasone 6mg once daily for up to ten days compared to usual care [45]. Consequently, the Spine Intervention Society (SIS) alerted interventional pain physicians regarding a possible dexamethasone shortage and prioritizing procedures, by weighing risks and benefits for each individual patient (SIS Guidance on Interventional Pain Procedures During the COVID-19 Global Emergency) [46].

3.6. Interventional Ultrasound Procedures

Ultrasound has become a mainstay of pain management, both for patients' evaluations and for the performance of interventional techniques with precision and safety. Regarding the risk of transmitting infectious diseases, ultrasound-guided procedures range from minimally invasive to critically invasive. Pain management procedures under ultrasound guidance can be considered minimally critical and semi-critically invasive procedures; they may involve micro-trauma to the skin and mucosal membranes, particularly when performing intra-articular injections or deep injections into spinal structures such as facet joints or the epidural space.

Ultrasound probes are sensitive devices and may be damaged with the use of certain chemical compounds, in particular cleaning that is performed with the use of alcohol-based products [47]. SARS-CoV-2 is considered the least resistant to inactivation by common disinfectants used in LLD based on quaternary ammonium compounds [48]. The structure of these viruses includes a lipid envelope, which is easily disrupted with 1 min by most disinfectants such as 62–71% ethanol, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite. Other biocidal agents such as 0.05–0.2% benzalkonium chloride or 0.02% chlorhexidine digluconate are less effective [49]. HLD (high-level disinfectant) is based on glutaraldehyde-based formulations, highly concentrated hydrogen peroxide (7.35%) or 0.23% peracetic acid. These substances can effectively remove all bacteria, fungi or viruses from surfaces. For non-critical devices and for general room and materials disinfection, as the risk of infection transmission is low, ultrasound transducers can be cleaned and disinfected using an LLD or intermediate-level disinfectant; both will denature most bacteria, some fungi and some viruses, such as SARS-CoV-2, influenza A and human immunodeficiency virus [50]. No specific guidelines or recommendations have been published regarding the use of ultrasound for pain management interventions in patients with suspected or confirmed SARS-CoV-2 infection. Thoroughly cleaning environmental surfaces with water and detergent and applying commonly used hospital-level disinfectants (such as 0.1% sodium hypochlorite) are considered effective and sufficient procedures. The World Federation for Ultrasound in Medicine and Biology issued a position statement regarding the safe performance of an ultrasound exam and proper care of the equipment during the pandemic period [51]. In order to maintain the highest degree of safety for both patients and physicians, the following measures should be considered:

- Screening of patients with possible SARS-CoV-2 infection;
- Protection of the patient and healthcare personnel;
- Proper caring and cleaning of examination rooms and equipment.

Moreover, the number of patients moving through hospital facilities should be limited, and the possibility of cross-infectivity among clinical staff members should be minimized.

For example, in Italy, hospitals have been formally mandated to develop a strategic plan to organize appointments, surgical planning and clinical staff surveillance. Thus, every patient scheduled for elective day-hospital procedures or surgeries must undergo a test for SARS-CoV-2 detection in the 72 h prior to being admitted to the hospital and, if positive, the procedure will be postponed and the patient sent home to quarantine. Body temperature is checked for every individual (staff and patients) entering the facility and anyone positive for a fever > 37.5 °C or respiratory symptoms (cough, rhinorrhea, anosmia, shortness of breath) is denied access and undergoes testing for SARS-CoV-2. The duration of appointment slots has also been expanded in order to allow sufficient time for disinfection and cleaning following each procedure.

Interventional pain procedures reduced opioid consumption [52], which is a cause of immune-suppression, which predisposes individuals to develop COVID-19 disease. Furthermore, interventional procedures can improve the quality of analgesia, provided that they are provided judiciously through evaluation on a case-by-case basis, ideally involving interdisciplinary team discussion [53,54].

3.7. Opioids

The association between chronic pain and the immune system, and pain's ability to induce immunosuppression, has long been recognized [55]. Opioids are known to cause serious adverse events in some patients, including modification of the endocrine system and immunosuppression [56–58]. In fact, opioids can interfere with the innate and acquired immune response by acting on the hypothalamic-pituitary-adrenal axis and the autonomic nervous system; therefore prolonged therapy and higher dosages may intensify endocrinologic disorders [59,60].

However, it is essential to note that various opioids differ in their effects on the immune system, with morphine and fentanyl having the greatest immunosuppressive action and buprenorphine the weakest [61–67]. Research suggests a potential increase in the incidence and severity of lung infection in patients on chronic long-acting, high-dosage opioids [68–71], although these studies were not focused on viral infections. Even if SARS-CoV-2 has a profound impact on the immune system, there are no clinical or experimental data regarding increased severity of the disease associated with concomitant opioid utilization. Therefore, no clear recommendations can be made regarding possible suspension or modification of current treatment in patients with chronic opioid exposure [72]. Hence, pain physicians should consider making changes to opioid therapy regimens only subsequent to in-person evaluation of current treatment. This should include obtaining a thorough history and a physical examination. However, due to the COVID-19 health emergency and related distancing measures, physicians may not be able to follow some of the recommended practices.

Taking these factors into consideration, therapy may include administration of short-term opioids to patients experiencing acute pain episodes or severe chronic pain aggravation. This is only advised assuming careful risk stratification and appropriate screening for signs likely to signify potential risks for aberrancy. Furthermore, consultation with the prescription drug monitoring program and an exit strategy with which patients are in agreement should be the standard of care. In patients requiring opioid therapy for a period of more than 1 or 2 weeks, an in-person examination is recommended within 4 weeks to allow physicians to assess the severity of the pathology through physical examination, if possible [72,73].

For patients already receiving high-dosage, long-term opioid therapy, increased opioid treatment for a limited period may be suggested, provided that appropriate risk mitigation practices are utilized. However, we recommend an in-person visit, other than in situations in which doing so is not feasible, within 8 weeks to help identify an advance of the disease process requiring treatment or signs of opioid tolerance or opioid-induced hyperalgesia [73].

Interactions between opioids and antiviral medications should be considered in patients with SARS-CoV-2 infections. Despite conflicting data, Lopinavir/Ritonavir and Remdesivir have been used as a standard aspect of infection treatment for patients admitted with COVID-19 disease. These medications have a profound impact on metabolism of opioids, with Ritonavir inhibiting CYP3A4, which is a key aspect of most opioids' metabolic pathways. Further, oxycodone plasmatic levels are greatly increased with concomitant lopinavir use [74], thereby increasing the risk of respiratory depression and overdose. On the other hand, methadone plasmatic levels have been determined to dramatically decrease with concomitant use of Lopinavir/Ritonavir (possibly due to an induction of methadone metabolic clearance, involving either or both CP450 3A and CYP450 2D6). Induction of other enzymes, such as intestinal glycoprotein P-450, could also contribute to decreases in drug levels, thus increasing the likelihood of withdrawal syndromes [75]. Remdesivir seems to have less pronounced interactions with other drugs, making it a safer choice in patients taking multiple medications. Morphine, buprenorphine, or tapentadol (drugs whose metabolism is not dependent on CYP450 enzymatic activity [76] could potentially be safer in patients on antiviral therapy. In patients for whom opioid rotation is not possible, careful dosage adjustment is strongly recommended [77].

3.8. Telemedicine

Telemedicine refers to the electronic exchange of medical information through a variety of platforms including telephone consultation, video conferencing and short message services for the delivery of health care services remotely. It is used throughout most of the western nations and seeks in general terms to be analogous to traditional care [78]. Research has demonstrated that patients using telemedicine are highly satisfied with telehealth services, appreciating the comfort and convenience offered [79,80]. These data supporting telemedicine's efficacy include those for patients suffering from chronic diseases or requiring post-procedural follow-up. The time savings and reductions in cost are undoubtedly of considerable interest to health organizations that have increased their reliance on telehealth services [79,80].

Following the appearance of SARS-CoV-2, the role of telemedicine [81] has become of fundamental importance, not only in an attempt to mitigate the spread of the disease, but also as a means of reducing the consumption of personal protective equipment and preserving it for physicians on the front lines. Due to the fact that clinicians are increasingly required to use remote strategies to clinically assess patients, in-person visits have become limited only to those of extreme urgency. One such strategy is the use of patient-reported outcome measures (defined as any report of the status of a patient's health condition that comes directly from the patient) which can be carried out remotely through the use of mobile phones with cameras, and also as a means of sharing images of paper assessments. Furthermore, the electronic administration of measures is already an integral part of many electronic health record systems used in treating patients with pain. For example, the CHOIR system in the United States [82] or PAIN OUT in Europe [83] are web-based systems which have been specifically adapted for chronic pain sufferers.

Telemedicine is also useful for streamlining a series of procedures, such as patient procedural education, preauthorization prior to performing procedures, pre/post-procedural consultation, and intermittent remote outcome monitoring. Even aspects of the physical examination itself can be carried out via video conferences, e.g., when judging appearance and movement, or when conducting self-examination under guidance. An element of considerable interest is the development of telemedicine in determining which patients are emergent, rather than urgent or elective [84], thereby allowing clinicians to prioritize which procedures to perform. Telemedicine communication, by using real-time interactive audio-visual communication systems, could also be useful for monitoring patients for opioid withdrawal; checking for an elevated heart or pulse rate, for example, which are classic signs of opioid withdrawal. Although promising, there are concerns related to the empirical evidence supporting remote monitoring. For example, relatively few studies

have assessed telehealth for potential harm, and dropout rates related to telehealth can be high due to patients' perceptions that telehealth is inferior to in vivo treatment because it is less "personal" [85] and is subjected to digital discrimination [86,87].

As aforementioned, a practical example in which use of remote monitoring or more generally, of telemedicine, is suggested, are the programming and control of spinal cord stimulators remotely or opioid addiction control or dosage adjustment.

3.9. Psychological Considerations

During the COVID-19 pandemic, a high incidence of psychological distress and symptoms have also been observed, including mental health disorders, posttraumatic stress disorder, psychosomatic disorders, and substance abuse [88–90].

Many suffer from affective disorders (particularly depression), while others suffer from substance abuse, personality disorders, and various somatoform disorders such as conversion, hypochondriasis, and somatization disorder (not to be confused with "somatization" as a normal process). In some patients, certain of these varied disorders may be secondary to chronic pain, but in others they predate the onset of pain or reflect alternative expressions of the same underlying psychobiological disorder [91].

Furthermore, individual and societal disruption associated with COVID-19 are likely to increase their likelihood of emergence [89,92]. Moreover, while the prevalence of Borderline Personality Disorder is inordinately high among chronic pain patients, the severity of the disorder itself is likely to be increased during the COVID-19 outbreak [93]. A failure to address these issues has the potential to adversely impact pain-related treatment outcomes [94,95]. This has created the need to deliver immediate mental health screening and treatment interventions to large populations, with concerns regarding the supply of adequately trained mental health clinicians arising. [95] Fortunately, telehealth lends itself well to psychotherapeutic approaches [96], and reports of their success during the ongoing COVID-19 crisis are already emerging [97,98].

As recommended by the WHO, a practical example of psychosocial support during SARS-CoV-2 outbreak would be that provided to older adults. Although always a vulnerable population, those living in isolation and those with cognitive decline/dementia, are prone to becoming more anxious, angry, stressed, agitated and withdrawn during the outbreak or while in quarantine [99] older adults.

4. Discussion

Due to the COVID-19 pandemic, there exists an increased risk of chronic pain patients failing to receive critical treatment. Chronic pain patients may also be at increased risk of COVID-19 disease due to multiple factors, such as chronic opioid therapy potentially making them more susceptible to the COVID-19 infection due to immunosuppression [54–59]. As outlined, added precautions relating to appropriate social distancing and more conscientious sanitization processes in hospitals and clinics need to become a greater focus for those treating patients with pain. Triage of pain patients, while always important, becomes even more imperative due to the need to distinguish between those who may be adequately treated via telemedicine and those requiring in-clinic consultations.

Based on the limited extant literature in conjunction with our clinical experiences, we suggest that interventional pain management can be reinitiated, albeit cautiously, to more effectively treat chronic pain patient population. As steroids are associated with immunosuppression, as well, throughout the remainder of the COVID-19 pandemic, epidural steroid injections should be performed judiciously and with the lowest possible effective dose [100]. SCS and ITP difficulties or technical problems should, when possible, initially be addressed remotely, with in-person visits only in cases of infection or other emergencies. A key element for the future should be even more conscientious planning of pain management with appropriate patient selection. Without exception, efforts should be geared toward enhancing safety conditions in order to protect patients', physicians', and support staff's health and well-being. Given that the duration of the COVID-19 pandemic

is uncertain, pain clinicians can adopt "new best practices" that may allow them to treat patients with pain now, as well as more safely and effectively in the future. This review has several limitations, while we analyzed the relevant publications and recommendations that we reviewed between June and December of 2020, we are aware that this review may not be completely exhaustive given that the knowledge on this topic is evolving. We mainly focus on the organization of the clinical practice and did not cover specific clinical topics. The authors work in different countries and regions where regulations, hospital organization, security and screening protocols are different, therefore some recommendations could not be applied everywhere.

However, we hope that this review serves as source of guidance to chronic pain clinicians in the future, and believe that it will remain relevant, irrespective of the course of the pandemic.

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CHAPTER V

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COVID-19 Related Acro-Ischemic Neuropathic-like Painful Lesions in Pediatric Patients: A Case Series

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Abstract

Background: A variety of skin manifestations have been associated with COVID-19 infection. Acral lesions on hands and feet, closely resembling chilblains, have been reported in association with COVID-19, which are nonspecific. These acro-ischemic painful lesions have been described mainly in asymptomatic and mildly symptomatic pediatric COVID-19 positive patients, without a precise pathogenetic mechanism. COVID-19-induced chilblains may portend an indolent course and a good outcome. In young patients, the IFN-1 response induces microangiopathic changes and produces a chilblain lupus erythematosus-like eruption with vasculitic neuropathic pain features.
Objectives: This paper presented a case series of pediatric patients with COVID-19-related skin lesions and neuropathic-like pain.
Methods: Clinical outcomes were collected from 11 patients diagnosed with painful erythematous skin lesions with neuropathic-like pain and positive IgG for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
Results: It is a mildly symptomatic condition not related to severe pain rates, and it is treated with paracetamol due to the transitory nature of the problem, which provides good results.
Conclusions: A particular point of interest is skin lesion manifestation as a further indirect sign of SARS-CoV-2 infection. Due to the initial manifestation of chilblains in pauci-symptomatic pediatric patients, they need to be immediately tested and isolated. Chilblains can be considered a clinical clue to suspect SARS-CoV-2 infection and help in early diagnosis, patient triage, and infection control.

Keywords: COVID-19, Child, Vasculitis, Neuropathic-like Pain, Coronavirus

1. Background

On Dec 31, 2019, the World Health Organization reported an unexplained lower respiratory tract infection in Wuhan, China (1). A new virus belonging to the coronavirus (CoV) family has been attributed as the etiological agent for the disease, and it has been named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) (2).

The virus originates from a reservoir of bats and an unknown intermediate host, infecting humans through an interspecies transmission (3-5). The novel coronavirus has an extraordinary capacity to spread due to prolonged contagiousness and infectivity among asymptomatic hosts. The rapid spread was declared a pandemic due to SARS-CoV-2 on Mar 11, 2020 (6).

Interestingly, various skin manifestations have been associated with COVID-19 infection, including urticaria, erythematous and exanthematic rash. However, skin lesions reported in association with COVID-19 are nonspecific and lack prognostic significance (7, 8).

There is an increasing concern about the clinical im-

plications of clotting disorders underlying acute acro-ischemic lesions in asymptomatic or mildly symptomatic COVID-19 patients (9). These acro-ischemic painful lesions have been described mainly in asymptomatic and mildly symptomatic pediatric COVID-19 positive patients, without a precise pathogenetic mechanism.

2. Objectives

This paper presented a case series of pediatric patients with COVID-19 concomitant skin lesions and neuropathic-like pain. A particular point of interest is skin lesion manifestation as a further indirect sign of SARS-CoV-2 infection.

3. Methods

3.1. Study Cohort

Clinical outcomes were collected from 11 COVID-19 pediatric patients diagnosed with painful erythematous skin lesions with neuropathic-like pain. Data from the patients' acro-ischemic skin lesions were gathered in April 2020 at Ospedale dei Colli, Naples. Informed consent was obtained from the patients' parents to present this case series.

3.2. Clinical Work-up

Multiple diagnostic procedures like nasopharyngeal swabs and laboratory tests were conducted as part of the standard infection work-up in this series of patients. Moreover, the serological tests for SARS-CoV-2 virus-antibodies were assessed.

3.3. Pain Assessment and Treatment

Patients suffering from neuropathic-like pain without a history of the Raynaud phenomenon or acrocyanosis were treated in a multidisciplinary pain management center. During the physical examination, pain characteristics, including intensity and neuropathy, were analyzed using the numeric rating scale (NRS) and DN4 questionnaire (DN4), respectively (10). All the patients were treated with age- and weight-adjusted paracetamol 15 mg/kg per dose, to a maximum of 750 mg per dose, every 6 - 8 hours, with a maximum of 3,000 mgs daily for ten days. The treatment's primary goal was to achieve pain relief over the skin lesions.

3.4. Statistical Analysis

Descriptive statistics were used for socio-demographic data, diagnoses, and pain characteristics. Data summarized as continuous variables were expressed as mean and standard deviation (SD), and categorical variables were expressed as numbers and percentages.

4. Results

4.1. Study Cohort

This case series presented 11 pediatric patients treated in April 2020 (mean age, 11 $\pm$ 2,19 SD, years old; range, 8 - 15 years old), including seven males and four females. The diagnosis made by a pediatrician and a first aid physician was established through the presence of "acro-ischemic skin lesion," with positive IgG antibodies for SARS-CoV-2 laboratory test results.

4.2. Clinical Work-up

At the first clinical evaluation, two of the patients had presented fever and cough in the previous month, and four of the patients had bilateral conjunctivitis. None of the patients had a past medical history of the Raynaud phenomenon or acrocyanosis. All the patients admitted to our pain center were diagnosed with painful or itchy erythematous skin lesions affecting distal extremities (especially the digits), with a self-limiting course associated with neuropathic-like pain features. The serological tests for SARS-CoV-2 virus-antibodies revealed IgG (> 5 AU / mL) in all the case series patients. Moreover, all the patients had a positive PCR test. They were admitted to the Pain Clinic between 3 and 13 days after the serological test resulted positive.

4.3. Pain Assessment and Treatment

At the time of the physical examination performed in our pain center, nine out of the 11 (81.8%) patients complained of mild-moderate pain, and the mean pain score among all the patients was 4/10 on the NRS and 7/10 on the DN4 questionnaire (Figure. 1).

Table 1 summarizes information on neuropathic pain characteristics, as defined by the DN4 questionnaire in our series. All the patients experienced three or more neuropathic pain characteristics (100%). Typical pain features experienced by all the patients over the cutaneous lesions, were an aching pain with itching and burning of mild intensity.

The lesions showed a chilblain-like pattern, with red to purple macules, plaques, and nodules, as well as an erythema multiforme-like pattern (i.e., rounded erythematous macules and vesicles that tend to coalesce). The lesions were localized in the upper and lower extremities in two (18.1%) and nine (81.8%) out of the 11 cases, respectively (Figures 2 - 4).

The natural history of these skin lesions showed an evolution from an edematous to an erythematous state. Three (27.3%) of the cases evolved into ulcerative lesions, and one (9.1%) of the cases developed an infection and was treated

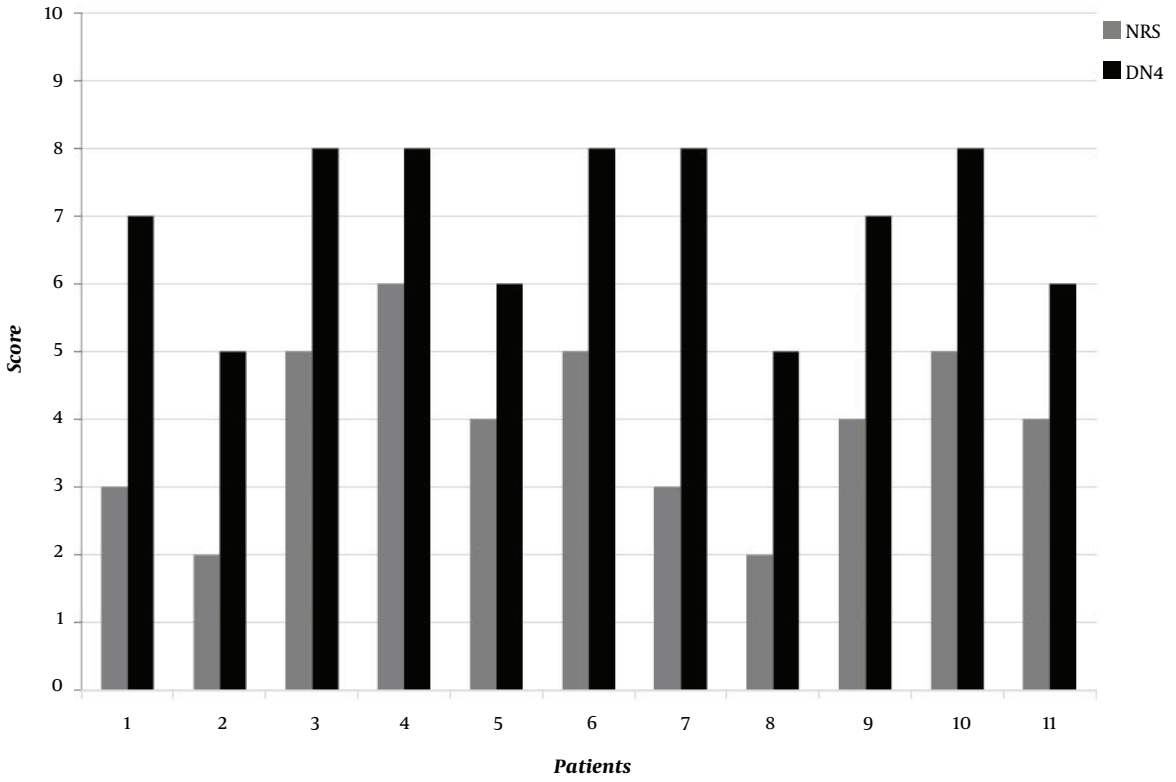

Figure 1. Values of NRS (gray) and DN4 (black) for each of the 11 patients

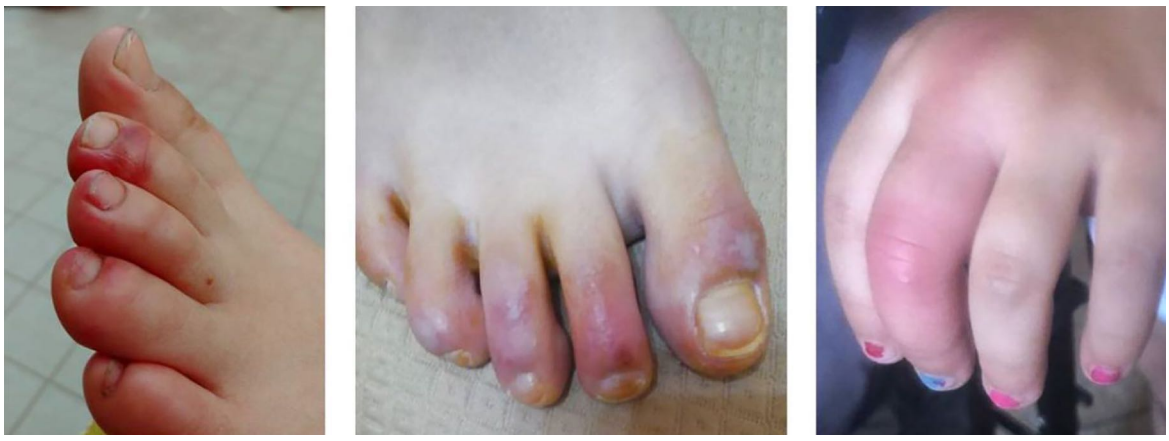

Figure 2. Chilblain-like pattern

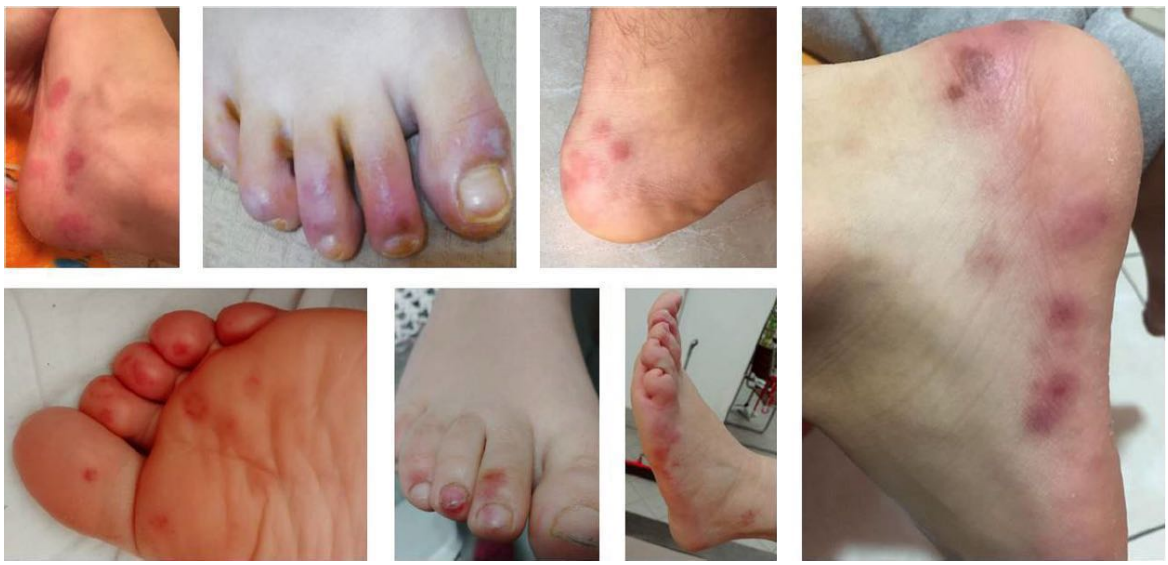

Figure 3. Red to purple macules, plaques, and nodules, also with erythema multiform-like

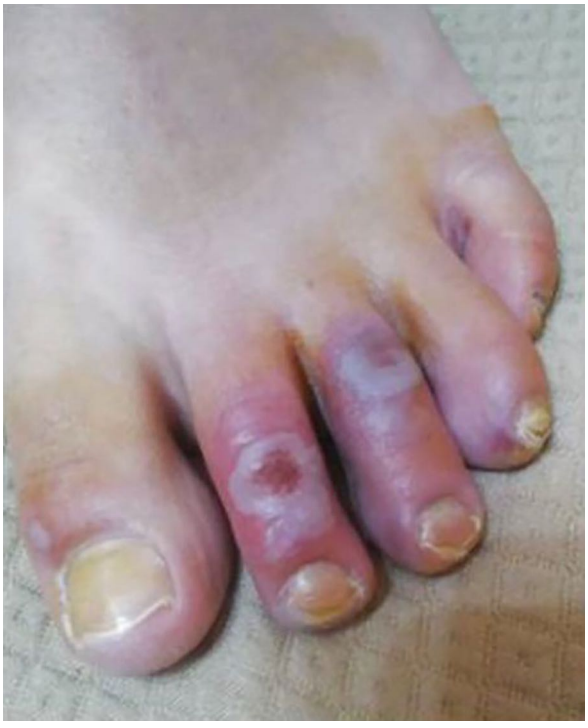

Figure 4. Skin ulcers

Table 1. Symptoms and Personal History of the Patients

Symptom and Personal History	No. (%)
Allodynia	10 (90.91)
Itching	8 (72.73)
Burning	10 (90.91)
Pain	11 (100)
Acrocyanosis	11 (100)
Family history	0 (0)
Infection	4 (36.36)
Neuropathic features	11 (100)

with Mupirocin 2% ointment three times per day. Twelve to 15 days after the clinical evaluation of the skin lesions, complete healing was obtained in all the patients with the zeroing of the NRS.

5. Discussion

Chilblain is a localized disease that manifests acral inflammatory lesions (11). The lesions can be erythematous or purple and are intensely pruritic or painful. Furthermore, the lesions are more likely to appear during the winter, affecting the proximal phalanges' toes and dorsum, and frequently affect female teenagers (12, 13). Chilblains can present as a secondary feature of diseases, such as systemic lupus erythematosus (LE), Behçet disease, chronic

myelomonocytic leukemia, metastatic breast carcinoma, cryoglobulinemia, cold agglutinin disease, macroglobulinemia, Aicardi-Goutieres syndrome, and anorexia nervosa (14, 15). In our case series, pediatric patients presenting chilblains did not show any history of skin manifestations, such as Raynaud syndrome, vascular diseases, or cutaneous LE. Coronavirus has been suspected as the etiology of the recent increase of acro-ischemic lesions, specifically chilblains, in pediatric patients, during the COVID-19 outbreak (16).

Skin lesions have been reported in different disease stages, presenting an indolent course, either as the first sign or as a late manifestation in positive COVID-19 patients (16). The lesions are located mainly on distal limbs, and the feet are more affected than the hands.

The monogenic autoinflammatory interferonopathies provoke microangiopathy, which manifests clinically as chilblains. The clinical similarities with LE chilblains are not surprising due to the type 1 interferons (IFN-1) etiopathological mechanism. The antiviral and immunostimulatory properties of IFN-1 have been confirmed in acute viral infections, like Epstein-Barr, or IFN-1 mediated diseases, like LE, whose pathogenesis simulates a viral-induced immune response (17, 18).

INF-1 is critical in the immune response to SARS-COV-2, triggering the expressions of INF-1 inducible genes. Elderly patients mount an inadequate or postponed IFN-1 response, developing hypercytokinemia and increasing morbidity and mortality due to the typical damage pattern in COVID-19 patients with high interleukin levels in the second phase of the disease.

Like in this case series, pediatric patients develop an INF-1 response, and they are affected by skin lesions (19), indicating the benignity of COVID-19 without developing the cytokine storm. The reason is the surge in IFN-1 that causes downregulation of other cytokines.

Hence, microangiopathic-associated chilblain lesions in pediatric patients have a different pathological mechanism from thrombotic-related acral-ischemia lesions observed in severely ill COVID-19 patients. Thrombotic-related acral-ischemia lesions show an hypercoagulopathy state and elevated D-dimer levels with a subsequent higher likelihood of thrombi formation and consequent thromboembolic events, increasing tissue susceptibility to ischemia (20).

COVID-19-induced chilblains may portend an indolent course and a good outcome. In young patients, the IFN-1 response induces microangiopathic changes and produces a chilblain LE-like eruption with vasculitic neuropathic pain features (21, 22).

Vasculitis neuropathy usually has patchy and asymmetrical distribution, affecting mainly distal lower limbs (23, 24). Pain is a critical clinical feature of neuropathy in more than 80% of patients. It is often severe, and it may be aching or throbbing rather than burning and characteristically more neuropathic in quality (22, 24). It may also be present in patients in intensive care (25).

Neuropathic pain has been defined as "pain initiated or caused by a primary lesion or dysfunction in the nervous system," which can affect both the peripheral and central nervous systems, causing various pathophysiological mechanisms, such as inflammatory reactions and neuroplastic changes (26, 27). It is characterized by sensory abnormalities ranging from numbness to hypersensitivity (hyperalgesia/allodynia) and can be objectively assessed by quantitative sensory testing considering perception thresholds for a light touch, vibration, and thermal and pain sensation (28, 29). It affects the quality of life (30) and may be treated both pharmacologically or non-pharmacologically (31-33). The same neurological illnesses causing neuropathic pain also, or instead, have been suggested to cause itching. Thus, neuropathic pain or itching indicates pathophysiological abnormalities in the peripheral or central nervous system (34). In our case series, the skin lesions were defined by a neuropathic-like pain pattern assessed with the DN4 questionnaire.

5.1. Conclusions

Acro-ischemic lesions, described in our case series, with neuropathic-like features of pain are present in asymptomatic and mildly symptomatic pediatric COVID-19 IgG positive patients, without a precise pathogenetic mechanism.

Coronavirus has been suspected as the etiology of the recent increase of acro-ischemic lesions, and further studies are needed to confirm this correlation.

SARS-CoV-2 infection-induced chilblains may portend in pediatric patients an indolent course and a good outcome of the illness. The mechanism in young patients is related to the rise of INF-1 levels, downregulating other cytokines, and preventing the cytokine storm.

Paracetamol, in young patients, appears to be effective in treating moderate and transitory pain associated with these lesions.

It is a mildly symptomatic condition not related to severe pain rates due to the transitory nature of the problem. Our patients were treated only with paracetamol, which provided good results.

To conclude, we aim to alert clinicians to the initial manifestation of chilblains in pauci-symptomatic pediatric patients, who need to be immediately tested and isolated. The reason is that chilblains can be considered a clinical clue to suspect SARS-CoV-2 infection and help in early diagnosis, patient triage, and infection control.

Footnotes

Authors' Contribution: AMS, AS, GLB, MT, and MTDD initially screened the cases. AP cared for the final diagnosis and therapy. GV, FI, and GAA made most of the literature search. All the authors participated in the elaboration of the data and contributed to preparing the first draft of the manuscript.

Conflict of Interests: The authors declare that they have no conflicts of financial and other interests.

Ethical Approval: This case series was based on reports of cases treated in the regular everyday clinical practice and thus did not need any previous approval by the Institutional Ethics Committee.

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Informed Consent: The consent to report the cases as a group was obtained from the studied children's parents by preserving their privacy.

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CHAPTER VI

RADIOFREQUENCY ABLATION FOR CHRONIC LUMBAR ZYGAPOPHYSEAL JOINT PAIN USING A V-SHAPED ACTIVE TIP NEEDLE: AN OBSERVATIONAL RETROSPECTIVE STUDY

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Significance: The use of V-shaped active tip needles for radiofrequency ablation (RFA) procedures in the treatment of chronic lumbar zygapophyseal joint pain may have potential advantages compared to other approaches. The larger lesion size created by the V-shaped electrode might overcome the anatomical variability of the medial branch nerves, thus improving clinical outcomes. This study aims to evaluate the efficacy and the feasibility of RFA for lumbar chronic pain using this technique.

Keywords: arthralgia; chronic pain; zygapophyseal joint; pain management, radiofrequency ablation, neuromodulation, lumbar facet joint.

ABSTRACT

Background: Lumbar zygapophyseal joint dysfunction represents one of the major sources of chronic axial low back pain. Radiofrequency ablation (RFA) disrupts the transmission of nociceptive impulses via the medial branch nerves. A V-shaped active tip needle may offer a larger size lesion with improved clinical efficacy when treating chronic lumbar zygapophyseal joint pain. The aim of our study is to evaluate the efficacy and the feasibility of RFA using a V-shaped active tip needle.

Methods: This is a single-center observational retrospective study. Clinical records of all patients diagnosed with chronic lumbar zygapophyseal joint pain and treated with V-shaped needle RFA were screened and analyzed, if they met the following inclusion criteria: adult patients (>18 years), diagnosis of chronic lumbar zygapophyseal joint pain, failure of conservative treatments, ability to provide informed consent for data analysis and publication. Exclusion criteria were: lumbar pain not related to zygapophyseal joints, incomplete data, absence or withdrawal of informed consent for data analysis and publication. The primary outcome of the study was changes in pain intensity at follow-up. The secondary outcomes were the evaluation of quality-of-life improvement, the occurrence of adverse events and the impact on post-procedural analgesic consumption. For this purpose, pre- and post-treatment numeric rating scale (NRS), neuropathic pain 4 questions (DN4), EuroQoL - EQ-5D-3L, EQ-VAS, EQ-index and north american spine society (NASS) index were retrieved. Comparison of these variables through follow-up visits was performed using the Friedman's test with post-hoc analysis using the pairwise Wilcoxon signed-rank test. Fisher's exact test was applied where appropriate. P-values <0.05 were considered to be statistically significant.

Results: 64 patients were included. Pain relief of more than 80% in NRS was experienced by 7.8% of patients at T1 (CI95% 0.026, 0.173), 37.5% at T3 (CI95% 0.257, 0.505), 40.6% at T6 (CI95% 0.285, 0.536) and 35.9% at T9 (CI95% 0.243, 0.489). At T6, 78.1% (CI95% 0.66, 0.875) of patients reported a reduction of at least 40% to 60% of their pain. Statistical analysis indicated a significant change in NRS (p-value < 0.001), DN4 (p-value < 0.01), EQ-index (p-value < 0.001), and EQ-5D-VAS (p-value < 0.001) at the different follow-up time-points.

Conclusion: RFA using a V-shaped active tip needle might be a feasible and effective treatment for chronic lumbar zygapophyseal joint pain.

INTRODUCTION

Chronic back pain is a significant cause of disability, with increasing prevalence and an increasing economic impact. [1-3] Lumbar zygapophyseal joint ("z-joint") pain represents a clinically burdensome source of chronic axial low back pain (LBP), estimated to affect between 10% and 15% of patients [4]. Radiofrequency ablation (RFA) of the lumbar medial branch nerves is a common treatment modality for patients with z-joint mediated pain. [5-7] RFA aims to prevent the conduction of nociceptive impulses through the use of an electric current that damages the medial branch nerves, which are the z-joints' pain-conducting nerves. The effectiveness of radiofrequency denervation performed with rigorous standards and appropriate selection criteria has been demonstrated. [8-9] However, medial branch nerves exhibit a wide range of anatomical variability, along with their small size and the inconsistency of their number. [10] Therefore, the success of RFA is contingent upon creating a large enough lesion that overlaps the sensory nerve supplying the affected z-joint. [2] Given this variability, a larger lesion should increase the possibility of capturing the target nerve. Additionally, this would potentially obviate the need to conduct numerous lesions, therein reducing procedure times. [11-14]

Monopolar RFA is the most commonly used technology, employing a single electrode probe inserted under fluoroscopic guidance adjacent to the target nerve. The use of a V-shaped needle, in which the electrode forks off from the active tip, has been demonstrated to result in increased lesion size, [15] thus having the potential to compensate for the anatomical variability of the medial branches.

The aim of our study is to evaluate the effectiveness and feasibility of RFA procedures using a V-shaped active tip needle for chronic lumbar z-joint pain.

METHODS

This is a single-center observational retrospective study of patients undergoing percutaneous RFA using a V-shaped active tip needle for chronic lumbar z-joint pain, conducted from September 2020 to January 2022. The study has been conducted at Fondazione Istituto "G. Giglio" – Cefalù, Palermo, after Local Ethics Committee and Hospital Scientific Committee approval.

Inclusion criteria were: Adult patients (>18 years), diagnosis of chronic lumbar zygapophyseal joint pain, failure of conservative treatments, and ability to provide informed

consent for data analysis and publication. Exclusion criteria were: Lumbar pain not related to zygapophyseal joints, incomplete data, and absence or withdrawal of informed consent for data analysis and publication. One hundred and twenty (120) consecutive adult patients treated with this method were included. Data from 56 patients were omitted as they were incomplete (n=50), due to follow-ups not reaching the minimal number of observations required for analysis, or because of consent withdrawal (n=6).

For the remaining 64 patients, all medical records were independently screened by three investigators (G.L.B., G.M., C.G.). Patients' characteristics including gender, age, diagnosis, timeline, and clinical presentation of chronic LBP were extracted from the records (Table 1). We evaluated the pain level and their impacts on patients' daily life assessing the NRS (scale 0-10), [16] the DN4, [17] the EuroQoL - EQ-5D-3L, EQ-VAS and the EQ-index (Figure1). [18] The EQ-5D-3L has been developed with the purpose to describe and value health. This is an instrument which includes a descriptive system questionnaire and a visual analogue scale. The EQ-VAS is a 0-100 scale on which respondents are asked to indicate their overall health on the day of questionnaire completion. However, in our study, we decided to rescale it from 0 to 10, with the aim of simplifying the phone-call questionnaire administration. The individual health status can also be expressed as a summary index value (EQ-index), obtained when the descriptive system profile is linked to a value set, which is a collection of index values for all possible EQ-5D health states. For the purpose of our study, UK value sets were used.

Pre-treatment (T0, baseline) and post-treatment (follow-up) NRS, DN4, EQ-5D-3L, EQ-index and EQ-VAS were recorded and analyzed, as well as pre-treatment use of analgesic drugs (type and dose of analgesic in order to obtain a NRS <3). Follow-up was performed at 1-, 3-, 6-, and 9-months post- procedure (named, respectively, T1, T3, T6, T9). Type (unilateral or bilateral) and sites (lumbar and sacral levels) of RFA procedure were retrieved for all included patients. We screened clinical records for early and late-onset adverse events. While follow-up at 1 month was performed by the physician who carried out the procedure, re-evaluation at the different timepoints was conducted via a telephone-call questionnaire by an independent investigator. This was done in order to avoid a potential investigator bias, which might have influenced the evaluation of clinical results over time. At the last follow-up, patients were also asked to complete a NASS4-point patient satisfaction questionnaire. [19] A score of 1 or 2 on the NASS patient satisfaction index was considered a successful response to the procedure. Patients were also asked whether use of post-procedural analgesics was resumed.

We adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement. [20] Figure 1 illustrates the timeline of the follow-up protocol applied.

Technical procedures

Screening medial branch blocks: Needle placements for the screening medial branch blocks were conducted in accordance with the Spinal Intervention Society (SIS) Guidelines. [12] Patients were positioned prone with C-arm fluoroscopy with an anteroposterior view of the appropriate level of the spine. After local anesthetic was administer at entry points, 22-gauge spinal needles were placed at the appropriate site. Lumbar z-joint pain was investigated through diagnostic blocks using 1% lidocaine. Patients with lidocaine-positive results were further studied using 0.25% bupivacaine on a separate occasion (3 to 4 weeks after the first injection). Following each block, the patient was examined and asked to perform previously painful movements. A positive response was defined as at least a 50% reduction of pain within 30 to 90 minutes post-procedure, lasting at least 2 hours when lidocaine was used and at least 3 hours in cases in which bupivacaine was used. Patients with a double-positive response to diagnostic blocks were scheduled for an RFA procedure.

Radiofrequency ablation: The RFA procedures were performed in operating rooms under continuous monitoring of patients' vital parameters. All patients were administered procedural sedation with short-acting intravenous agents (benzodiazepines, e.g., midazolam), supplementing local anesthesia of the skin and underlying tissues. An 18-gauge 100 mm needle with a V-shaped active tip (Venom cannula, Stryker®) was introduced at each entry point, with RFA electrodes placed according to SIS guidelines for lumbar medial branch thermal radiofrequency neurotomy. [12] Position of the cannula was checked on anteroposterior (AP) and lateral views (Figure 2). The depth was adjusted until the cannula tip touched the bone (between the transverse vertebral process and the superior articular process) at the level of the target medial branch (Figure 3). The V-shaped active tip was placed parallel to the medial branch that was being treated. To improve the accuracy of needle positioning prior to lesioning, sensory and motor stimulation were performed (lower threshold range for detecting sensory stimulation at 50 Hz between 0.3 and 0.7 V; upper threshold range for ruling out motor stimulation at 2 Hz between 0.9 and 3 V). The presence of paresthesia at the site of patients' usual pain was considered a positive sensory test, whereas the absence of contraction of major muscle groups was considered to be an

acceptable motor test. Following the above-described test, 1 mL of lidocaine 1% was injected through the needle prior to the RFA procedure. RFA was conducted at 85°C for 90 seconds for each level. Prior to cannula removal, dexamethasone 2 mg and 1 ml ropivacaine 0.25% were injected for each treated level.

STATISTICAL ANALYSIS

Data are expressed as mean ± standard deviation (SD) or as median and interquartile range (IQR), where appropriate. Categorical variables are expressed as proportions (frequencies and percentages). Normality of data distribution was verified through the Shapiro-Wilk normality test. Considering the non-normal distribution of the variables, comparisons over different time-points was performed using the Friedman's test with post-hoc analysis using the pairwise Wilcoxon signed-rank test. P-values were adjusted according to the Bonferroni multiple testing correction method. Fisher's exact test was used to determine whether there was a significant association between the type of RFA procedure applied (unilateral or bilateral) and the use of post-procedural analgesics. P-values <0.05 were considered to be statistically significant. The statistical analysis was performed using R software. [21]

RESULTS

Of the 64 patients (50 women and 14 men, mean age: 64.22 years ± 11.71) included in the study, patients between ages 60-70 years were the most represented group (25; 39.1%). Monolateral RFA procedures were performed on 48 patients (75%). Analgesics consumption was present in 60 patients (93.8%; CI95% 0.848, 0.983) prior to the RFA procedure in 31 patients (48.4%; CI95% 0.358, 0.613) at the final follow-up, while 33 patients (51.6%; CI95% 0.387, 0.642) confirmed that they resumed their use at 9 months following the procedure. Table 1 illustrates the baseline characteristics of the studied population.

The median baseline NRS was 8.00 (IQR 6.00, 8.00). Follow-ups post-RFA procedures demonstrated a reduction of pain score, with a NRS decreasing from 5.50 (IQR 3.75, 7.00) at T1 to 2.00 (IQR 1.00, 4.00) at T9 (Table 2). Considering the percentage of pain reduction at the different post-procedural time-points (Table 3), relief of greater than 80% in NRS was experienced by 7.8% of patients at T1 (CI95% 0.026, 0.173), 37.5% at T3 (CI95% 0.257, 0.505), 40.6% at T6 (CI95% 0.285, 0.536) and 35.9% at T9 (CI95% 0.243, 0.489). At T6, 78.1% (CI95% 0.66, 0.875) of patients reported a reduction of at least 40% to 60% of symptoms. Only 1 patient experienced exacerbation of symptoms at 1 month post-RFA

procedure, while no exacerbations were subsequently observed at the rest of the time-points.

According to the NASS index, 47 subjects (73.4%) reported a successful outcome (NASS score of1 or 2) and 17 (26.6%) reported an unsuccessful outcome (NASS score of 3 or 4). When NRS modifications over time are stratified as either success or failure, patients with a NASS score of 1 or 2 demonstrated a -2 point (IQR -4.50, 0.00) reduction in their NRS pain scores at T1, -6 (IQR -7.00, -4.50), at T3, -6 (IQR -7.00, -5.00) at T6 and -6 (IQR -7.00, -4.00) and at T9 (Table 4A/4B).

When considering repeated measures over the different time-points, the analysis indicated a statistically significant change in NRS (Friedman chi-squared = 175.13, df = 4, p-value < 0.001), DN4 (Friedman chi-squared = 117.9, df = 4, p-value < 0.01), EQ-index (Friedman chi-squared = 132.8, df = 4, p-value < 0.001), and EQ-5D-VAS (Friedman chi-squared = 129.71, df = 4, p-value < 0.001) at the different time-points (Table 2).

For the purpose of the secondary outcome, subjects were stratified into 2 groups according to pain reduction at the different time-points (greater vs. less than 50% when compared to T0 baseline evaluation) and quality of life assessed using EQ-5D-3L (table x). Patients with greater than 50% pain reduction at T6 and T9 referred a fair (46% at T6; 42.2% at T9) to optimal (54% at T6; 57.8% at T9) quality of life when compared to pre-procedural assessment. When considering patients with less than 50% pain reduction, only 14.3% and 10.5% (at T6 and T9, respectively) reported a worsened post-procedural quality of life (Table 5).

There was no significant statistical association between the type of RFA procedure applied (monolateral or bilateral) and the use of analgesics after the RFA procedure (p-value= 0.7758), nor between the post-procedural use of analgesics and NASS index assessment (p-value= 0.779). No adverse events were observed or reported by patients during follow-up.

DISCUSSION

There are few conditions in interventional pain medicine as controversial as lumbar z-joint pain treatment. Despite facet joint interventions representing the second most common pain management procedures in the USA, [22] the safety and efficacy of RFA for the treatment of chronic LBP has yet to be well-substantiated. Patients who were included in our study demonstrated a reduction in pain scores, with a peak reduction of pain occurring at 6 months following the procedure. Up to 78.1% (CI95% 0.66, 0.875) of the patients experienced a

reduction of NRS of at least of 40-60% at 6 months post-RFA for z-joint chronic lumbar pain. Despite the re-emergence of pain within 6-9 months of the procedure, the symptoms reported were significant reduced when compared to baseline assessment (-6 points in NRS after 6 and 9 months within the success group; 46 patients with NRS $\leq$ 3 at T9). In addition, when considering the EQ-index scores between the different time points analyzed, the impact on the re-emergence of pain on daily life seems to have been contained. Our results are in line with extant published data. It is generally accepted that relief following radiofrequency denervation typically lasts for between 6 and 12 months, [23] although it has been reported to provide relief for greater than 2 years in some cases. Repeating RFA up to 3 times has demonstrated to possibly relieve z-joint pain and maintain results over time. [24] However, RFA treatment success remains inconstant, and a small proportion of patients do not experience any pain relief or only a very time-limited benefit from the procedure. When analyzing our study cohort, patients undergoing an unsuccessful procedure (26.6%) reported a limited median reduction of NRS as compared to subjects undergoing a successful RFA procedure (73.4%) using the same technique, with a significative difference between these 2 groups at 9-month follow-up (Table 2-3). The rate of nerve regeneration and subsequent return of previous LBP symptoms is thought to be related to the failure of procedure technique (failure of direct nerve coagulation or minimal ablation of a limited section of the target nerve) and whether correct anatomical placement of the RFA electrode is achieved. As reported by Bogduk, [25] nerve regeneration following coagulation requires a longer period of time than the 1 mm per month observed in nerve transection injuries. For this reason, post-RFA pain relief might last longer when a larger area of the nerve is contacted, and a greater length of the nerve segment is coagulated. [26] Different techniques have been described with the purpose of increasing the likelihood of success rates and durations of pain relief following RFA for chronic z-joint related LBP. [27] The two-needle RFA technique was developed to heat a wider volume of tissue and minimize technical failure due to incomplete coagulation. This approach uses a dual needle placement of two 10 mm active tip RFA cannulas separated by 6 mm. [28] Some of the major limiting factors of the two-needle RFA technique are improper needles placement, difficulties in their correct positioning and the time for the operator to accurately place the active tips. As a result, the costs and time constraints, and the limited availability of long-term clinical results of this procedure, have hampered its widespread adoption. As demonstrated by Cedeno and colleagues, [15] the use of V-shaped active tip needles provides an additional 0.6 x 0.6 mm lesion size when compared with standard monopolar

RFA needles, using equivalent settings. Thus, V-shaped active tip RFA may provide a wider lesion using a single needle, with additional cost and time savings. It is important to recognize that a technical limitation is that achieving the maximum lesion generated at the target location requires that the V-shaped electrode be placed in the correct plane parallel to the nerve (Figure 4,5,6). As is the case with any procedure involving damage to the peripheral nervous system, RFA poses a risk of post-procedural neuropathic pain. Corticosteroids might have a beneficial impact, although their concomitant administration during RFA procedures at the level-sites treated remains controversial. To date, only a randomized controlled pilot study [28] has identified a potential protective effect of dexamethasone injections against post-procedural neuropathic pain emergence. All patients included in our retrospective study underwent local injections of dexamethasone for each site treated. Considering DN4 assessment at T6 (1; 0.00-3.00) and T9 (2; 0.00, 3.00), one may speculate an influence of dexamethasone administration in avoiding post-procedural neuropathic pain development. However, these results are of limited value and require further studies in order to determine whether corticosteroids might be helpful in containing post-RFA adverse events. There are several limitations to our study, most of which are inherent in any non-controlled retrospective observational study with a small sample size. Although demonstrating that RFA using V-shaped active tip needles is effective, a larger prospective RCT comparing the conventional monopolar technique to V-shaped active tip needle RFA is necessary in order to clarify the efficacy and safety of this novel technique. Second, the accuracy of a diagnostic block is contingent on several technical, anatomical, and psychological factors. As a result, there exists the possibility of false-positive responses, which undermine RFA treatment results over time. Furthermore, a bias might be introduced by telephone-questionnaire administration during follow-up; even if interviews and data analysis were performed by an independent investigator, patients may be reluctant to report poor outcomes due to their desires to please medical professionals. Third, we did not consider potential co-intervention (e.g., physical therapy, spinal manipulation, educational or psychological therapies) which might have interfered with the results of the analyzed treatment. In addition, some of the improvements seen may be attributable to spontaneous relief and/or placebo effect.

CONCLUSION

Radiofrequency ablation for chronic lumbar z-joint pain using a V-shaped active tip needle is a feasible and effective technique. However, the relative efficacy of this technique compared to conventional RFA following rigorous criteria remains unclear. Accordingly, the results of our study should be considered as preliminary, and we believe that future randomized controlled trials building on our reported results will further clarify the overall benefits of this novel approach.

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Authors' contribution:

GLB conceived the content, retrieved the data and wrote the manuscript. GM analyzed the data and wrote the manuscript. CG retrieved the data and gave important intellectual contribution. AS, MD and KDJ wrote the manuscript and gave important intellectual contribution. MS provided rewriting of the manuscript and input regarding statistical analyses. All the authors approved the final version of the manuscript before submission.

Population characteristics	Group	Overall
N. of patients		64
Age (mean ± SD)		64.22 (11.71)
Age categories(%)	<50	12 (18.8)
	50-60	3 (4.7)
	60-70	25 (39.1)
	70-80	22 (34.4)
	>80	2 (3.1)
Sex (%)	F	50 (78.1)
	M	14 (21.9)
RFA procedure (%)	monolateral	48 (75.0)
	bilateral	16 (25.0)
Level (%)	L2	4(6.2%)
	L3	40 (62.5%)
	L4	60 (93.8%)
	L5	64 (100%)
	S1	29 (45.3%)
	S2	14 (21.8%)
	S3	8 (12.5%)
Analgesics pre-RFA (%)	no	4 (6.2)
	yes	60 (93.8)
Analgesics post-RFA (%)	no	33 (51.6)
	yes	31 (48.4)

TABLE 1: Demographic and baseline characteristics of patients' population (RFA: radiofrequency ablation; SD: standard deviation).

Variables	T0	T1	T3	T6	T9
NRS					
10	4 (6.2)	0 (0)	0 (0)	0 (0)	0 (0)
9	8 (12.5)	2 (3.1)	0 (0)	0 (0)	0 (0)
8	21 (32.8)	7 (10.9)	1 (1.6)	1 (1.6)	2 (3.1)
7	14 (21.9)	8 (12.5)	1 (1.6)	0 (0)	1 (1.6)
6	7 (10.9)	15 (23.4)	1 (1.6)	1 (1.6)	3 (4.7)
5	9 (14.1)	14 (21.9)	6 (9.4)	6 (9.4)	7 (10.9)
4	0 (0)	2 (3.1)	5 (7.8)	5 (7.8)	6 (9.4)
3	1 (1.6)	4 (6.2)	8 (12.5)	7 (10.9)	6 (9.4)
2	0 (0)	9 (14.1)	20 (31.2)	19 (29.7)	17 (26.6)
1	0 (0)	3 (4.7)	20 (31.2)	23 (35.9)	20 (31.2)
0	0 (0)	0 (0)	2 (3.1)	2 (3.1)	2 (3.1)
NRS (median)	8.0	5.5	2.0	2.0	2.0
IQR	[6.0, 8.0]	[3.75, 7.0]	[1.0, 3.0]	[1.0, 3.0]	[1.0, 4.0]
p-value		<0.005	<0.005	<0.005	<0.005
			<0.005	<0.005	<0.005
				0.89	1.00
					0.14
EQ-index (median)	-0.19	0.52	0.52	0.73	0.69
IQR	[-0.51, -0.02]	[0.02, 0.52]	[0.52, 0.73]	[0.52, 0.85]	[0.02, 0.52]
p-value		<0.005	<0.005	<0.005	<0.005
			<0.005	<0.005	<0.005
				<0.005	0.60
					1.00

TABLE 2: Pain scores (NRS) and quality-of-life assessment (EQ-index) of patients at baseline and at different times of follow-up, with Friedman's test and pairwise comparisons results (IQR: interquartile range, NRS: numeric rating scale).

Change in NRS (%)	T1 (%)	cumulative proportion T1	T3 (%)	cumulative proportion T3	T6 (%)	cumulative proportion T6	T9 (%)	cumulative proportion T9
80-100	5 (7.8)	0.078	24 (37.5)	0.375	26 (40.6)	0.406	23 (35.9)	0.359
60-80	9 (14.1)	0.219	20 (31.2)	0.687	19 (29.7)	0.703	17 (26.6)	0.625
40-60	4 (6.2)	0.281	5 (7.8)	0.765	5 (7.8)	0.781	6 (9.4)	0.719
20-40	11 (17.2)	0.453	7 (10.9)	0.873	6 (9.4)	0.875	6 (9.4)	0.813
0-20	34 (53.1)	0.984	8 (12.5)	1.0	8 (12.5)	1.0	12 (18.8)	1.0
worse	1 (1.6)	1.0	0 (0.0)	1.0	0 (0.0)	1.0	0 (0.0)	1.0

TABLE 3: Change in NRS pain score (expressed as percentage of NRS reduction after treatment), with number and cumulative proportion of patients obtaining various degrees of pain improvement at different time-points during follow-up.

North American Spine Society Patient Satisfaction Index – NASS index
1) The treatment met my expectations
2) I did not improve as much as I had hoped, but I would undergo the same treatment for the same outcome
3) I did not improve as much as I had hoped, and I would not undergo the same treatment for the same outcome
4) I am the same or worse than before treatment

TABLE 4A: North American Spine Society Patient Satisfaction Index (NASS index). NASS index of 1 or 2: successful response to the procedure; NASS index of 3 or 4: unsuccessful response to the procedure.

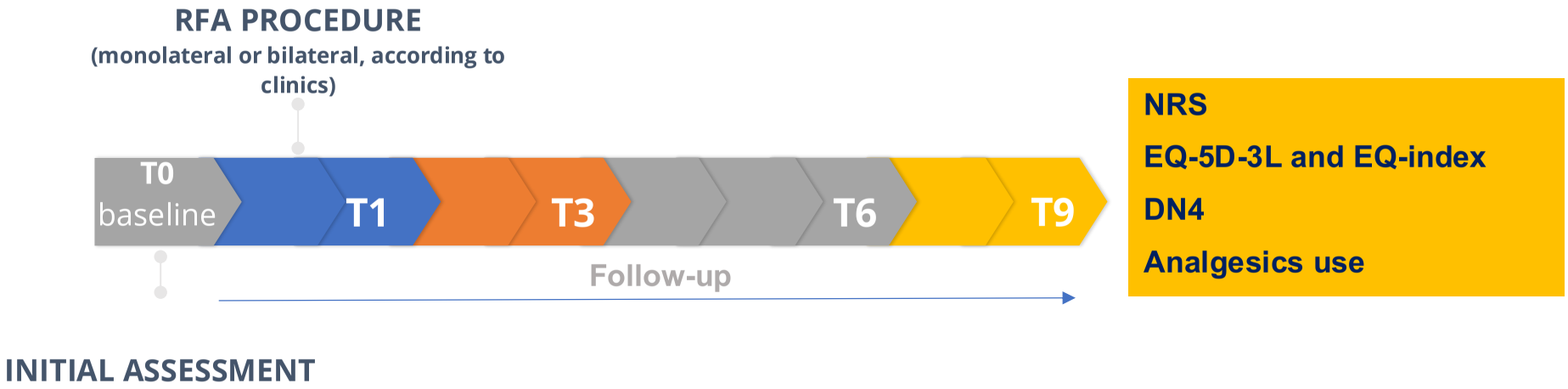
Change of NRS (post-pre)	Success (n=47; 73.4%)	Failure (n=17; 26.6%)	p.value
T1	-2.00 [-4.50, 0.00]	0.00 [-2.00, 0.00]	0.191
T3	-6.00 [-7.00, -4.50]	-4.00 [-6.00, 0.00]	0.005
T6	-6.00 [-7.00, -5.00]	-4.00 [-6.00, 0.00]	0.002
T9	-6.00 [-7.00, -4.00]	0.00 [-5.00, 0.00]	<0.001

TABLE 4B: Change of NRS pain score at the different time-points. Success and failure outcomes are defined according to NASS index (NASS index of 1 or 2: successful response to the procedure; NASS index of 3 or 4: unsuccessful response to the procedure).

	pain reduction (%)	<50	>50	p-value
		T1		
n.		47	17	
QoL T1 (%)	worsened	13 (27.7)	3 (17.6)	0.275
	decent	34 (72.3)	13 (76.5)	
	optimal	0 (0.0)	1 (5.9)	
		T3		
n.		15	49	
QoL T3 (%)	worsened	2 (13.3)	2 (4.1)	0.035
	decent	11 (73.3)	24 (49.0)	
	optimal	2 (13.3)	23 (46.9)	
		T6		
n.		14	50	
QoL T6 (%)	worsened	2 (14.3)	0 (0.0)	<0.001
	decent	11 (78.6)	23 (46.0)	
	optimal	1 (7.1)	27 (54.0)	
		T9		
n.		19	45	
QoL T9 (%)	worsened	2 (10.5)	0 (0.0)	<0.001
	decent	16 (84.2)	19 (42.2)	
	optimal	1 (5.3)	26 (57.8)	

Table 5: Stratification at the different time-points during follow-up of quality-of-life assessment (according to EQ-index value) for patients reporting a variation of pain scores (NRS) of more or less than 50% (when compared to baseline T0 NRS) after treatment.

Figure 1: Timeline of follow-up time points and variables analyzed.



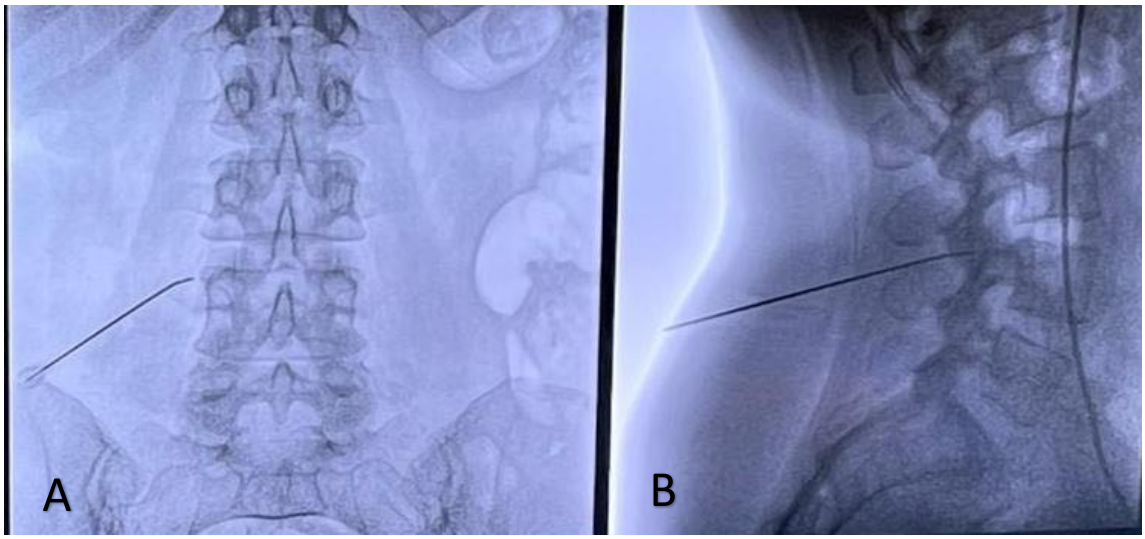


Figure 2

A. Antero-posterior view showing the electrode inserted along an oblique trajectory to avoid the mamillo-accessory ligament.
B. Lateral view showing the active tip of the electrode placed across the middle two-quarters of the neck of the superior articular process.

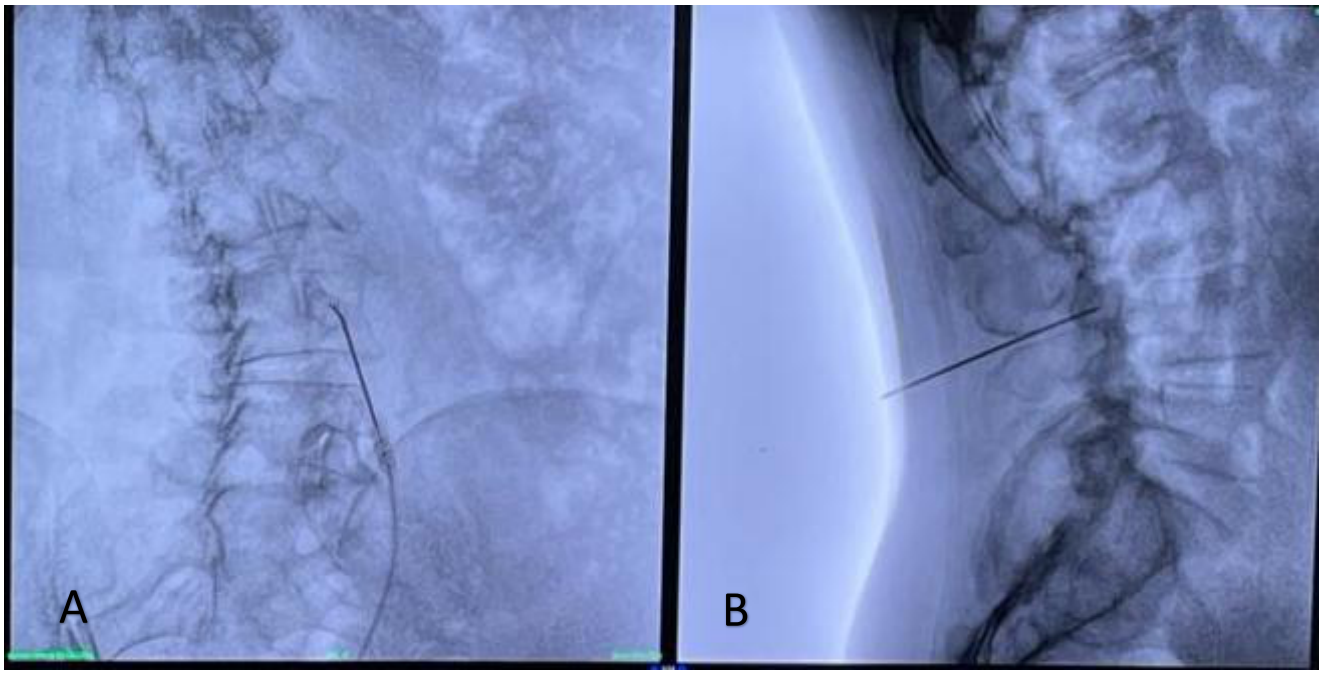


Figure 3

A. Oblique view showing the cannula passing across the sulcus for the medial branch.
B. Lateral view showing the cannula placed across the middle two-quarters of the neck of the superior articular process.

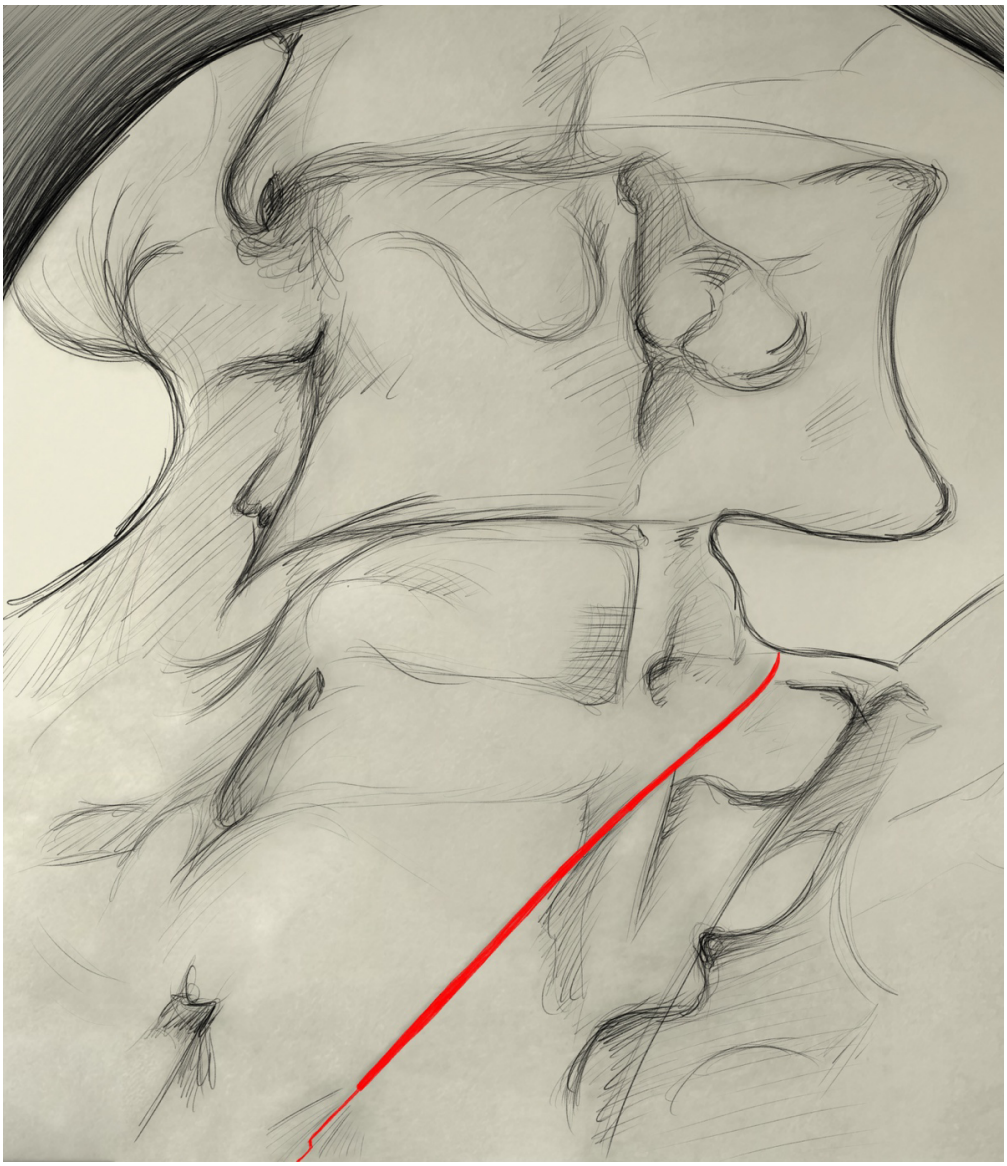


Figure 4
Oblique view showing the cannula (red) passing across the sulcus for the medial branch.

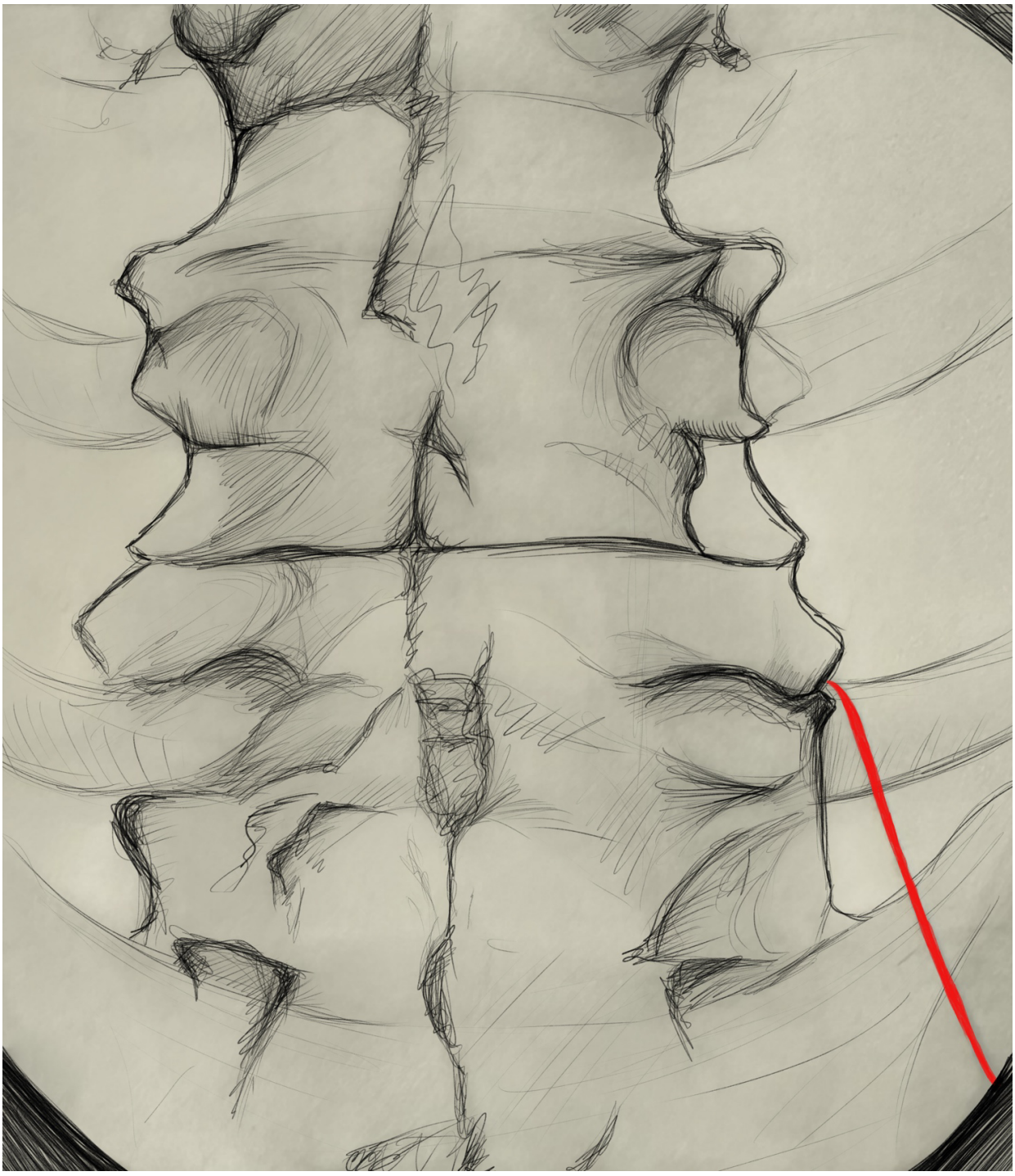


Figure 5
Antero-posterior view showing the cannula (red) crossing the ala of the sacrum and lying against the superior articular process of L5.

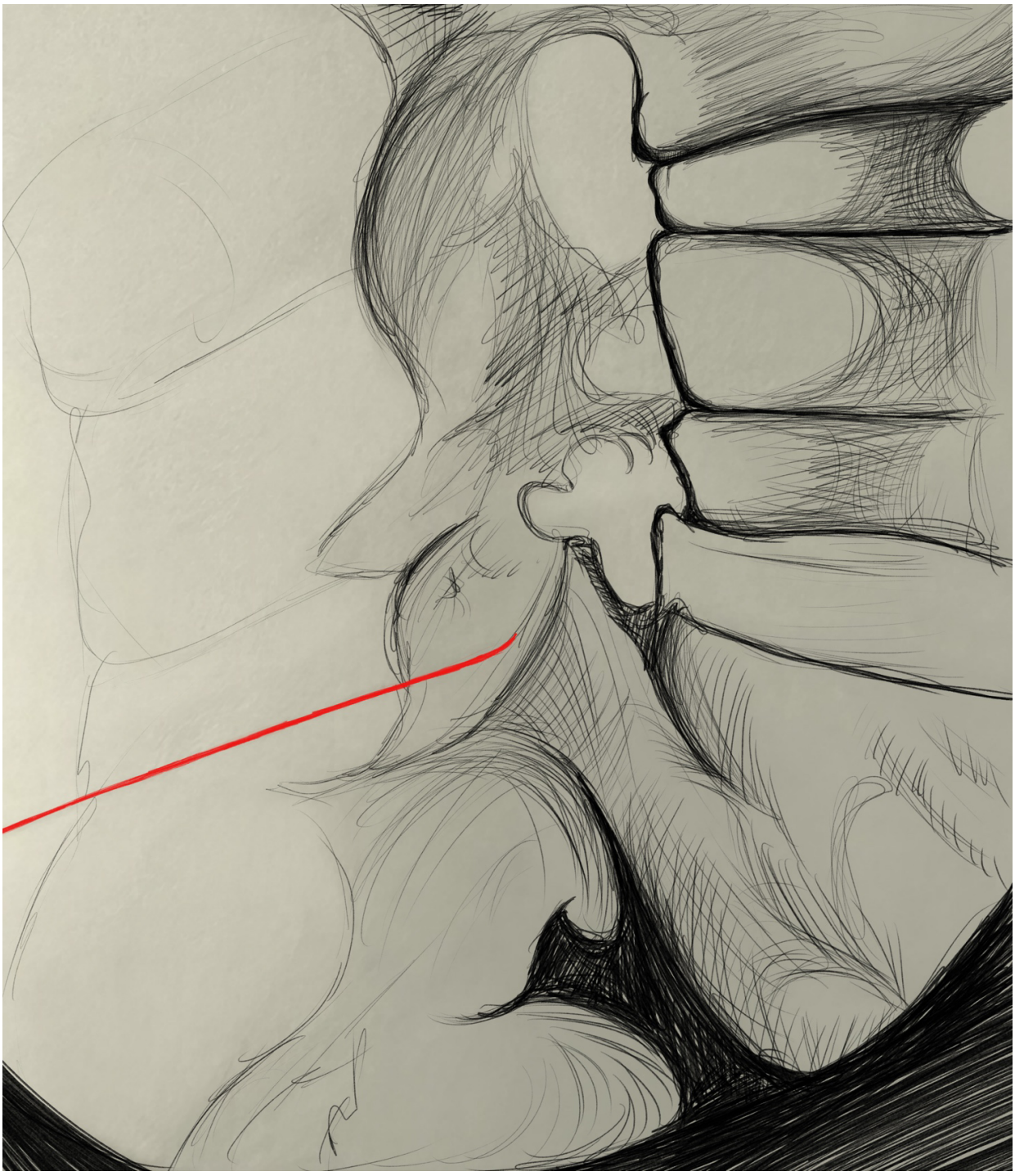


Figure 6
Lateral view showing the cannula (red) placed across the middle two-quarters of the neck of the superior articular process.

DISCUSSION

Neuromodulation mechanisms of action

Neuroplasticity is natural response of the human nervous system involving functional and structural changes in response to stimuli. Although neuromodulation modalities do not use the same mechanisms, it similarly promotes neuroplasticity through functional convergence.[14,15] This may occur via synaptic plasticity and functional modifications (i.e., ion channels) which can change neuronal excitability. Stimuli are able to change the electrical state of singular neurons at the cellular level, they can induce neurotransmitter activity in neurohumoral signalling; alter neuronal circuits at the network level; and modify pain and function at the behavioural level, stimuli can lead to changes in pain and function. [14,15]

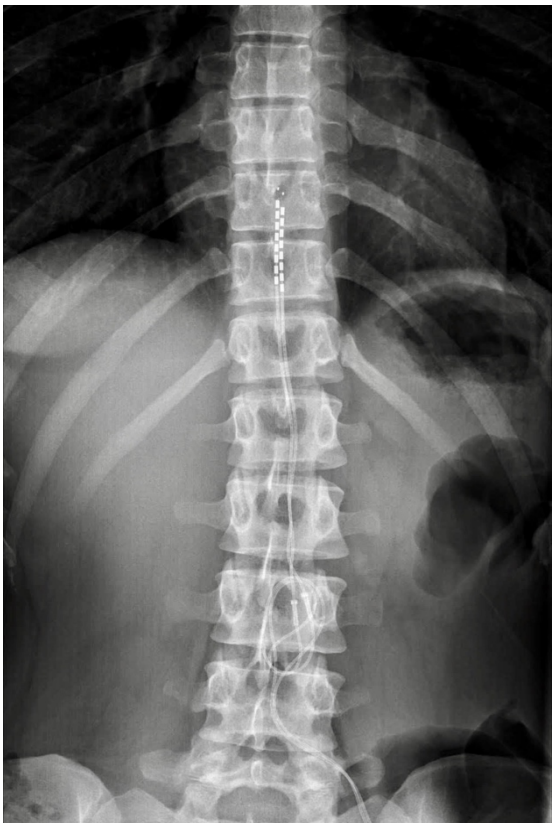
There is evidence that transient neuromodulation evokes long-lasting changes in neuronal and non-neuronal activity even after stimulation has been interrupted. Furthermore, the early or pre-emptive use of this method is attracting a great deal of conference discussion and innovative research protocols.[16,17] As response to neuromodulation depends on a range of factors, such as age, sex, psychological and genetic factors but also waveform variables, pain pathology and timing of neuromodulation, being able to predict outcomes for patients has proved challenging for all forms of the therapy.

Like all analgesic treatments, the effects of neuromodulation lessen with time. Kemler and colleagues [18,19] demonstrated in a randomized, controlled study that SCS in CRPS provided relief for a maximum of 2 years. This reduction in effect might be due to wind-up of the nervous system as a result of a range of reasons, including repetitive stimulation (maladaptive neuroplasticity), diminution of the placebo effect, disease progression, lead migration, and other complications. However, it must be added that lead migration and other complications will undoubtedly decrease further as technology continues to undergo miniaturization.

Placebo effect

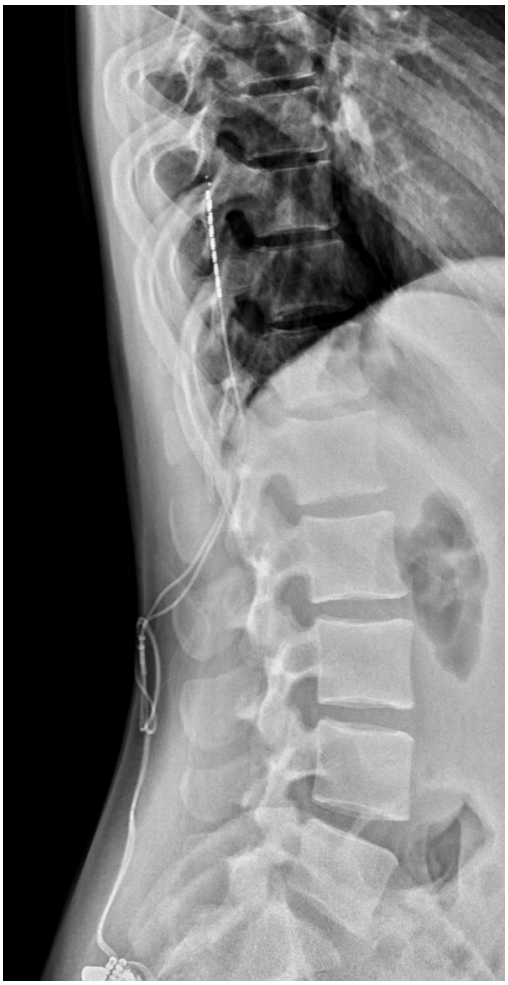
A strong placebo effect is linked to neuromodulation, which is found to be greater for procedures than medications.[20,21] This could be due to a range of factors; repeated visits, for example, the doctor-patient relationship, patient expectations of highly specialised technology, or evident treatment effects, such as paraesthesias. [22] Nonparaesthesia-based treatments may be able to limit some of the abovementioned factors in the future, however, there are few studies using this waveform to date. In a number of small studies which analysed a range of frequencies in the treatment of axial low back pain in Failed Back Surgery Syndrome (FBSS), high frequency demonstrated greater results than low frequency stimulation. This latter did not appear to differ significantly from sham stimulation. [23] On a physiological level, placebo treatments evoke neurophysiological changes which hinder pain (i.e., sympathetic nervous system inhibition, serotonergic agonism, and the release of dopamine and endogenous opiates in the brain).[24] The placebo effect for neuromodulation, like most chronic pain therapies, is greater in many people than any intrinsic effect.

Spinal cord stimulation



In SCS, a pulse generator connected to two electrodes is implanted subcutaneously with leads which travel into the epidural space posterior to the spinal cord dorsal columns. The mechanisms behind pain inhibition and neuroplasticity from neurostimulation are intricate; however, the gating of dorsal horn neurons seems to play a part, through activation of Aβ fibres and inhibitory interneurons. 2 Studies on animals have found that the inhibitory neurotransmitter γ-amino butyric acid (GABA) plays a central role in SCS analgesia and blocking GABA can reverse analgesia.[25,26] Descending modulatory pathways indicate that supraspinal mechanisms are also essential. [27]

Studies on functional magnetic resonance demonstrate how suprathreshold stimulation activates frontal gyrus, limbic, and thalamic areas, for example, in different ways. [28] In general, clinical data on pain reduction and improved quality of life (QoL) show that SCS is more effective for neuropathic than non-neuropathic (axial back) or central (phantom limb) pain in patients showing a response to trials. [29]
Meta-analyses and systematic reviews have uncovered weaknesses in earlier SCS studies. [23,30] In many studies, patients unresponsive to surgery or conservative treatments were directed randomly to either further similar treatments or to receive SCS. [18,19,31,32]



Newer technologies are now available which do not induce paraesthesias. Paraesthesia-free SCS indicates that the vast majority of patients do not sense any physical reaction; this should theoretically permit double-blind trials.

High frequency SCS

SCS therapy consists of short-duration (30 μs) electrical pulses delivered at a high frequency (10 000 Hz) and low-amplitude (1–5 mA), without paraesthesias, to T8–T11 spinal levels for lumbar or lower extremity pain. [33,34] This empirical form of lead placement does not take anatomical differences or variations in pain patterns reported by the patient into consideration.
The UK National Institute for Health and Care Excellence has issued guidelines in support of high-frequency SCS as potentially effective for chronic neuropathic pain. However, the guidelines specify the need for the careful selection of patients, such as low failure-risk patients (without secondary gain, co-existing psychopathologies, or high-dose opioid therapy). [35]
As regards pain reduction with improved QoL in CRPS [18], FBSS [31], and neuropathy [36,37] and pain reduction without improved QoL in FBSS [32], many nonblinded research findings have

demonstrated the effectiveness of traditional SCS. Despite this, mostly small-scale industry-sponsored research has shown mixed findings when comparing traditional SCS with sham stimulation [38-41], and SCS with newer modalities, including high-frequency stimulation. [33,40,42-44]

Burst spinal cord stimulation

Burst SCS is a low-energy modality that applies 5-pulse trains at a specific internal frequency (500 Hz) and pulse width (1 ms with 1 ms intervals) delivered at 40 times per s. [45] Burst SCS mimics the dual firing properties of thalamic cells, which can fire in tonic (single spikes) and burst modes (rapid spiking followed by quiescent periods). [41] Most studies [39,41,44,46] (mainly industry-sponsored) which compared burst to traditional SCS found burst more effective for pain reduction (excepting papers from *Kriek et al* [40] and *Tjepkema-Cloostermans et al* [46]), and some [49] findings also noted improved QoL (excepting papers from Deer et al [44] and *Tjepkema-Cloostermans et al* [46]).

Closed loop spinal cord stimulation

In traditional SCS, an open-loop system is used to set stimulation variables. Closed loop stimulation, however, delivers real-time recordings of evoked compound action potentials (a measure of nerve fibre activation). This may be useful to gauge spinal cord proximity, a factor which can mutate with patient movement and pain. Closed loop SCS modifies stimulation intensity to reduce differences between target evoked compound action potentials and those measured. [43,47] Although an industry-sponsored randomised trial demonstrated substantial pain reduction and improvements in QoL compared to traditional SCS in patients with back and leg pain over a 12-month period, a number of misgivings were expressed concerning the effectiveness of blinding and accuracy of reporting. [43,48]

Dorsal root ganglion stimulation

Dorsal root ganglion stimulation (via electrode insertion through the neural foramen), may block signalling of pain fibre action potential from primary sensory units and thus relieve pain. [49,50]

This method is widely recommended for patients with pain in the distribution of discrete dermatomes from T10 to S2. An industry-sponsored trial comparing dorsal root ganglion stimulation with conventional SCS for CRPS reported more favourable findings for dorsal root ganglion stimulation for pain reduction and improved QoL over 12 months. [51]

Summary of Spinal Stimulation

For FBSS, quality of evidence that traditional SCS excels conventional medical management or reoperation for pain reduction is low-to-moderate, and low regarding QoL improvement for at least 2 years. Evidence demonstrating its advantage over sham stimulation and improvements in QoL is contrasting. [38,39] As regards CRPS, moderate quality evidence demonstrates more favourable results for traditional SCS than conventional medical management for pain reduction and QoL improvement,8 with contrasting evidence regarding its advantage over sham stimulation. [40,52]

Two comparative studies focusing on effectiveness in peripheral neuropathy with low/moderate quality of evidence and a number of non-randomised studies show that traditional SCS is favoured over conventional medical management for pain reduction, with low-quality evidence for QoL improvement. [53]

Essential factors limiting SCS trials include the fact that the success rate for repeat spine surgeries declines precipitously, and that most studies comparing SCS with conventional medical management re-randomized patients to treatments to which patients did not previously respond successfully. There is conflicting evidence of low-to-moderate quality that some types of SCS are superior to others for pain reduction or QoL improvement (or both) with discrepancies observed between industry-sponsored and non-industry-sponsored studies (table 2). [30,54] Nearly all randomised studies examined the use of SCS for conditions associated with either neuropathic pain or CRPS, making it impossible to offer recommendations for the treatment of non-lumbar nociceptive pain.

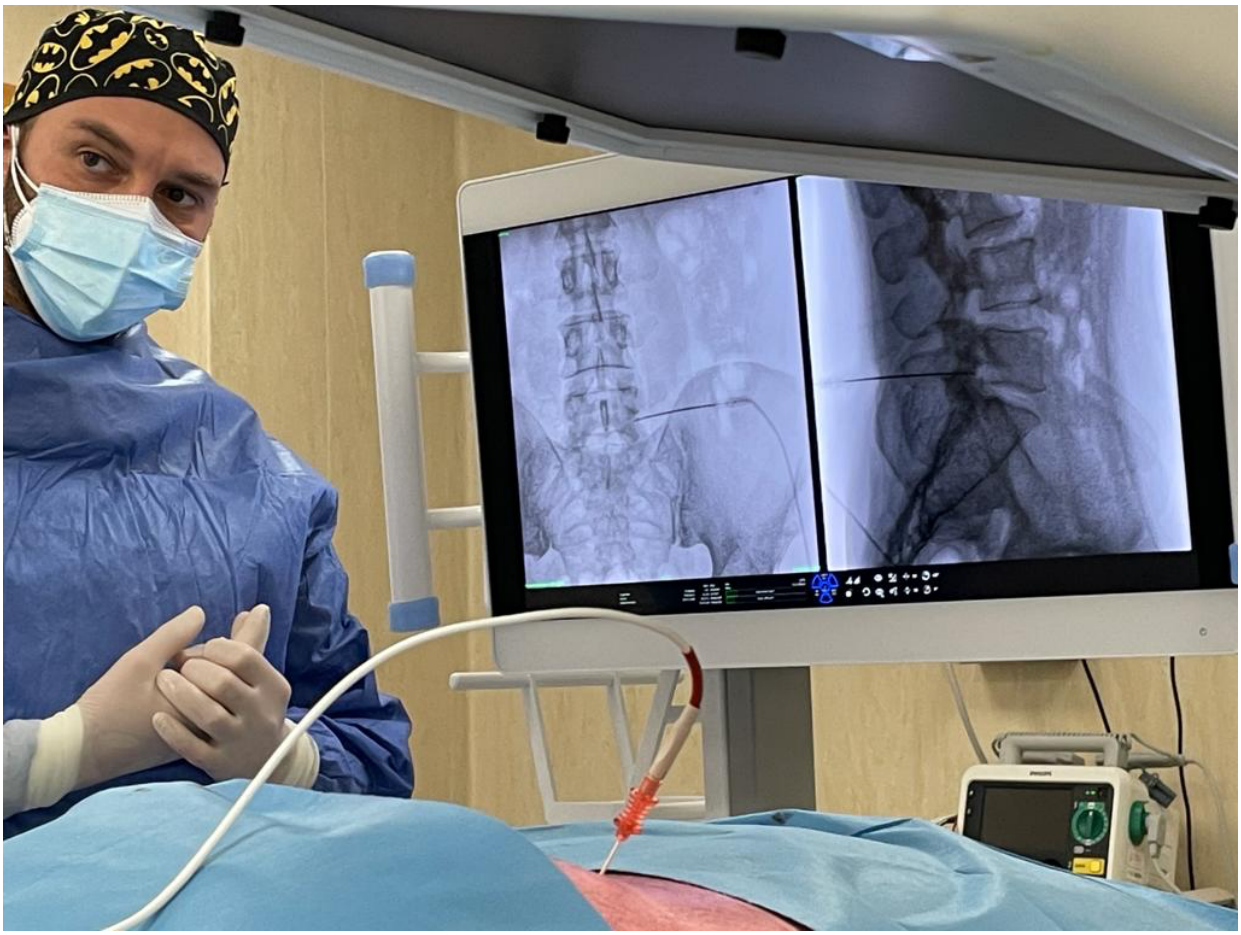
SCS could be considered in individuals with regional pain when more conservative therapies have not provided meaningful benefit and following careful selection of patients based on positive trials (≥50% pain relief), psychological evaluation, when indicated, thorough assessment of the risks and benefits of SCS, and a clear understanding of outcome expectations, including the limited data on long-term (>1 year) effectiveness.

Dorsal root ganglion stimulation invasiveness is similar to SCS; however, it requires a modified placement technique and might be associated with a greater complication rate

(e.g., lead migration and damage). [55] There is low-quality evidence based on a single industry-sponsored study that dorsal root ganglion stimulation is more effective than traditional SCS for pain reduction and QoL improvement in focal CRPS (appendix pp 9, 10). [51]

Radiofrequency

Pulsed radiofrequency (PRF) is an interventional pain management technique used for treating chronic neuropathic pain (thoracic postherpetic neuralgia, trigeminal neuralgia, radicular pain, and many other indications). [56-58] PRF delivers a low-energy electrical field in rapid pulsations to target nervous tissue and associated microglia. Compared to high-temperature radiofrequency ablation (RFA), PRF is not ablative, but instead neuromodulating. [59-61] Although PRF has demonstrated efficacy in the treatment of neuropathic pain conditions and has itself been widely adopted, a comprehensive review of mechanisms of action has not been published in almost a decade despite significant breakthroughs in the understanding of the molecular and cellular effects of PRF. [59]



PRF modulates many different pathways involved in nociceptive signaling, immune activity, and synaptic function, which, individually and in concert, are thought to pathologically result in chronic neuropathic pain.

Moreover, not all PRF is the same. With different parameters (frequency, pulse width, temperature, time, cannula, and active tip size) variably utilized from study to study, it is possible that some of the tissue effects and mechanisms of action varied with changes in parameter, not only based on parameters as a whole, but for different sets of parameters in different tissue types (i.e., sympathetic ganglia, peripheral nerves, DRG) and different species (i.e., humans versus rodents). The multitude of potential parameters and their effects on different nerve tissue types remains to be studied to further subclassify the mechanism of action for various sets of PRF parameters.

The majority of studies were performed in rodents which, while useful in the identification and evaluation of cellular and molecular mechanisms, may or may not be translatable to human neuropathic pain pathophysiology and the human response to PRF therapy. Further investigation is warranted to fully elucidate the direct mechanisms of action of PRF for treatment of neuropathic pain in humans.

It was found that pulsed radiofrequency impacts many different biological pathways involved in the modulation of chronic neuropathic pain (neuralgia). With regards to nociceptive signalling, PRF treatment modulates ion channels (Na/K ATPase, HCN, P2X3), CGRP, neurotransmitters (aspartate, citrulline, M-ENK, glutamate), postsynaptic receptors (AMPA-R, GABA-B), and synaptic function (KCC2). PRF treatment also modulates immune activity, including microglial markers (CD3, CD56, Iba1), inflammatory cytokines (IL-6, IL-17, IRF8, IFN-γ, TNFα), and intracellular proteins implicated in immune mediated neuropathic pain (BDNF, β-catenin, JNK, p38, ERK1/2). [62]

CONCLUSION

Although the use of neuromodulation has surged in the past two decades, the future of invasive therapies most likely depends on high-quality studies documenting effectiveness.[63] For all types of neuromodulations but especially implantable modalities, the risks involved warrant predictive markers to better identify which patients will respond, including advanced psychological testing and counselling, genetic testing, and neuroimaging. The refinement of clinical trials (eg, industry-independent programming and more objective outcome measures), and strategies to prevent the loss of effectiveness (novel waveforms, closed-loop and combination stimulation, and pharmacological strategies) will also be crucial for neuromodulation to continue moving forward in primary care patient populations.

The current literature on neuromodulation is mostly limited to a biomedical framework, but future studies should consider neuromodulatory therapies in the context of an interdisciplinary biopsychosocial model.

Progress in neuromodulation requires advancements in user-tailored technologies supported by a deeper understanding of the underlying neurophysiological mechanisms, insight into the relationship between neurophysiological effects and functional outcomes, and the better identification of clinical and non-clinical factors affecting responsiveness. Clinical applications of neuromodulatory techniques cannot advance without patient-tailored stimulation protocols that encompass long-term effectiveness and safety data.

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