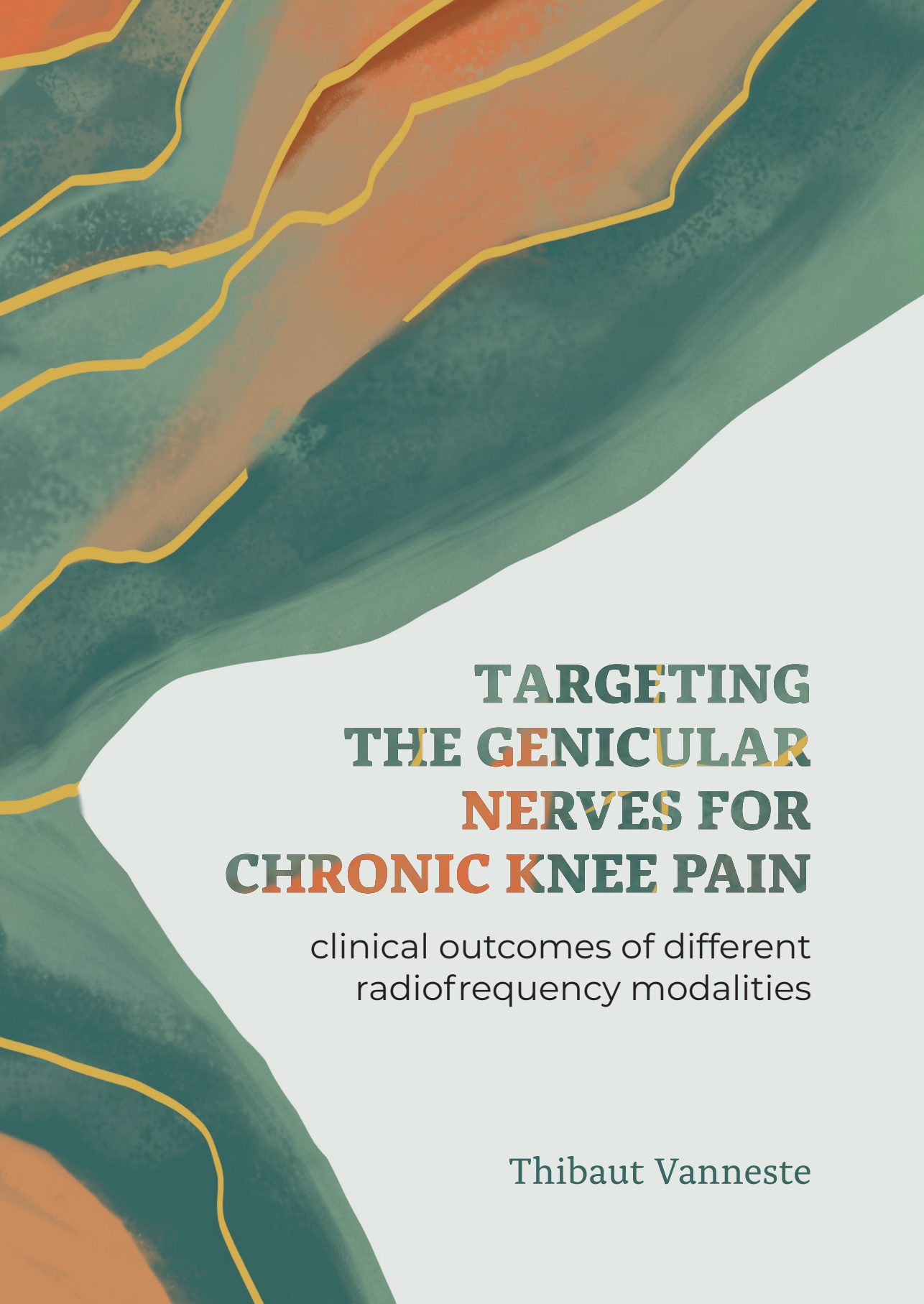


TARGETING THE GENICULAR NERVES FOR CHRONIC KNEE PAIN

clinical outcomes of different radiofrequency modalities

Thibaut Vanneste

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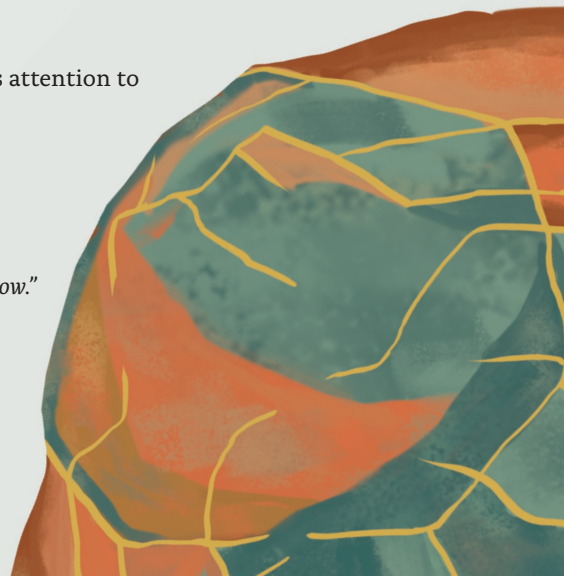
Targeting the genicular nerves for chronic knee pain:

clinical outcomes of different radiofrequency modalities

By Thibaut Vanneste

Maastricht, November 18th 2026

1. Optimal treatment of chronic knee pain requires a multidisciplinary approach in which interventional pain techniques complement rather than replace conservative care.
   ~ Chapter 2
2. The effectiveness of genicular nerve radiofrequency depends not only on the intervention itself but also on appropriate patient selection.
   ~ Chapter 4
3. Both conventional and cooled radiofrequency of the genicular nerves are promising new treatment options for chronic knee pain due to osteoarthritis and persistent post-surgical pain after total knee arthroplasty.
   ~ Chapter 5 and 6
4. Persistent post-surgical pain after total knee arthroplasty warrants a different interventional approach than osteoarthritis-related knee pain.
   ~ Chapter 5 and 6
5. Large pragmatic randomized trials are essential to distinguish promising innovations from meaningful clinical advances.
   ~ Chapter 7
6. The greatest contribution of a well-conducted pilot study is not answering the research question, but defining the next one.
   ~ This thesis
7. Successful treatment of chronic knee pain requires attention to the patient as much as to the knee.
   ~ This thesis
8. *"Walking is man's best medicine."*
   ~ 370 BC Hippocrates
9. *"The more I learn, the more I realize how much I don't know."*
   ~ Unknown
10. *"Mon corps n'est pas fait pour souffrir."*
    ~ 2021 Paul Duchesne



Targeting the genicular nerves for chronic knee pain:

clinical outcomes of different radiofrequency modalities.

Thibaut Paul Pierre Vanneste

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Targeting the genicular nerves for chronic knee pain:

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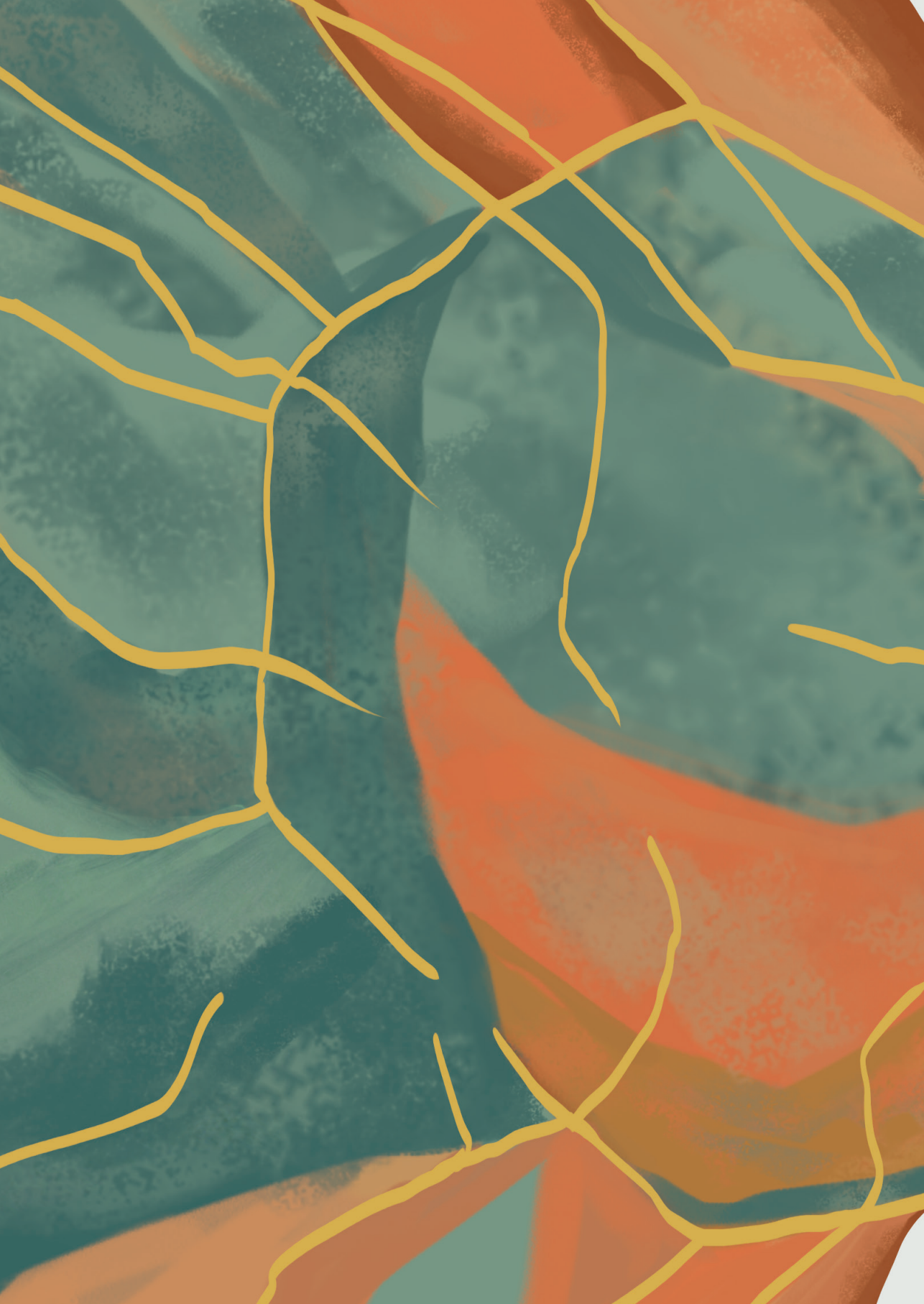
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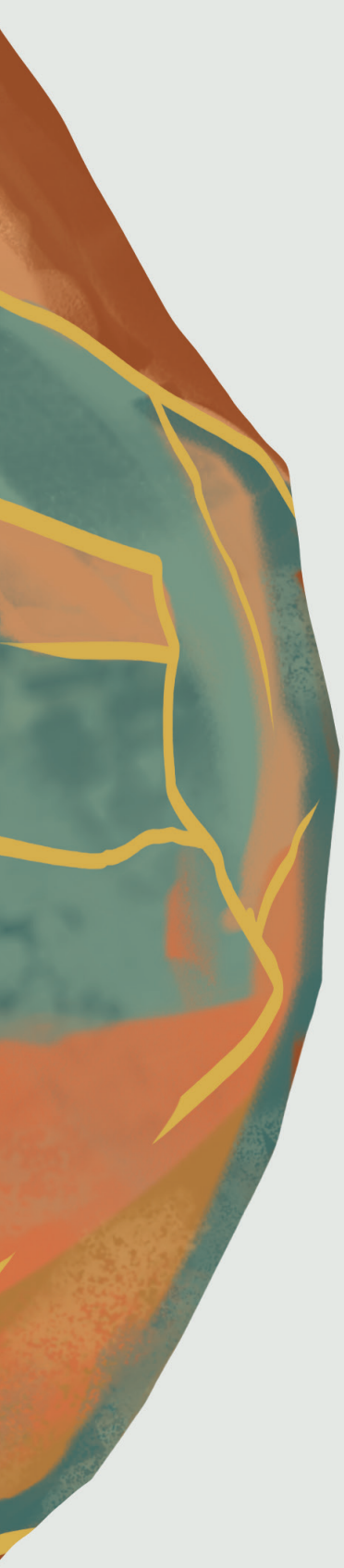
List of abbreviations

ACR	American College of Rheumatology
AE	Adverse Events
AP	Anteroposterior
BI	Blinding Index
BMI	Body Mass Index
CBT	Cognitive Behavioral Therapy
CEAC	Cost-Effectiveness Acceptability Curve
CI	Confidence Interval
CNARF	Continuous Neuroablative Radiofrequency
CONSORT	Consolidated Standards of Reporting Trials
cRF	Cooled Radiofrequency
CRPS	Complex Regional Pain Syndrome
DN4	Douleur Neuropathique 4
DOI	Digital Object Identifier
DRG	Dorsal Root Ganglion
EQ-5D-3L	EuroQol – 5 Dimension – 3 Level
EQ-5D-5L	EuroQoL – 5 Dimension – 5 Level
EURLAR	European League Against Rheumatism
FU	Follow-up
GCP	Good Clinical Practice
GEE	Generalized Estimating Equation
GLM	Generalized Linear Model
GNB	Genicular Nerve Block
HADS	Hospital Anxiety and Depression Scale
HEA	Health Economic Evaluation
IA	Intra-Articular
IACS	Intra-Articular Corticosteroid Injection
IAHA	Intra-Articular Hyaluronic Acid
ICER	Incremental Cost-Effectiveness Ratio
ICRS	International Cartilage Repair and Joint Preservation Society
ILGN	Inferolateral Genicular Nerve
IMGN	Inferomedial Genicular Nerve
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials

IPBSN	Infrapatellar branch of the saphenous nerve
KL	Kellgren–Lawrence
LA	Local Anesthetic
MQS III	Medication Quantification Scale III
MRI	Magnetic Resonance Imaging
NGF	Nerve Growth Factor
NNT	Number Needed to Treat
NRS	Numerical Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
OCD	Osteochondritis Dissecans
ODI	Oswestry Disability Index
OKS	Oxford Knee Score
OR	Odds Ratio
PCS	Pain Catastrophizing Scale
PGIC	Patient's Global Impression of Change
PNMRF	Pulsed Neuromodulative Radiofrequency
PNS	Peripheral Nerve Stimulation
PPSP	Persistent Post-Surgical Pain
PRF	Pulsed Radiofrequency
PRP	Platelet-Rich Plasma
RCT	Randomized Controlled Trial
RF	Radiofrequency
RFA	Radiofrequency Ablation
RFN	Recurrent Fibular Nerve
RQ	Research Question
SCS	Spinal Cord Stimulation
SD	Standard Deviation
SF-12	12-Item Short Form Health Survey
SKOAP	Sequenced Strategy for Knee Osteoarthritis Pain
SLGN	Superolateral Genicular Nerve
SMGN	Superomedial Genicular Nerve
SORT	Study of Osteoarthritis Real World Therapies
TENS	Transcutaneous Electrical Nerve Stimulation
TKA	Total Knee Arthroplasty
TN	Trigeminal Neuralgia

TNF	Tumor Necrosis Factor
TUG	Timed Up and Go test
VAS	Visual Analog Scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WPAI	Work Productivity and Activity Impairment





CHAPTER 1

General Introduction

History

Development of radiofrequency treatment

The first description of a radiofrequency (RF) treatment was provided by Kirschner in 1931 as a therapy for trigeminus neuralgia.[1, 2] It was not until the 1950s that Cosman and Arnoff developed the first commercial radiofrequency generator.[3] In 1965, Rosomoff et al described the use of an RF treatment targeting the anterolateral spinal cord for intractable pain.[4] In 1974, the first dorsal root RF treatment was reported.[5] One year later, in 1975, Shealy described the first use of an RF treatment for lumbar facet joint pain.[6] In 1980, Bogduk and Long introduced a novel technique for performing an RF treatment for lumbar facet joint pain by positioning the electrode parallel to the medial branch of the lumbar dorsal rami.[7] Building on this work, Sluijter and Mehta later introduced a 22-gauge cannula through which a thermocouple probe could be inserted. This thermocouple probe allowed for direct monitoring and control of the tissue temperature at the electrode tip, ensuring the temperature remained within an effective yet safe range creating a more controlled lesion.[8] In 1996, Van Kleef published the first double-blind randomized controlled trial investigating radiofrequency treatment near the dorsal root ganglion for cervicobrachial pain, demonstrating its effectiveness.[9] Furthermore, in 1999, Van Kleef published the first randomized controlled trial evaluating a refined radiofrequency technique for lumbar facet denervation in patients with chronic low back pain, showing significant pain relief.[10]

In the following years, the technique gained increasing popularity as the number of indications for chronic pain expanded. It was noted that an RF lesion near the dorsal root ganglion caused temporary sensory loss, yet could provide longer lasting pain relief.[11, 12] Furthermore, there was also the potential risk of a deafferentation syndrome.[13] These finding encouraged the search for a less destructive approach resulting in the development of pulsed radiofrequency (PRF) in 1998.[11] The first study investigating the clinical effects of PRF reported good pain relief in patients with lumbosacral radicular pain after applying PRF next to the DRG.[11] In 2007, the first randomized controlled trial on PRF near the cervical dorsal root was published as treatment for chronic cervical radicular pain and demonstrated significant pain relief.[14]

In response to anatomic variability, a new RF modality, cooled RF, was developed. By cooling the RF probe with water during the heating process, a larger lesion could be created. This increased the likelihood of effectively interrupting the targeted nerves. Although a larger lesion may potentially translate into improved clinical outcomes, this effect is inherently limited, as lesion size cannot be increased indefinitely

without risking damage to adjacent tissues. Consequently, an optimal lesion size that maximizes efficacy while maintaining safety has not yet been clearly established. Initially, the technique was developed for applications such as tumor ablation and the treatment of cardiac arrhythmias.[15, 16] In 2008, it was first reported as a treatment for chronic sacro-iliac joint pain.[17] Later that year, the first randomized placebo-controlled trial was also published on cooled RF for sacroiliac joint pain showing significant pain relief.[18] Since that time, the technique has demonstrated efficacy across a broad range of clinical indications, supporting its role in the management of various pain syndromes.[19-21]

Radiofrequency treatment for knee osteoarthritis

Along with advances in the technique and materials, the targets of RF treatment evolved as well. While spinal nerves were initially the focus, peripheral nerves became a new target. In 2011, Choi first described the use of RF to target the genicular nerves as treatment of chronic knee pain caused by knee osteoarthritis (OA).[22] Comparing this treatment with a sham procedure, he found a statistically significant difference at three months, which lead to the initiation of numerous studies exploring its effectiveness in managing chronic knee pain.

In conclusion, over the past 90 years, radiofrequency treatments for chronic pain have undergone significant evolution. This ongoing evolution of RF techniques has not only refined existing treatments but also paved the way for innovative approaches to pain management across a variety of clinical conditions. For patients with chronic pain who failed conservative therapies, these interventions can be a therapeutic option that can provide meaningful pain relief. There has been increasing interest in developing novel and innovative applications, suggesting that an even broader patient population may benefit in the future.

Different radiofrequency modalities

During a radiofrequency (RF) treatment an electrode is placed percutaneously in the proximity of a sensory nerve, thought to be responsible for the conduction of a painful stimuli, after which a high frequency electrical current at 500 kHz is applied. This leads to the production of heat surrounding the non-insulated tip of the electrode and causes coagulation with a thermal lesion which interrupts pain conduction in the targeted nerve. The thermal energy creates a predictable area of coagulative necrosis closest to the electrode tip, which contains the nerves responsible for transmitting and modulating pain sensation.[23]

During a PRF treatment, a pulse of high-voltage radiofrequency current is delivered for 20 milliseconds, followed by a wash-out phase of 480 milliseconds during which no current is applied. (figure 1) This cycle is repeated for a total of four to eight minutes, producing one pulse every 500 milliseconds (2 Hertz).[24] This pattern allows the generated heat to dissipate, thereby limiting the temperature increase to maximal 42°C. The exact mechanism of action still remains unclear.[25-27] Although the initial assumption was that PRF does not produce a thermal lesion, Cosman demonstrated that PRF can generate brief bursts of heat within the range of tissue destruction.[23] Nevertheless, histopathologic studies in animal dorsal root ganglia and sciatic nerves showed only transient endoneurial edema, suggesting that any thermal damage caused by PRF is minimal and unlikely to account for its clinical effect.[28, 29] Pain relief from PRF may also result from the strong electrical fields it generates. Neurophysiological studies indicate that these fields can alter neuronal membrane behavior. One popular theory proposes that the rapidly fluctuating electric fields modulate pain signaling, amongst others, via a c-Fos–related pathway, although this explanation remains debated because consistent histopathological support is lacking.[23, 30] The electromagnetic field was also considered as a potential cause of pain relief, but the field produced is limited and therefore unlikely to account for any clinical effect.[23] Since the first publication on PRF, numerous studies have been conducted, progressively expanding its clinical indications.[31]

A third RF modality is cooled RF. (figure 2) Like conventional RF, it uses a continuous application of a high frequency electrical current to create a thermal lesion. During heating, the probe is internally cooled with sterile water, which dissipates heat from the surrounding tissue. By preventing charring and the subsequent increase in impedance, the delivered energy can propagate further, thereby creating a larger lesion.[15] This technique was developed in response to anatomic variability: by creating a larger lesion, the likelihood of effectively targeting and disrupting the intended nerves increases.[32]

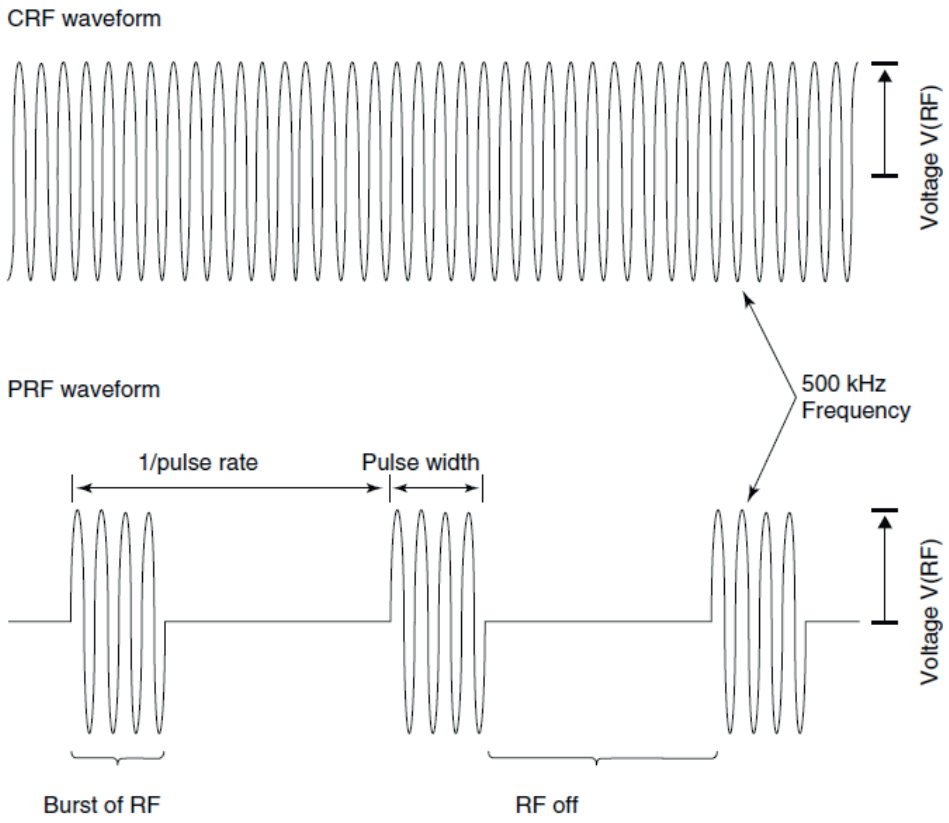


Figure 1 Schematic presentation of a conventional and pulsed radiofrequency waveform.[11]

In addition to cooled RF, several other RF techniques have been developed to enhance their effectiveness by creating larger lesions. One such method is a bipolar radiofrequency treatment, where two probes are positioned near the genicular nerves.[33] In contrast to the monopolar RF technique, where the electrical current flows between the electrode tip and the grounding pad, the bipolar technique generates an electrical current between both electrode tips, resulting in a larger lesion. Another approach is the trident technique, which uses a single probe with three deployable tines which are deployed when the tip is in the correct position. These tines are arranged in a pyramid shape, thereby creating a larger lesion.[34] Additionally, performing multiple monopolar lesions during a conventional RF procedure is another technique which can also increase the size of the lesion. While there are some publications on these techniques, literature is still scarce. Therefore, the focus of this thesis is on the three initially mentioned RF methods.

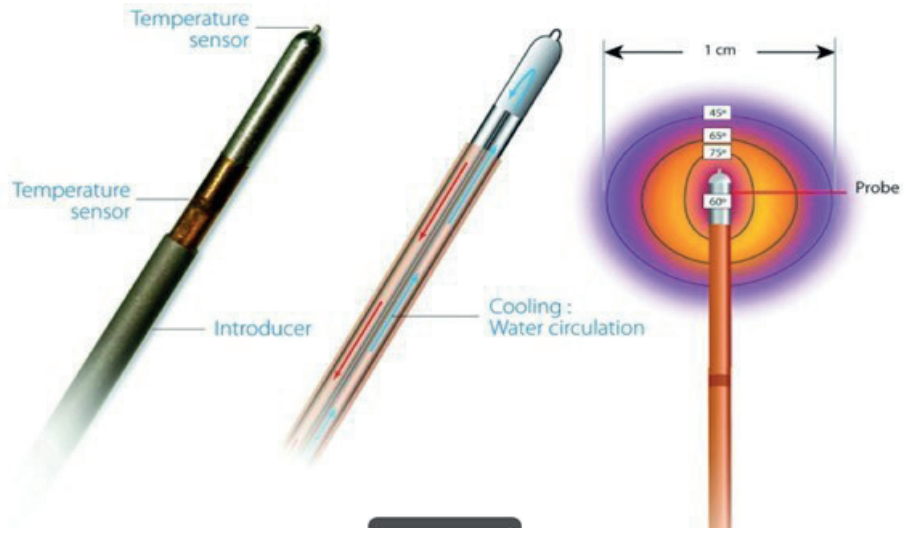


Figure 2 Working mechanism of cooled RF.

Another alternative to interrupting pain signaling through RF lesions is **chemical ablation**, which involves the use of ethanol (50-100%) or phenol (6-10%).[35-39] However, there is limited research on chemical ablation of the genicular nerves compared to RF treatment of the genicular nerves. Most studies are observational and report positive outcomes.[40] Since chemical ablation and other RF techniques fall outside the scope of this thesis, they will not be further discussed.[41]

Chronic knee pain

Chronic knee pain is defined as pain that is located in the knee joint and persist or recurs for more than 3 months.[40, 42] It can be caused by various underlying diseases of which the most common is degenerative OA.[40, 43] Other etiologies include rheumatoid arthritis, crystal and spondylo-arthropathies, post-traumatic pain and persistent postsurgical pain (PPSP). OA is a degenerative condition caused by biomechanical, inflammatory and metabolic factors leading to the progressive loss of articular cartilage and remodeling of the underlying bone, fibrocartilage, and synovium.[44-47] OA can develop in any joint but the knee is the most common site in different studies. [48-52] It can affect all three compartments of the knee joint: the medial or lateral tibiofemoral and the patellofemoral compartment.[45] Patients with chronic knee pain can express different types of pain, ranging from nociceptive to neuropathic and nociplastic pain. Nociceptive pain can be further divided into inflammatory, mechanical or bone marrow lesions – associated pain with all types requiring a different treatment. [53, 54] OA is a leading cause of disability, with its prevalence increasing worldwide.[43, 55] The age-standardized prevalence rate rose to 4294,27 per 100.000 and the age-standardized incidence rate to 353,67 per 100.000 in 2021 globally.[55] Both the prevalence and incidence increase with age.[45] Knee pain, functional loss, and the accompanying psychological burden may lead to substantial disability and major socio-economic costs, which were estimated at over $140,000 per person in the United States in 2013.[52, 56-59] Risk factors of OA include advanced age (especially those >55 years), obesity, female sex, previous knee injury, and occupational factors.[45, 60] The incidence of knee OA is expected to increase because of the aging of the population and an increase in obesity.[51]

Anatomy

Pain signaling from the knee begins when specialized nerve endings, called **nociceptors**, detect harmful stimuli like injury or inflammation. These nociceptors generate electrical signals that travel along **A-delta** and **C fibers**. The A-delta fibers transmit sharp, immediate pain, while the C fibers carry slower, aching pain signals.[61]

The anterior knee is innervated by ten articular nerve branches.[62, 63] (figure 3) These can be categorized into four quadrants. The superolateral quadrant is innervated by branches from the nerve to the vastus lateralis, the nerve to the vastus intermedius, the superolateral genicular nerve and the common fibular nerve. The inferolateral quadrant is innervated by branches from the inferolateral genicular nerve and the recurrent fibular nerve. The superomedial quadrant is innervated by branches from the nerve to the vastus medialis, the nerve to the vastus intermedius and the superomedial genicular nerve. The inferomedial quadrant is innervated by branches from the inferomedial genicular nerve and the infrapatellar branch of the saphenous nerve. The posterior side of the knee joint is innervated by articular branches from the obturator nerve, the tibial and the common peroneal nerve.

All these articular branches transmit pain signals through the femoral and sciatic nerve, ultimately reaching the spinal cord for further processing.

Once in the spinal cord, the signals enter the **dorsal horn,** where they may be modulated before continuing to the thalamus in the brainstem. The **thalamus** acts as a relay center, sending pain signals to different parts of the brain, including the **somatosensory cortex** for localization and the **limbic system** for the emotional response to pain. The brain also uses the **prefrontal cortex** to evaluate the pain and decide how to respond.[61] Additionally, the brain can send descending signals back to the spinal cord to modulate the pain, either increasing or decreasing its intensity. The **periaqueductal gray** in the brainstem is responsible for triggering the release of natural painkillers like endorphins.

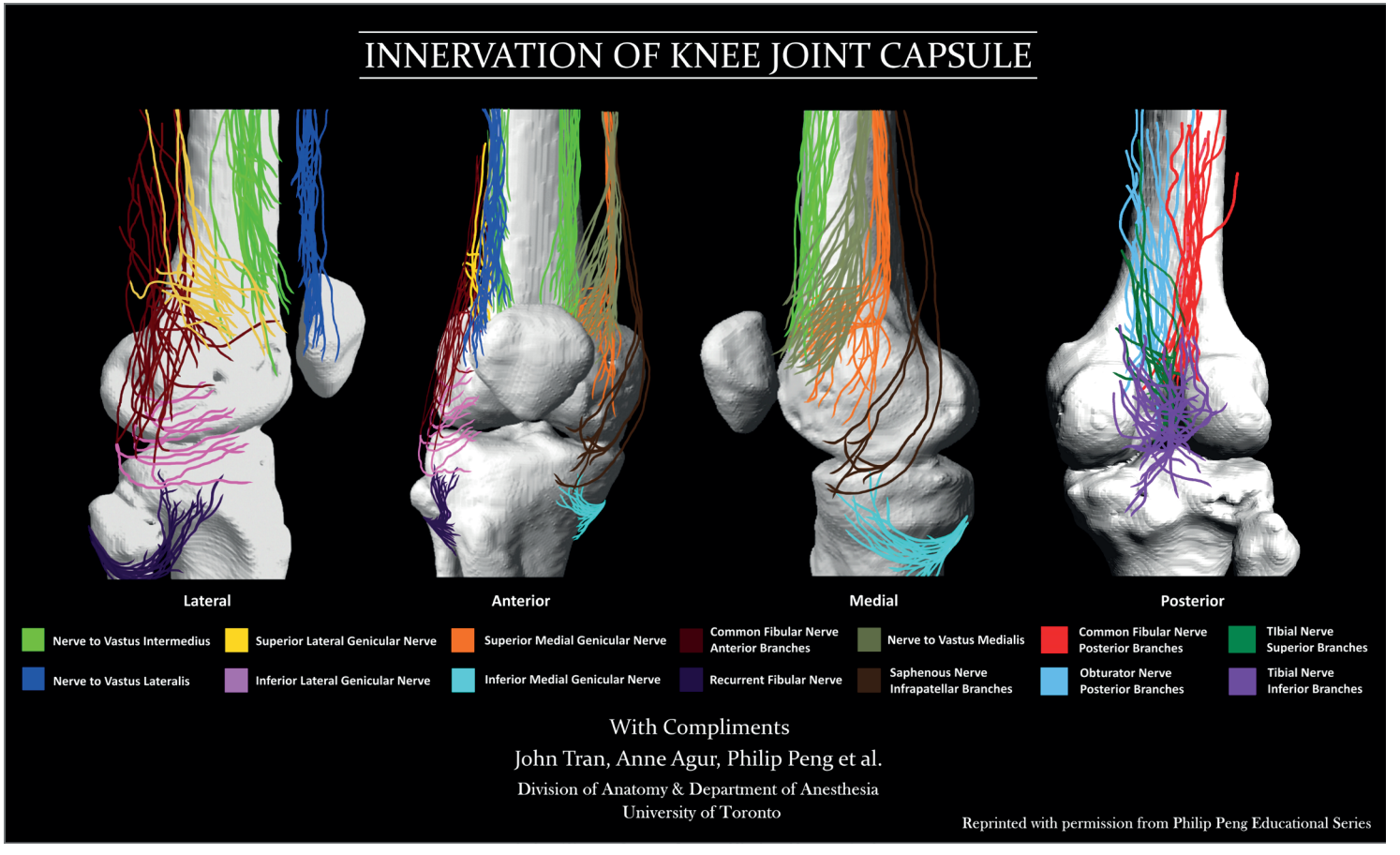


Figure 3 innervation of the anterior and posterior knee.[62]

Treatment algorithm

Because no single therapy can be deemed fully effective or adequate in treating knee OA, effective management necessitates a multi- and interdisciplinary approach. This approach enables coordinated decision-making, optimizes treatment outcomes, and ensures that patients receive comprehensive care addressing all physical, functional, and pain-related aspects of their condition. Conservative treatment is the first-line option for knee osteoarthritis, particularly in the early stages of OA.[64] This focus on non-surgical strategies to reduce pain and improve mobility. It consists of life style changes such as weight loss in obese people, self-management programs, exercise, the use of aids or medication. Medications, such as NSAIDs or capsaicin, can be applied locally to minimize side effects, though most medications are typically administered systemically. These medications include paracetamol, NSAIDs, duloxetine and tramadol.[40] If this does not alleviate the symptoms enough, intra-articular infiltrations are an option. Although intra-articular injections with corticosteroids can provide short to medium term pain relief, concerns have been raised about their association with increased progression of osteoarthritis on MRI after two years compared with controls.[65] Infiltrations with hyaluronic acid are an alternative that may slow the progression of osteoarthritis, but they remain controversial due to ongoing debate about their effectiveness.[40] At the moment no disease modifying agents are yet identified. Around 50% of the population first diagnosed with symptomatic knee OA are estimated to eventually undergo surgical treatment in the form of a total knee arthroplasty (TKA) which comprises the highest percentage of direct medical costs.[40] However, between 10% and 35% of patients undergoing TKA experience persistent pain, with 15% reporting that pain has a high impact.[66, 67] A headroom analysis, that calculated the theoretical cost savings per person in euro as a consequence of theoretical new treatments, found that, when the need of all TKAs was prevented, this resulted in a cost reduction of 43.076 euro per person. Furthermore, they found that interventions that improve patient satisfaction after a TKA amounted up to a cost reduction of 16.622 euro.[68] An radiofrequency treatment of the genicular nerves is a new treatment that can be an alternative minimal invasive treatment option for chronic knee pain due to OA or PPSP.[22, 69-71]

Challenges

As with all emerging techniques, ongoing evolution and refinement are inevitable, reflecting the fact that not all aspects are currently fully understood. Consequently, several controversies remain and international consensus on the optimal protocol for the procedure is not yet achieved.[72-74] Since the first randomized sham controlled trial by Choi et al, most studies compared RF of the genicular nerves with another active treatment. Furthermore the study of Choi was criticized by its small sample size, selecting only three out of ten nerves that innervate the anterior knee and possibly a placebo effect by selecting patients with more than 24 hours pain relief after a prognostic block. Other controversies include the role and clinical value of prognostic nerve blocks, the optimal number of genicular nerves to target during radiofrequency treatment, the ideal anatomical target points, and whether specific radiofrequency modalities may lead to improved clinical outcomes.[72]Another challenge or discussion point is the reciprocal balance between pain and load. With a symptomatic RF treatment, we reduce or eliminate pain, which allows patients to increase their activity and loading. However, by removing pain, we also remove an important warning signal, which could potentially lead to faster structural damage. Furthermore, follow-up should not focus solely on pain levels. Monitoring should also include functional capacity, as stable pain complaints may actually reflect progressively reduced function rather than true stability of the underlying condition.

Thesis aims and research questions

This dissertations aims to investigate the clinical effects of a radiofrequency treatment of the genicular nerves as treatment of chronic knee pain due to osteoarthritis or persistent post-surgical pain after a total knee arthroplasty. The research questions are the following:

- Is a radiofrequency treatment of the genicular nerves effective in reducing pain and improving other patient outcomes?

Chapter 7 "Comparison of conventional and cooled radiofrequency treatment of the genicular nerves versus sham procedure for patients with chronic knee pain: protocol for a multicentre, double-blind, randomised controlled trial (COGENIUS)" reports the protocol of a large randomized controlled trial comparing conventional and cooled radiofrequency of the genicular nerves with a sham procedure for chronic knee pain due to osteoarthritis and persistent post-surgical pain after a total knee arthroplasty up to 2 years.

- Is there a difference in effect between different radiofrequency modalities such as conventional, pulsed or cooled radiofrequency?

Chapter 4 "A Randomized Controlled Trial to Compare Analgesia and Functional Improvement After Continuous Neuroablative and Pulsed Neuromodulative Radiofrequency Treatment of the Genicular Nerves in Patients with Knee Osteoarthritis up to One Year After the Intervention.", chapter 5 "Comparison of cooled versus conventional radiofrequency treatment of the genicular nerves for chronic knee pain: a multicenter non-inferiority randomized pilot trial (COCOGEN trial)." and chapter 6 "Cooled versus conventional radiofrequency treatment of the genicular nerves for chronic knee pain: 12-month and cost-effectiveness results from the multicenter COCOGEN trial." describe the results of randomized controlled trials comparing the clinical effects of pulsed and cooled radiofrequency of the genicular nerves with conventional radiofrequency as treatment of knee pain due to osteoarthritis or persistent post-surgical pain after a total knee arthroplasty.

- What is the place of a radiofrequency treatment of the genicular nerves in the treatment algorithm of chronic knee pain?

Chapter 2 "chronic knee pain" and Chapter 3 "pulsed radiofrequency in chronic pain" present an elaborative overview of the pathology, diagnosis and treatment algorithm of chronic knee pain and the use of pulsed radiofrequency for different indications, including chronic knee pain, as treatment for chronic pain.

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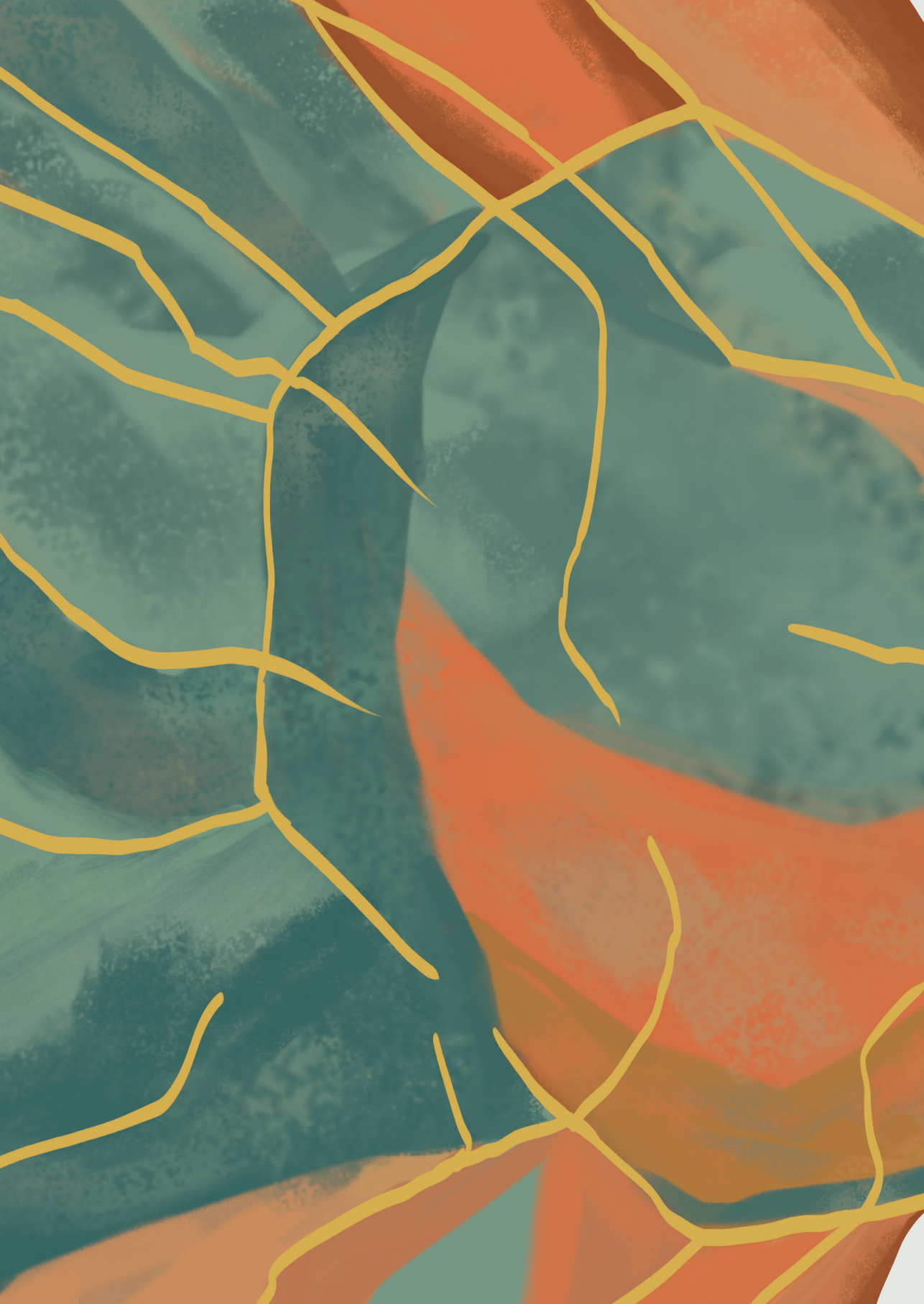
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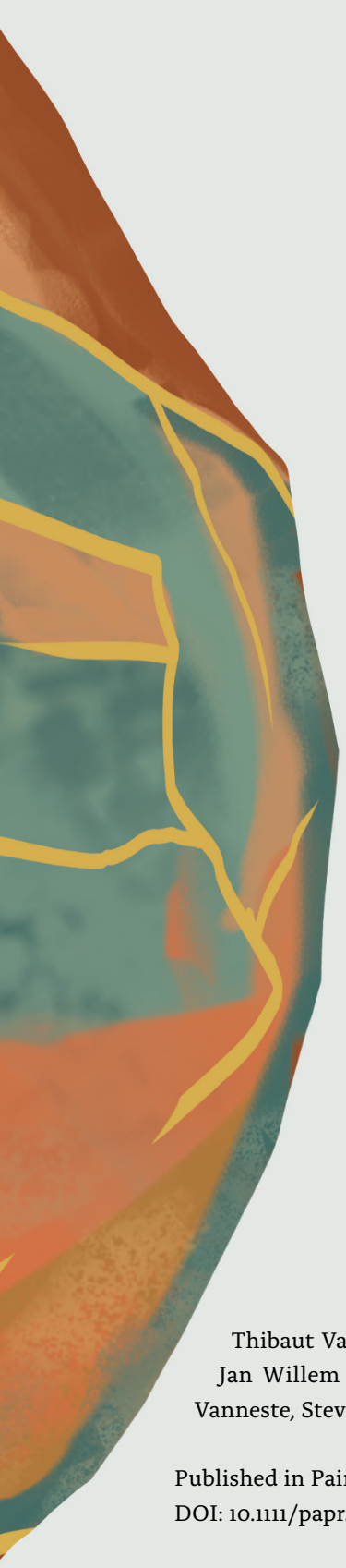
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CHAPTER 2

9. Chronic knee pain.

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Abstract

Introduction

Chronic knee pain is defined as pain that persists or recurs over 3 months. The most common is degenerative osteoarthritis (OA). This review represents a comprehensive description of the pathology, diagnosis, and treatment of OA of the knee.

Methods

The literature on the diagnosis and treatment of chronic knee pain was retrieved and summarized. A modified Delphi approach was used to formulate recommendations on interventional treatments.

Results

Patients with knee OA commonly present with insidious, chronic knee pain that gradually worsens. Pain caused by knee OA is predominantly nociceptive pain, with occasional nociplastic and infrequent neuropathic characteristics occurring in a diseased knee. A standard musculoskeletal and neurological examination is required for the diagnosis of knee OA. Although typical clinical OA findings are sufficient for diagnosis, medical imaging may be performed to improve specificity. The differential diagnosis should exclude other causes of knee pain including bone and joint disorders such as rheumatoid arthritis, spondylo- and other arthropathies, and infections. When conservative treatment fails, intra-articular injections of corticosteroids and radiofrequency (conventional and cooled) of the genicular nerves have been shown to be effective. Hyaluronic acid infiltrations are conditionally recommended. Platelet-rich plasma infiltrations, chemical ablation of genicular nerves, and neurostimulation have, at the moment, not enough evidence and can be considered in a study setting. The decision to perform joint preserving and joint-replacement options should be made multidisciplinary.

Conclusions

When conservative measures fail to provide satisfactory pain relief, a multidisciplinary approach is recommended including psychological therapy, integrative treatments, and procedural options such as intra-articular injections, radiofrequency ablation, and surgery.

Keywords

Chronic knee pain, osteoarthritis, corticosteroids, hyaluronic acid, genicular nerves, radiofrequency treatment, Spinal cord stimulation

Introduction

This narrative review on chronic knee pain is part of a series "Update of evidence-based interventional pain medicine according to clinical diagnoses.

Chronic knee pain is defined as knee pain that persists or recurs for more than 3 months. [1] The most common cause of chronic knee pain is degenerative osteoarthritis (OA). [2-4] Other etiologies of knee pain include rheumatoid arthritis, crystal and spondylo-arthropathies, posttraumatic pain, and persistent postsurgical pain (PPSP). Discussion of all these conditions is beyond the scope of this narrative review, and we will focus on a comprehensive description of the pathology, diagnosis, and treatment of OA of the knee. Special attention will be given to minimally invasive interventional treatments of knee pain due to OA, how they are performed, and their complications. Based on the discussed literature, recommendations are formulated for these treatment techniques.

OA is a degenerative condition that causes progressive loss of articular cartilage and remodeling of the underlying bone, fibrocartilage, and synovium. [3] OA can affect any joint, with the knee being the most common site in many studies. [5-7] OA is a leading cause of disability, with its prevalence increasing worldwide. [4,8-10] OA can affect all thee compartments of the knee joint: the medial tibiofemoral, the lateral tibiofemoral, and the patellofemoral compartment. [11,12] Pathogenesis of OA results from an interplay of biomechanical, inflammatory, and metabolic factors that contribute to cartilage damage, synovitis, and various subchondral bone abnormalities. [11-15] The global prevalence of knee OA is 16.0% in individuals aged 15 and older and 22.9% in individuals aged 40 and older. The global incidence of knee OA was 203 per 10,000 person-years in individuals aged 20 and older. [7] Both the prevalence and incidence increase with age. [11] Knee pain, functional loss and the accompanying psychological burden may lead to substantial disability and major socio-economic costs, which were estimated at over $140,000 per person in the U.S. in 2013. [16-19] Risk factors of OA include advanced age (especially those > 55 years), obesity, female sex, previous knee injury, and occupational factors. [8, 11] The 10%–15% are attributed to trauma.[20] The incidence of knee OA is expected to increase because of aging of the population and an increase in obesity. [10,11,21] Around 50% of the population first diagnosed with symptomatic knee OA are estimated to eventually undergo surgical treatment in the form of a total knee arthroplasty (TKA) which comprises the highest percentage of direct medical costs. [11, 22] Between 10% and 35% of patients undergoing TKA experience persistent pain, with 15% reporting that pain as high impact. [23-28]

Methodology

The paper includes peer-reviewed literature found by a search conducted in February 2024 using the terms "knee" AND "pain" AND "osteoarthritis" in PubMed and Cochrane databases (Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews). Only studies pertaining to chronic knee pain were included. Since this is the first review of interventional pain medicine on chronic knee pain, there were no limitations in the time frame for the literature search, and all types of original studies (randomized and nonrandomized trials, prospective and observational trials, and case series and case reports) and reviews were included. Based on this initial search, the main domains relevant to the topic were identified. Afterward, multiple searches were performed based on the selected domains (eg, prevalence, diagnosis, pharmacological treatments, and interventional treatments). The literature search on interventional pain management techniques included the following terms: "Intra-articular corticosteroid injections" OR (("steroid" OR "corticosteroid") AND "injection"); "Intra-articular hyaluronic acid injection" OR (("hyaluronic" OR "hyaluronic acid" OR "viscosupplementation") AND "injection"); "Intra-articular injections with platelet rich plasma" OR ("platelet rich plasma" AND "injection"); ("radiofrequency" OR "pulsed radiofrequency" OR "conventional radiofrequency" OR "cooled radiofrequency") AND "genicular nerves"; ("chemical ablation" OR "phenol" OR "alcohol" OR "neurolysis") AND "genicular nerves." The initial literature search and screening of articles were performed by two authors AB and TV. In addition to the literature search, the included papers were screened for relevant articles and the authors of the manuscript proposed other important missing articles. The data were gathered and summarized per specific domain

The group of authors included in this paper then determined whether each intervention should be recommended or not. The author team was chosen based on their expertise in the topic of chronic knee pain and consists of anesthetists and surgeons with broad international representation. Based on the summarized data, a table with each recommendation was composed together with a treatment algorithm for chronic knee pain. The possible grades of recommendation were "not recommended," "not enough evidence for recommendation outside of a study setting," "conditionally recommended," "recommended," and "highly recommended." These recommendations were based on a critical evaluation of the literature focusing on the quality of the trials, the relevance of the intervention to the current clinical practice, the balance between the invasiveness of the intervention and the effect size, and the balance between the risk of adverse events and the effect size of the intervention. These recommendations were sent to the author team for review and a modified

Delphi approach was used to achieve consensus.[29] This included multiple rounds of comments via email followed by video meetings. During the video meetings, the comments were addressed, disagreements resolved, and a consensus was forged. This same process was repeated for the technique section. Finally, the manuscript for publication was prepared and submitted to the author team for approval.

Diagnosis

History

Patients with knee OA commonly present with insidious, chronic knee pain that is gradually worsening. Pain caused by knee OA is predominantly nociceptive with nociplastic characteristics occurring in approximately 35% of patients, and neuropathic qualities occasionally present in severely diseased knees.[11, 30] Although pain is the most prominent symptom, patients with OA can experience reduced knee function, muscle weakness, morning stiffness, joint instability, and psychological distress. Knee pain due to OA is usually mechanical and worsens with activity due to the weight-bearing capacity of the joint. [31, 32] While pain may be absent during the early stages, symptomatic OA pain is typically described as sharp and fluctuating depending on the activity level. Moderate knee OA is often described as constant pain and joint stiffness that affect daily activities. Severe knee OA can result in significant disability, function restriction, and decreased quality of life. Patients often report flare-ups for up to 72h that include swelling, increased warmth, worsening pain, and functional limitations. [33] Burning electrical pain, paresthesia, hypoesthesia, hyperalgesia, and allodynia over the diseased joint are all characteristics of nociplastic and occasionally neuropathic pain. Multiple joint pain, morning stiffness that lasts longer than 30min and other accompanying systemic symptoms in a patient with knee pain should prompt a rheumatology consultation to rule out rheumatoid arthritis and other arthropathies. Other red flags such as fever, a history of trauma, osteoporosis, cancer, deep vein thrombosis, or peripheral vascular disease can point toward a serious differential diagnosis and require further investigations and imaging.

Physical examination

A standard musculoskeletal and neurological examination is required for the diagnosis of knee OA.[34, 35] A comparison of the diseased knee to the contralateral knee facilitates examination. First, the appearance of the knee is inspected for redness, edema, muscle atrophy, and trophic changes. Mild warmth, edema, and redness are compatible with OA while marked signs of inflammation should prompt tests for infectious or inflammatory arthritis. [31] Second, the flexed knee is palpated for bony enlargements, crepitus, and tenderness along the joint line, patella, tibial and femoral condyles, fibular head, and tibial tuberosity. Patients should be evaluated for the presence of knee joint effusion in a maximally extended knee. The following extra-articular knee compartments should also be examined and palpated: the quadriceps tendon, the patellar tendon, the iliotibial band on the lateral side of the knee, and the posterior knee fossa. Pain where the iliotibial band crosses the lateral knee is characteristic of iliotibial band syndrome, especially in runners. Discomfort at the popliteal fossa

could indicate the presence of popliteal cysts (eg, Baker's cyst). Tenderness around the knee could also indicate the presence of inflamed bursae, the most important of which are the supra-, pre-, and infra-patellar bursa and the bursa surrounding the pes anserine. Third, the patient's gait, standing and walking knee alignment (varus and valgus), active and passive range of motion, and stability of the knee joint are evaluated. Examinations used to assess joint stability are the valgus and varus stress tests that evaluate medial and lateral instability respectively; the Lachman test; and the anterior and posterior drawer tests to assess anterior and posterior knee stability problems due to anterior and posterior cruciate ligament injuries. A knee compression-rotation test is used to detect damaged meniscus. In general, the medial compartment tends to deteriorate faster than the patellofemoral and lateral compartments absent asymmetrical stressors (eg, valgus deformity predisposing to lateral compartment OA).[36]

It is important that radicular pain is excluded as the cause of the knee pain. Radicular pain resulting from compression of the L3, L4, and L5 spinal nerve roots can result in anterior (or lateral for L5 radiculopathies) knee pain while S1 and S2 nerve root compression can lead to posterior knee pain. Evaluation of the patellar reflex and the femoral stretch test can determine the integrity of the L3 and L4 nerve roots.[37] Allodynia and hypoesthesia to touch and prick of the knee should be also evaluated to identify neuropathic pain. Questionnaires such as the Douleur neuropathique 4 (DN4) and PainDETECT questionnaire can be used to determine the probability of non-nociceptive pain. [30] Due to changes in gait biomechanics, other (extra-articular) structures such as the attachment of the patella tendon and hamstring muscles at the tibia can become painful due to relative overuse resulting from altered locomotion. [38] Lastly, trophic, sudomotor, vasomotor, or sensory changes in the joint should raise the possibility of complex regional pain syndrome (CRPS). [39]

Technical investigations

A diagnosis of knee OA does not require radiography. The American College of Rheumatology (ACR) outlines three different means to diagnose knee OA. The use of history and physical exam alone requires chronic knee pain and at least three of the following criteria: age > 50 years, < 30 min morning stiffness, crepitus with motion, bony tenderness, bony enlargement, and no palpable synovial warmth. This is the most sensitive way to diagnose knee OA, but the least specific (sensitivity 95% and specificity 69%). The addition of radiographic abnormalities (e.g., subchondral sclerosis) to history and physical requires pain in knee, osteophytes, and at least one of the following: age > 50 years, < 30 min morning stiffness, and crepitus with motion. This method only slightly reduces the sensitivity to 91% but significantly improves the specificity to 86%.

Finally, combining history and physical exam with labs (e.g., erythrocyte sedimentation rate < 40 mm/h, rheumatoid factor < 1:40 and synovial fluid signs consistent with OA provides an intermediate sensitivity and specificity of 92% and 75%, respectively). [40]

As noted above, typical clinical OA findings are sufficient for diagnosis according to the ACR diagnostic criteria and EURLAR recommendations for diagnosis of knee OA. [31, 40, 41] Whereas disease modification is probably only possible at early stages of OA, because patients often experience minimal symptoms at this time, the ACR diagnostic criteria are frequently not sufficiently sensitive to detect all cases of knee pain secondary to degenerative etiologies. [42] The diagnosis of OA is more reliable if more affirmative signs of OA are present. [43] These include risk factors, symptoms, and physical examination. Additional testing in the form of imaging (radiography, magnetic resonance imaging (MRI), and bone scintigraphy), laboratory testing and synovial fluid analysis should be considered in young patients with symptoms of OA, knee joint instability, recent traumatic event, persistent post-operative pain, systemic symptoms, and when there is a need to rule out joint infection, inflammatory arthritis, or malignancy. [41]

Knee radiography, the gold standard imaging for knee OA, can identify the affected knee compartment: medial or lateral tibiofemoral (weight-bearing) arthrosis and patellofemoral arthrosis. Based on radiologic findings, the severity of tibiofemoral arthrosis is graded using the Kellgren–Lawrence (KL) grading scale from 0 to IV. [44] KL grade I indicates minimal radiological findings of OA while KL grade IV indicates severe OA with large osteophytes, marked narrowing of the joint space, severe sclerosis, and definite deformity of bone ends. Radiographic changes become more common after 1-2 years of symptoms. [45, 46] Compared to plain radiography, MRI has a higher sensitivity for identifying earlier stages of OA that include only cartilage defects and subchondral bone lesions, and as such might aid in the early detection of knee OA. [31, 47]

It is widely assumed that treatments such as lifestyle changes or efforts aimed at reducing load bearing and improving gait mechanics such as kinesiotaping are mainly useful at an early stage of OA when there is no or little pain, in an attempt to modify the disease course. From this perspective, there is an ongoing discussion on the function of pain as a protective mechanism to offload mechanical burdens and prevent further structural damage. If a treatment adequately reduces pain, this could theoretically lead to an increased rate of structural degeneration. However, aside from extreme levels of activities that unduly stress the knee joint, studies have consistently found that higher activity levels either have no significant effect or in the case of otherwise sedentary patients, possibly a protective effect on radiographic joint degeneration. [48] Further research is still needed to explore the effects of physical activity versus a sedentary lifestyle on pain. [49]

Radiographic changes in the knee should be carefully interpreted as knee symptoms tend to exhibit a poor-to-moderate correlation with the severity of radiographically observed joint alterations. [47] The proportion of patients with knee pain suffering from radiographically-confirmed OA ranges between 15% and 76%, with 15%– 81% of patients with radiographically-confirmed knee OA experiencing knee pain. [50] In one systematic review, most but not all studies, found a positive correlation between effusion and synovitis and knee pain, with another study finding that up to 25% of patients with KL grade IV did not experience knee pain. [51, 52]

Differential diagnosis

The differential diagnosis of chronic knee pain depends largely on clinical presentation, medical history, imaging, and sometimes labs. Knee OA can be divided into primary and secondary OA. Whereas primary OA is a result of idiopathic degenerative processes, secondary OA occurs secondary to trauma, and other bone and joint disorders such as rheumatoid arthritis, arthropathies, and infections. [41] Post-traumatic knee pain is preceded by trauma which can be acute, prolonged over extended periods (eg, distance runners), and occur secondary to an acute traumatic event that predisposes the knee to increased stress and motion (eg, ligamentous and meniscal injuries). When preceded or accompanied by trauma, surgery, or an intervention, CRPS may ensue. [39] Radicular back pain is characterized by pain involving a specific dermatome and typically occurs with concomitant sensory and/ or motor deficits.

Differential diagnosis of chronic knee pain:

- OA
  - Primary OA
  - Secondary OA: OA enhanced by other factors such as trauma, other bone and joint disorders such as rheumatoid arthritis, arthropathies, and infections. [22]
  - Patella malposition or mal-tracking [53]
  - Malalignment
  - Post meniscectomy pain (degenerative or traumatic)
  - Osteochondritis Dissecans (OCD)
- Persistent post-surgical knee pain
  - Mechanical problems (e.g., prothesis malalignment, mal-sizing, component dislodgement, periprosthetic fractures, ligament instability)
  - Joint infection
  - Inappropriate surgery (e.g., joint replacement when OA was not the primary cause)
  - Inflammatory or allergic response for implanted material (metal allergy)
  - Nociplastic pain

    - Neuropathic pain (e.g., due to surgical damage to the infrapatellar branch of the saphenous nerve)
    - CRPS
    - Idiopathic
- Post-traumatic knee pain
    - Fracture
    - Soft tissue trauma and peri-articular disorders (e.g., ligament tear, meniscal tear, cartilage defect)
- Referred knee pain:
    - Radicular pain
    - Hip pain
- Infection of periarticular tissue (e.g., bursitis and tendinitis)
- Infectious arthritis
- Inflammatory arthritis (e.g., rheumatoid arthritis and psoriatic arthritis)
- Crystal arthropathy (e.g., gout)
- Malignant knee pain

Treatment options

The treatment of knee OA should be comprehensive and multimodal. A combination of education, physiotherapy, weight management, and medical treatment is indicated for most OA patients. [41, 54-56] Treatment of knee OA is primarily symptomatic, aimed at relieving pain and improving functionality. [56] The importance of changes in lifestyle, self-efficacy, and a proactive approach to knee pain should be stressed. Minimally invasive treatments such as intra-articular infiltrations or nerve treatment are indicated when the previously mentioned approaches are insufficient. Surgical interventions should be performed when symptoms are refractory to conservative treatment. [57, 58] We will further discuss pharmacological therapies, and the five minimally invasive treatments with the most supporting literature in knee OA: the intraarticular injection of corticosteroids, intra-articular injection of hyaluronic acid, intra-articular injection of platelet-rich plasma, radiofrequency treatment, and chemical ablation of the genicular nerves. We will discuss evidence of treatments from systematic reviews and results from distinguished individual trials addressing important clinical topics when aggregated data in systematic reviews is lacking.

Treatment of chronic knee OA can be classified into:

1. Conservative treatment
    - 1.1. Non-interventional
        - 1.1.1. Non-pharmacological (education, physiotherapy, braces, dietary weight management, lifestyle changes, kinesiotaping, and cranes)
        - 1.1.2. Pharmacological (NSAIDs, paracetamol, duloxetine, tramadol, and topical capsaicin)
    - 1.2. Minimally invasive interventional management
        - 1.2.1. Pharmacological Intra-articular infiltrations
            - 1.2.1.1. Intra-articular corticosteroid injection (IACS)
            - 1.2.1.2. Intra-articular hyaluronic acid injection (IAHA)
            - 1.2.1.3. Intra-articular injection with platelet rich plasma (PRP)
        - 1.2.2. Non-pharmacological interventions
            - 1.2.2.1. Nerve block (RF, cryotherapy and chemical neurolysis)
        - 1.2.3. Other (e.g., genicular artery embolization, stem cells, dextrose or hypertonic saline injection (prolotherapy), and ozone)
2. Surgical treatment
3. Neurostimulation

3.1 Peripheral nerve stimulation

3.2 Spinal cord stimulation

Conservative management

Non-pharmacological care

Non-pharmacological care is considered essential to all OA patients. Patients should be educated on disease pathology, progression, and treatment modalities. Physiotherapy in the form of structured land-based exercise programs, aquatic exercise which mitigates the effect of gravity and may be particularly beneficial in overweight patients, use of gait aids, and self-management programs are considered safe and efficacious. A Cochrane systematic review comparing the effect of land-based therapeutic exercise with different comparators in OA patients showed that exercise significantly diminishes pain and improves physical function in the intermediate term without additional harm or accelerated disease progression. [59] While the importance of non-pharmacological care is supported by scientific research and expert opinion, the implementation of education, physiotherapy, weight loss, and self-management programs in clinical practice is often suboptimal. [60] Nationwide initiatives on neuromuscular exercise such as the Good Life with osteoArthritis in Denmark (GLA:D) can improve pain and quality of life of knee OA patients. [61] Transcutaneous electrical nerve stimulation (TENS) is another non-invasive technique that could be considered in some knee OA patients with neuropathic-like or nociplastic symptoms; however, the level of evidence is low. [62]

Pharmacological treatments

Pharmacological treatments are deemed suitable for most OA patients; however, attention should be paid to patients with comorbidities due to possible adverse effects, drug interactions, and complications. Topical or oral non-inflammatory drugs (NSAIDs) and paracetamol are first-line pharmacological treatments for knee OA. The effect of NSAIDs is superior to paracetamol with a number needed-to-treat (NNT) of between 4.5 and 9.8 for topical and oral NSAIDs and 4 ONSAID16 for paracetamol. [63-65] Cyclooxygenase-2 inhibitors or topical NSAIDs can be used in patients suffering from frailty, and gastrointestinal comorbidities due to fewer adverse effects. [55, 56, 63] Duloxetine is the only anti-depressant that is recommended as a second-line treatment for knee OA. [66, 67] However, other antidepressants can be considered in patients with depressive symptoms or widespread pain disorders after careful patient selection, with tricyclic antidepressants having greater efficacy, albeit with more side effects, than serotonin-specific reuptake inhibitors. [54, 66] Topical capsaicin can be considered despite studies reporting a small effect size. [68] High doses of pure mu agonists should only be considered for non-malignant knee pain on a case-to-case basis after carefully weighing the risks and benefits, with predefined benchmarks for success and an exit strategy. [68] Mixed action opioids such as tramadol can be considered, but there is moderate-quality evidence that

tramadol has no important benefit on pain due to OA. [54, 69] Glucosamine, chondroitin and biologicals (e.g., anti-NGF/TNF antibody therapy) are not recommended for use in patients with knee OA. [54, 70] Presently, no disease modifying drugs are approved for OA. [54, 70]

Interventional Pain management

Intra-articular corticosteroid injections (IACS)

Intra-articular (IA) injections with corticosteroids have been extensively used in knee OA for over 50years and should be considered when the previously mentioned treatments are exhausted. Corticosteroids, being strong anti-inflammatory agents, are hypothesized to reverse intra-articular (synovial) and extra-articular inflammation involving the degenerative joint, especially during an OA flare. [71] Corticosteroids available for intra-articular injection are present in a crystalline and non-crystalline form. The most frequently used corticosteroids and their corresponding dosage are the crystalline triamcinolone 20–40mg, the non-crystalline prednisolone 50mg, and methylprednisolone 40–120mg.

IACS injections are shown to be more effective for pain reduction and improvement in functionality compared to placebo or no intervention in knee OA according to three recent systematic reviews and meta-analyses [72-74] The effect size is small to moderate with a peak effect occurring around 2–4 weeks depending on the formulation. [71] The NNT for IACS injection in knee OA ranges from 8 to 10. [72, 73] The duration of effect of IACS seems to be limited to the short-term, as a meta-analysis found no analgesic effect at 6 months. [72] Compared to an active treatment with IA hyaluronic acid or physiotherapy, IACS injections showed no statistically significant effect 6 weeks after treatment in knee OA patients. [74] Recurrent IACS do not provide additional symptom relief compared with other injectables at mid- and long-term follow-up. [75] Concomitant injection with viscosupplementation or local anesthetics has not been shown to increase effect of the treatment, though the addition of corticosteroids to hyaluronic acid has been shown in multiple studies to be superior to hyaluronic acid alone. [72, 76, 77] A higher equivalent dose than 40 mg of methylprednisolone does not increase the treatment effect. [72] Repeated injections have been shown in clinical trials to decrease cartilage volume. [78] There is insufficient data to advice the use of a specific short-acting or long-acting corticosteroid preparation.

Intra-articular hyaluronic acid (IAHA) injection

Hyaluronic acid (HA) is a non-sulfated glycosaminoglycan that is an important component of healthy articular cartilage and synovial fluid. [3, 79] The hypothesized mechanism of action of viscosupplementation is through anti-inflammatory, anabolic,

analgesic, and chondroprotective mechanisms; however, the physiological effect of HA has not been fully elucidated. [71, 79] Injection of IAHA could improve pain and joint function by increasing lubrication during articulation and restoring the viscoelasticity of synovial hyaluronan. [70] Viscosupplements are available in different formulations (hyaluronan and hylan), different molecular weights (high [>1.5 million Da] and low molecular weights, and in different molecular structures [linear, cross-linked, or both]). [80] Despite conflicting clinical results, differences in HA molecular weight are hypothesized to result in differences in biological activity, with high molecular IAHA generally favored. [81, 82] Although a growing trend is to perform a single IAHA injection, injection schedules per patient reported in studies vary from 1 to 5 injections. [71]

The clinical effect of IAHA in knee OA is controversial. Two meta-analyses comparing viscosupplementation to placebo or no intervention showed a small and non-clinically meaningful benefit for IAHA with an increased risk of adverse events, while another meta-analysis found significant improvement for pain and function compared to placebo up to 24weeks. [83-85] A meta-analysis comparing IAHA with IACS reported a stronger effect for IACS up to 4weeks, equal efficacy at 4–8 weeks, and higher efficacy of IAHA past 8 weeks. A network meta-analysis of different treatments for knee OA reported that IAHA leads to statistically significant improvement in pain and that IAHA was more effective than all conservative knee OA treatments including IACS. [86] The systematic reviews should be viewed with caution as most of the included trials were found to have low methodological quality, high heterogeneity, and were sponsored by industry. [87] If effective, IAHA reaches its peak effect at 4–8weeks and the effect is detectable until 24 weeks. [84] Regarding repeated IAHA injections, a study by Ha et al. [88] comparing a single to three IAHA injections in knee OA resulted in non-inferiority of a single IAHA. When IAHA injections are effective, how long to continue these injections in clinical practice is unknown. When comparing low- and high-molecular weight IAHA injections, subgroup analyses in systematic reviews are inconclusive. In a randomized, double-blind study comparing low- and high-molecular weight IAHA injections, Gigis et al. [89] reported that both lead to similar symptom reduction. A systematic review of 7 RCTs and 10 cohort studies examined the effect of repeat IAHA injections. The number of injections per treatment course varied from 1 to 5, with the number of repeat courses also ranging from 1 to 5 and follow-up periods varying between 26 and 174weeks. All studies showed significant improvement in pain after the first course of HA. After a repeat injection series, pain reduction remained significant compared to baseline. [90] The high degree of heterogeneity between studies should be considered when interpreting these results. The long-term follow-up of knee OA patients treated with IAHA does not indicate evidence for acceleration of knee OA progression, but future studies should address the potential for disease-modifying effects. [87]

Intra-articular injections with platelet-rich plasma (PRP)

Platelet-rich plasma (PRP) is a highly concentrated volume of platelets derived from centrifugation of autologous blood. Both plasma and platelets in PRP contain growth factors that can aid healing and tissue regeneration.[91, 92] PRP can be prepared by different methods (single-spinning method, double-spinning method, or selective blood filtration). Based on the leukocyte and fibrin content, PRP is classified into pure PRP, leukocyte-rich PRP, pure platelet-rich fibrin, and leukocyte- and platelet-rich fibrin. [91] Although some leukocytes can secrete growth cytokines, IA-injected leucocytes can also increase oxidative stress and inflammation, mitigating any clinical effect.[93] The PRP solution can also be exogenously activated. IA PRP is on average injected three times with 1, 2 or 3weeks intervals separating treatments. [94]

Evidence for the clinical effect of IA PRP infiltrations is mixed. Compared to placebo or no treatment, two systematic reviews reported a significant positive effect on pain. [94, 95] When compared to hyaluronic acid, there is moderate evidence that PRP is more effective for pain and function than IAHA. [94-99] Four systematic reviews found that PRP might be more effective in reducing pain and function for up to 9 months compared with IACS. [95, 99-101] Although the aforementioned research tended to show favorable results for IA PRP, it must be noted that the quality of data is low, and the included studies exhibited extensive heterogeneity. No knee OA guideline currently recommends PRP.

The heterogeneity of the studies is evident in the volume of plasma injected, method of PRP preparation, use of exogenous PRP activation, and frequency of injections. A direct comparison between single- versus double-spinned PRP by Filardo et al. [102] showed no statistical difference between preparation methods. Despite an absence of randomized, comparative effectiveness studies, systematic reviews have concluded that exogenously-activated PRP is more effective than non-activated PRP, [103] and that leukocyte-poor PRP may be superior to leukocyte-rich PRP for knee OA. [96] A systematic review that evaluated cartilage degeneration in knee OA patients up to 12months after PRP treatment concluded that PRP does not result in disease modification or an increase in degeneration compared to the expected OA progression. [99, 104, 105] There is no substantial evidence that simultaneous injection of PRP with hyaluronic acid or mesenchymal stem cells improves the clinical effect. [106-111] There is corroborating evidence that multiple PRP injections may be more beneficial than a single injection. [92, 112]

Radiofrequency of genicular nerves

Radiofrequency (RF) treatment of the genicular nerves aims to interrupt pain signal transmission from the sensory genicular nerves by means of a thermal lesion. [113, 114] RF treatment can be performed using three main different RF modalities: conventional

RF with various iterations intended to enhance lesion size, cooled RF, and pulsed RF. In bipolar RF, symmetrically placed electrodes are positioned around the targeted area. Both electrodes serve as a conduit for electrical current which results in larger lesions when compared to conventional RF.[115] The targeted genicular nerves are branches of the femoral, obturator, and sciatic nerves that innervate the anterior part of the knee. The superomedial, the superolateral, and the inferomedial genicular nerve are the traditional targets of RF treatment based on the inaugural sham-controlled trial by Choi et al. There is an ongoing discussion as to whether targeting more nerves could increase outcomes as there are over 10 sensory nerves supplying nociceptive input from the anterior knee joint. [116-119] Figures 1 and 2 display the anatomical variations of the genicular nerves that innervate the anterior knee and possible targets for the RF procedure for each nerve.

When results from all clinical studies are evaluated, regardless of the RFA modality employed, successful outcomes have been reported in between 30% and 74% of OA patients at 6 months. [120-126] When RF of the genicular nerves is compared to intra-articular injections in knee OA, the results from systematic reviews are contradictory. One reported the probability of benefit after RF to be 4.5 times higher compared to IACS and 1.8 times higher compared to IAHA, while another showed no significant difference in effect between IA injections, RF ablation, and genicular artery embolization. [125, 127] There seem to be differences in the efficacy between the three RF modalities. Conventional RF treatment was shown to be superior to pulsed RF in OA knee pain in an RCT, which is consistent with comparisons for other joints. [128, 129] Studies suggest that cooled RF may provide advantages over conventional RF but the incremental benefit is small. Cooled RF, which creates larger lesions and thus a greater likelihood of accurate denervation, could theoretically produce better and more prolonged pain relief compared to conventional RF based on a large cohort study.[130] The same study also demonstrated that larger needle size and thus larger lesion size was associated with longer pain relief. Conversely, although cooled RF provided better symptom control in a pilot RCT in patients with persistent postsurgical pain, it did not provide meaningfully better outcomes in OA patients.[131, 132] More studies are needed to support the routine use of the more expensive and resource-intensive cooled RF technique.

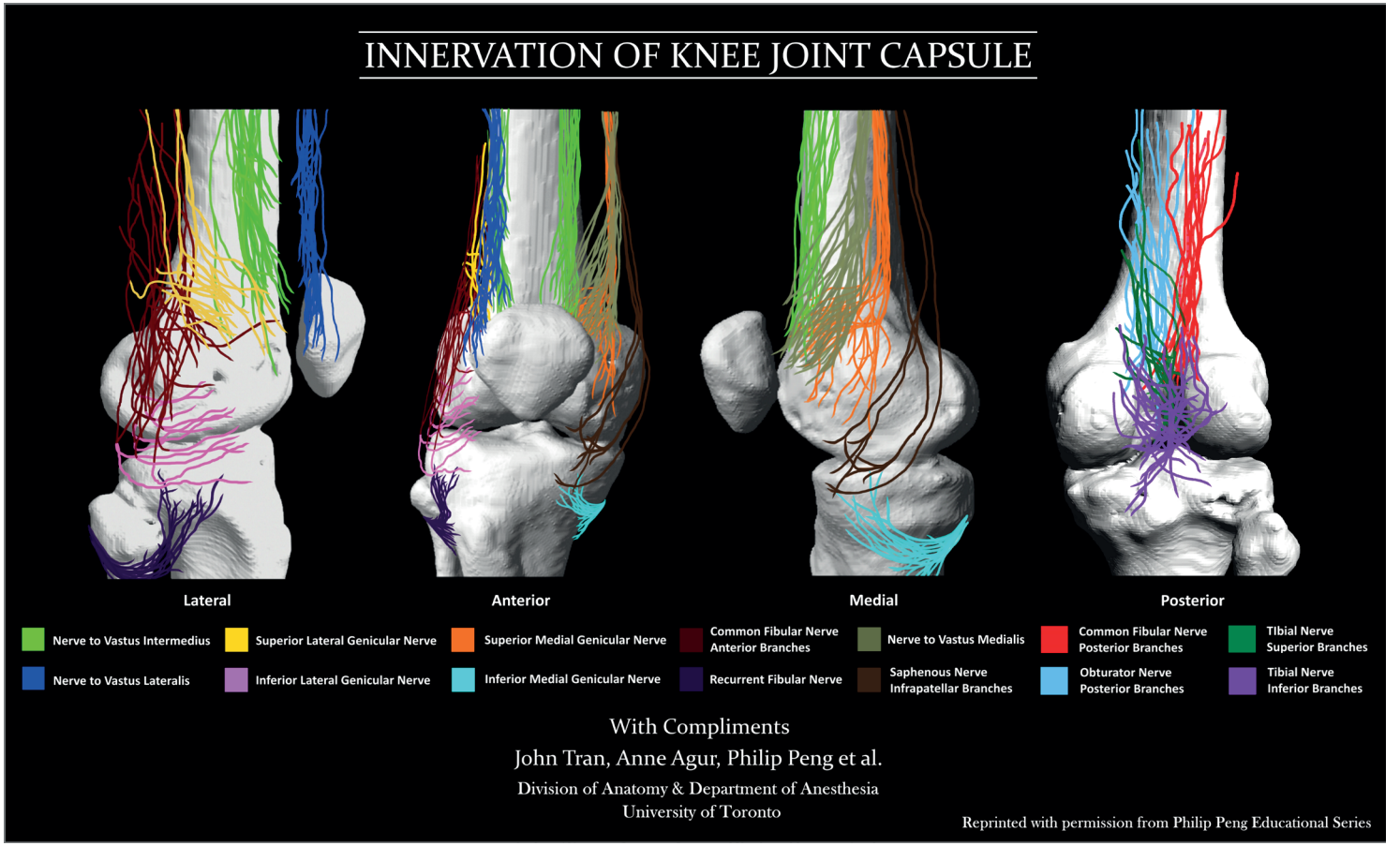


Figure 1 Anatomical variations of the genicular nerves that innervate the knee joint capsule – reproduced with permission of Philip Peng Educational Series [168] A. Lateral view. B. Anterior view. C. Medial view D. Posterior view.[168, 176]

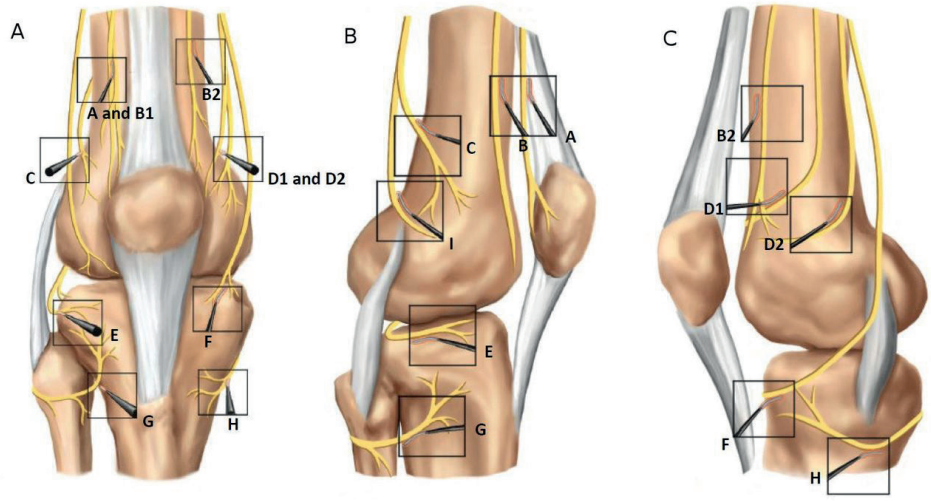


Figure 2 Innervation of the anterior knee capsule including possible target points for radiofrequency ablation – reproduced with permission of McCormick et al.[133] (A) Anterior view, (B) lateral view, and (C) medial view. (A) Nerve to vastus lateralis, (B1) Lateral branch of nerve to vastus intermedius, (B2) Medial branch nerve to vastus intermedius, (C) Superior lateral genicular nerve, (D1) Nerve to vastus medialis, (D2) Superior medial genicular nerve, (E) Inferior lateral genicular nerve, (F) Infrapatellar branch of saphenous, (G) Recurrent fibular nerve, (H) Inferior medial genicular nerve, and (I) Terminal articular branch of the common fibular nerve.

Concerning the number of targeted nerves, there is a theoretical advantage of lesioning more than 3 nerves. Most studies up to now targeted three traditional genicular nerves, but there are studies that advocate targeting more nerves. [133] Three retrospective studies examining factors associated with outcome demonstrated that greater KL grade, not being on opioids and adjuvant analgesics, not having psychiatric co-morbidities, and targeting more than 3 nerves foreshadowed positive RFA outcomes. [117, 134, 135] Furthermore, the study by Malaithong et al.[115] found no significant differences up to 12 months between the group that received local anesthetic and steroid injections with sham-RFA and the group with local anesthetic and steroid plus bipolar RFA targeting three genicular nerves. Both groups experienced significant reductions in pain. It should be noted that, unlike medial branch blocks before facet joint RFA, there appear to be some patients whose pain relief from genicular nerve blocks with steroids is sustained. [136-138] A study by Kose et al. randomized a total of 80 patients to receive either conventional RF of the three traditional nerves or conventional RF of three traditional nerves together with pulsed RF of the infrapatellar and recurrent fibular nerves. Both techniques provided pain reduction and functional improvement up to 6 months after the procedure but the 5-nerve-targeted group showed significant improvement compared with the 3-nerve-targeted group, though the 95% confidence intervals overlapped. [139]

Because of methodological flaws in existing studies comparing different nerve-targeting strategies, large comparative-effectiveness trials comparing the current standard 3-nerve technique to more aggressive ones are needed to determine optimal lesioning parameters.

Chemical ablation of genicular nerves

Ablation of genicular nerves can also be performed with chemical agents. [140-144] The use of alcohol (50%-100%) or phenol (6%- 9%) are both described to perform neurolytic blocks.

Alcohol neurolysis of genicular nerves was only described in a case report and series. [142,143] Both studies reported pain reduction, respectively at 6 weeks and 6 months follow up.

The phenolisation of genicular nerves was described in a prospective cohort study. [140] Forty-three patients underwent an ultrasound-guided injection of 1.5 mL phenol at each target. At 6 months follow-up, about 50% of patients had ≥50% pain reduction. Yildiz et al. randomized 64 patients into conventional RF or neurolysis with phenol 6%. There were no significant differences between the groups up to three months follow-up. [144] There are currently several ongoing studies using chemical neurolysis to target a larger number of genicular nerves.

In conclusion, only a small number of studies currently describe the use of chemical neurolysis of the genicular nerves. More research on the clinical effectiveness of chemical neurolysis is still needed.

Surgery

Whereas mild knee OA is generally well-managed by conservative treatments, a large number of patients experience inadequate pain and symptom relief as reported by the Study of Osteoarthritis Real World Therapies (SORT), a prospective observational study conducted in six European countries in 2015. [145] Patients with longer disease duration, bilateral knee OA, greater opioid use, and higher prevalence of co-morbidities are more likely to experience pain refractory to conventional treatments. It is estimated that 50% percent of patients diagnosed with symptomatic knee OA will undergo TKA procedure in their lifetime. [22] Currently the International Cartilage Repair and Joint Preservation Society (ICRS) focuses on joint-preserving treatments to postpone joint replacement, which typically lasts between 10 and up to 20 years. Surgery to unload joints (eg, joint distraction or osteotomy) and repair OCD have been shown to favorably alter biomechanics and improve symptoms. [146, 147] Surgery is indicated in patients with osteoarthritis refractory to conservative treatment.

Surgical procedures performed for knee OA are: [57, 58]

1. Arthroscopic debridement (synovectomy, meniscectomy, loose body removal, etc.)
2. (Osteo)chondral repair
3. Joint distraction
4. Subchondroplasty
5. Osteotomy around the knee
6. Knee arthroplasty (unicondylar or bicompartmental knee arthroplasty, total knee arthroplasty or revisions thereof)
7. Meniscus replacement/repair
8. Ligament repair (e.g., anterior cruciate ligament repair, medial collateral ligament repair)

Arthroscopy of the knee which was extensively performed before randomized controlled trials found evidence for a lack of effect, may lead to worse short-term outcomes and does not inhibit disease progression. [148] Osteochondral repair aims to repair damaged articular cartilage in early OA. The results are promising, but the technique is currently limited to study settings. [149] Early correction of mechanical factors (mal-tracking patella, malalignment, etc.) before they lead to deleterious (osteo) chondral structural changes should be pursued whenever possible to delay the development of OA and following joint replacement at a young age. [150] During osteotomy, the bones forming the knee joint are realigned to "unload" the damaged cartilage. Total or partial knee arthroplasty (TKA) is the treatment of choice in refractive end-stage knee OA. TKA is successful in diminishing pain and increasing functionality; however, 20% of the patients are dissatisfied postoperatively and many develop PPSP. [26-28]

Neurostimulation (central and peripheral)

Peripheral nerve stimulation (PNS) involves using electrical pulses from a peripherally positioned electrode to inhibit nociceptive input from small-diameter nerve fibers. [151] PNS of the femoral and the sciatic nerve have been reported to be effective in small trials for refractory postoperative and neuropathic knee pain. [152] Evidence of the clinical effect of PNS for osteoarthritis of the knee is based on case series and thus systematic use is not recommended outside of the study setting. [153, 154]

Spinal cord stimulation (SCS) and dorsal root ganglion (DRG) stimulation are two forms of central neurostimulation wherein an implanted pulse generator produces electrical stimulation directly at the spinal cord level or at the nerve root with the aim of reducing pain intensity. Literature on SCS and DRG stimulation describes the successful use of these techniques in severe refractory neuropathic knee pain due to pain after arthroplasty, post-traumatic pain, and CRPS. [152, 155] There are no trials on the use of SCS and DRG stimulation for chronic knee pain due to osteoarthritis..

Evidence for interventional management

The summary of evidence for interventional management of chronic knee OA is provided in Table 1.

Table 1 Summary of evidence for interventional management of chronic knee OA.

Technique	**Conclusion**	**Recommendation in clinical practice**
Intra-articular corticosteroid injections	Studies have demonstrated short-term efficacy in knee OA. [72-74, 156]	Recommended
Intra-articular hyaluronic acid injection	Studies failed to establish a benefit, and harm may be associated with these injections, therefore the conditional recommendation against is made. This is consistent with the use of hyaluronic acid injections, in the context of shared decision-making that recognizes the limited evidence of benefit of this treatment, when other alternatives have been exhausted or failed to provide satisfactory benefit. [83-85, 156]	Conditionally recommended
Intra-articular platelet rich plasma	Research tended to show favorable results for IA PRP, although it must be noted that the quality of data is low, and the included studies exhibited extensive heterogeneity. No knee OA guideline currently recommends PRP. [94-101, 156]	Not enough evidence for recommendation outside of a study setting
Radiofrequency of the genicular nerves	Studies have demonstrated efficacy of conventional and cooled RF in knee OA. [113, 125, 128-130, 157, 158]	Recommended
Chemical ablation of the genicular nerves	Only a small number of studies currently described the use of chemical neurolysis of the genicular nerves. More research on the clinical effectiveness of chemical neurolysis is still needed. [140-144]	Not enough evidence for recommendation outside of a study setting
Spinal cord / dorsal root ganglion stimulation	There are no trials on the use of SCS and DRG stimulation for chronic knee pain due to osteoarthritis.	Not enough evidence for recommendation outside of a study setting

Side effects and complications of interventional pain management

Intra-articular corticosteroid injections (IACS)

IA corticosteroid injection has been reported to lead to the following adverse events: transient local pain and swelling; septic arthritis; acute corticosteroid-microcrystalline joint flare; hemarthrosis; and systemic reactions due to absorption of corticosteroids including facial flush, hyperglycemia, and high blood pressure. [156] The incidence of adverse events due to IACS is low and serious adverse events are rare. [72, 156] Long-term adverse effects of IACS are controversial. Although the anti-inflammatory effect of corticosteroids might theoretically slow disease progression, there is evidence of time- and dose-dependent deleterious effects of corticosteroids possibly resulting in cartilage damage and chondrotoxicity. [157] A Cochrane systematic review from 2015 reported that there was no evidence of an effect of corticosteroids on joint space narrowing compared to sham or no interventions for up to 6 months; however, this conclusion was based on a single RCT.[72] McAlindon et al. published the results of a randomized, double-blind study in 140 patients with knee OA patients that found that IACS was associated with significantly greater cartilage volume loss compared to sham injections on magnetic resonance imaging at 2-year follow-up, while Latourte et al. reported that IACS injections did not significantly increase the 5-year incidence of total knee replacement or radiographic worsening in in knee OA. [72, 158] Future studies should address the long-term safety of IACS.

Intra-articular hyaluronic acid (IAHA) injection

IAHA has a low rate of adverse effects. [80, 86, 156, 159] Despite a higher number of serious adverse events and adverse event-related study withdrawal in the systematic reviews by Rutjes et al. and Pereira et al. [59, 76] the most frequent adverse events are short-term knee pain, swelling, arthralgia, and effusion. The network meta-analysis by Bannuru et al. [156] found similar adverse event rates for all IA injections. Unlike for IACS, there are no systemic effects of IAHA.

Intra-articular injections with platelet rich plasma

Literature on PRP asserts that IA PRP is not linked to any major safety issue and that adverse events are mild. [71, 94, 107, 109] Frequently reported adverse events, similar to IACS and IAHA, are infection, bleeding, bruising, peripheral nerve injury, and temporary exacerbation of pain typically lasting from 2 to 7 days. [156]

Radiofrequency of genicular nerves

Systematic reviews report the RF intervention to be safe with limited non-severe adverse events. [125, 126, 160, 161] Frequent adverse events are postoperative pain (transient neuritis), hypoesthesia, and bruising. Other possible adverse events are allergic reactions, knee hematoma, infection, and soft tissue damage including skin burns if the RF cannula is positioned incorrectly. [162]

Techniques

IACS injection

There is considerable heterogeneity in the dosage and volume of injection, with most studies reporting the use of an equivalent dose of 40mg prednisolone and a volume of 2–6mL of injectate.[72] One randomized study found no differences in any outcome measures when comparing 40 and 80mg of triamcinolone. We describe an ultrasound guided procedure using the suprapatellar approach as this technique results in a high rate of intraarticular spread even in the presence of knee effusions. [163]

The patient is placed in the supine position with the knee flexed 30°. A high-frequency linear ultrasound probe is placed on the patella in the transverse position and is gently slid proximally to visualize the quadriceps tendon. Subclinical knee joint effusions can be visible under the quadriceps and suprapatellar fat pad. The target point is the suprapatellar bursa between the suprapatellar fat pad and the prefemoral fat pad. The insertion point of the needle should be lateral to the probe so that the in-plane trajectory does not pass through the quadriceps tendon. After subcutaneous infiltration of local anesthetic, a 22–25-gauge needle is inserted into the joint recession or effusion. In case of excessive joint effusion, fluid can also be aspirated. Last, the volume of corticosteroid is injected with minimal resistance.

IAHA injection

The technique used for IAHA injections is similar to the IACS injections. Correct positioning of the needle in the intra-articular compartment is essential for an IAHA injection as injection of hyaluronic acid into the periarticular compartment results in little therapeutical effect. Studies report injection volumes ranging from 0.5 to 6.0mL and concentrations varying from 0.8 to 30mg/ mL. [79]

IA PRP injection

The technique of IA PRP injection is similar to the IA injection technique for IACS and IAHA. Intraarticular injections are performed in a "blinded" manner or using fluoroscopic or ultrasound guidance. Studies have found failure rates ranging between less than 5%–30% for landmark-guided injections. [164, 165] Image-guided procedures may result in larger effect sizes as shown by one large long-term cohort where patients who were treated with ultrasound-guided viscosupplementation were significantly less likely to undergo knee arthroplasty compared to patients treated with landmark-guided injections. [166] Compared to fluoroscopy, an ultrasound-guided procedure can ensure intraarticular needle placement without radiation, but unlike fluoroscopy cannot evaluate joint degeneration or identify capsular tears. [72]

RF of the genicular nerves

We describe here the technique for targeting three traditional genicular nerves: the superomedial (SMGN), the superolateral (SLGN), and the inferomedial genicular nerve (IMGN), as well as the technique to target the additional nerves. Whereas the described technique incorporates updated knowledge from recent anatomic studies evaluating the locations and trajectories of the genicular nerves, a number of different approaches to the genicular nerves are described in the literature, with no studies comparing effectiveness. [119, 167-170] Currently, the optimal targets for the US- or fluoroscopically-guided technique are the subject of debate and similar to all new techniques it will likely go through adaptations as new insights from scientific evidence emerge. The following description is based on the expert opinion of the author team and aims to present a roadmap for the clinician.

Anatomical variations of the genicular nerves are illustrated in Figure 1. Figure 2 shows the innervation of the anterior knee capsule.

The patient is placed in a supine position with the index knee flexed 10–15° by placing a cushion in the popliteal fossa. The patient can be monitored using pulse oximetry and if indicated, lightly sedated. The three genicular nerves are targeted using a high-frequency linear ultrasound probe or fluoroscopy under sterile conditions. Ultrasound- and fluoroscopically-guided RF needle placement have resulted in similar effectiveness. [171, 172] Although an ultrasound-guided procedure does not expose the patient and operator to radiation and enables visualization of soft tissues, gauging depth (especially in obese patients) is difficult, and aligning the electrodes parallel to the target nerve trajectories is easier with fluoroscopy. Therefore, which imaging guidance is preferred depends on the experience of the operator.

A prognostic block is sometimes performed prior to RF, though both direct (randomized trials) and indirect (comparisons of outcomes between studies that have used and not used prognostic blocks) evidence demonstrates consistently >80% response rates and no improvement in outcome. [173, 174] When blocks are used, the cut-off for designating a block as positive has generally been ≥50% pain relief, though one study found that using an 80% threshold resulted in a higher proportion of successful procedures. [117, 125, 174] The prognostic block is usually performed with volumes not exceeding 1mL of local anesthetic per genicular nerve. Due to the questionable prognostic effect and patient discomfort associated with the blocks, we presently advise against the routine use of a prognostic block.

RF cannula placement for ultrasound-guided RF
SMGN: The transducer is placed in a coronal orientation over the medial epicondyle of the femur and repositioned between the epiphysis and diaphysis of the femur. The target point is at the posterior half of the femur. After visualization of the target point, the transducer is then turned 90° into the transverse plane, and the RF cannula is inserted after local anesthetic infiltration to skin and soft tissues and advanced in an "in-plane" approach until contact is made with the bony cortex at the posterior half of the femur.

IMGN: The transducer is placed in a coronal orientation over the medial tibial epiphysis and diaphysis, the inferomedial genicular artery, and the medial collateral ligament. If the IM genicular artery is visualized below the medial collateral ligament and above the bony cortex, the RF cannula is directed next to the artery; otherwise, the target point is the junction between the epiphysis and diaphysis under the medial collateral ligament. After visualization of the target point an out-of-plane entry point for the needle is used. The transducer is then turned 90° into the transverse plane and the RF cannula is inserted after local anesthetic infiltration of skin and soft tissues, and advanced using an "in-plane" approach until contact is made with the bony cortex at the center of the tibia

SLGN: The transducer is placed in a coronal orientation over the femoral lateral epicondyle at the junction between the epiphysis and diaphysis. The target point is the posterior half of the junction between the epiphysis and diaphysis of the femur. The transducer is centered on short axis of the femur to visualize this target point. After the skin and soft tissue are anesthetized with lidocaine, the cannula is advanced using an anterior-to-posterior "in-plane" approach in the oblique plane until contact is made with the posterior half of the bony cortex of the femur.

RF cannula placement for fluoroscopically-guided RF:
The traditional target points for the fluoroscopically guided procedure are similar to those used for ultrasound. For the SMGN, IMGN, and SLGN, the cannulas are introduced under true AP fluoroscopic views of the tibiofemoral joint using a "co-axial (tunnel-view) technique." For the SMGN and the SLGN, the introducers are inserted medial and lateral to the junction of the femoral shaft and condyles, respectively, and advanced to between 50% and 100% across the depth of the femoral shaft. For the IMGN, the cannula is inserted medial to the junction of the medial tibial condyle and the shaft and advanced to 25%–75% depth across the tibial shaft. More nerves are recommended with the fluoroscopically guided approach and research on the outcomes incorporating those new targets is ongoing

Once the cannula position is confirmed in multiple views, an RF electrode is inserted into the cannula. Sensory stimulation (50Hz) is applied and should ideally produce paresthesia at a threshold of 0.5V or less, but this is not always reproducible. The absence of fasciculations below 1V is observed after motor stimulation at 2Hz, confirming sufficient distance to relevant motor branches, particularly for the ILGN and recurrent fibular nerve. If no sensory stimulation threshold is obtained at this position, the electrode can be repositioned until this is achieved.

For conventional RF, 100mm long, large electrodes (eg, 18G) with longer (eg, 10mm) active tips are often used to increase nerve capture rates although this could cause increased patient discomfort during the procedure. During cooled RF, a 100mm long, 17G RF introducer with an 18 G cooled electrode containing a 4mm active tip is used.

Summary of treatment recommendations

We recommend the following for patients with chronic knee pain due to osteoarthritis:

- All patients should be advised to engage in physiotherapy, perform aquatic and land-based exercises, use gait aids, participate in weight management and nutritional programs if indicated, consider self-management groups, and utilize pharmacological treatments.
- Knee osteoarthritis patients should undergo trials with the following medications unless contraindicated: paracetamol, topical or oral NSAIDs, and duloxetine. Opioids are not routinely recommended for chronic non-malignant knee pain. Mixed-action opioids such as tramadol, tapentadol, and buprenorphine in those with high-impact pain can be considered.
- Intra-articular infiltrations with corticosteroids are recommended for short-term pain relief in knee OA patients. Other injections such as hyaluronic acid, PRP, stem cells, and so on are not recommended, only in trial settings and not on a regular basis but may be considered in some circumstances.
- Conventional and cooled radiofrequency treatment of the genicular nerves is recommended in patients suffering from therapy-resistant knee pain due to OA if the pain is moderate to severe and KL grade is II–IV.
- A close collaboration between the surgical team and the pain/anesthesiology team is recommended to evaluate joint-preserving and joint-replacement options including using the recommendations outlined above, and implement individualized therapy plans in an iterative process.

These recommendations are summarized in the algorithm for the treatment of chronic knee pain due to OA in Figure 3. This algorithm is built on the updated ESCEO algorithm for the treatment of knee OA and is further extended to include RF of the genicular nerves and neurostimulation. [175]

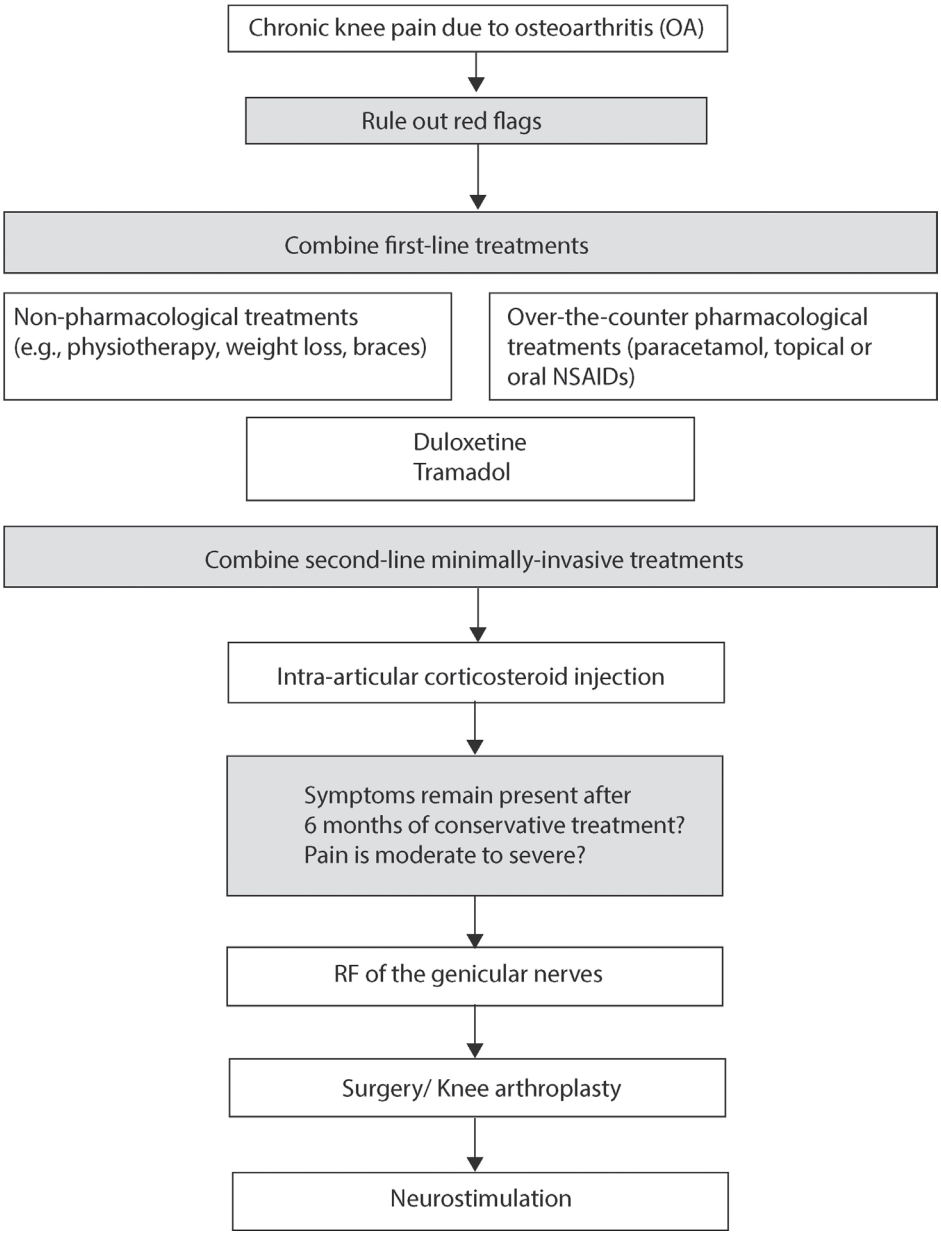


Figure 3 Clinical practice algorithm for treatment of chronic knee pain due to osteoarthritis. NSAID, Non-steroidal anti-inflammatory drugs; OA, osteoarthritis; RF, radiofrequency

Authors contribution

Thibaut Vanneste (TV) and Amy Belba (AB) performed the literature search, the reviewed the literature and wrote the article. Gezina T.M.L. Oei, reviewed and adapted the article with supplementary publications. Pieter Emans, provided input on the diagnostic process and revised the article. Loic Fonkoue, provided input on the anatomy and revised the article. Leonardo Kapural, Philip Peng and Steven P. Cohen thoroughly reviewed the article and edited the paper. Jan Willem Kallewaard, Micha Sommer and , Bert Vanneste reviewed the article and provided additional input on treatment options and techniques. Jan Van Zundert controlled the paper, provided comments, and had full responsibility.

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Conflict of interest statement

The authors declare no conflicts of interest. Jan Van Zundert and Leonardo Kapural are Editorial Board members of Pain Practice and co-author of this article. To minimize bias, he was excluded from all editorial decision-making related to the acceptance of this article for publication.

Data availability statement

Data sharing is not applicable, as no new data were created or analyzed in this study.

Patients consent

No patient information was retrieved or analyzed; all information is derived from published literature. Therefore, no patient consent was needed.

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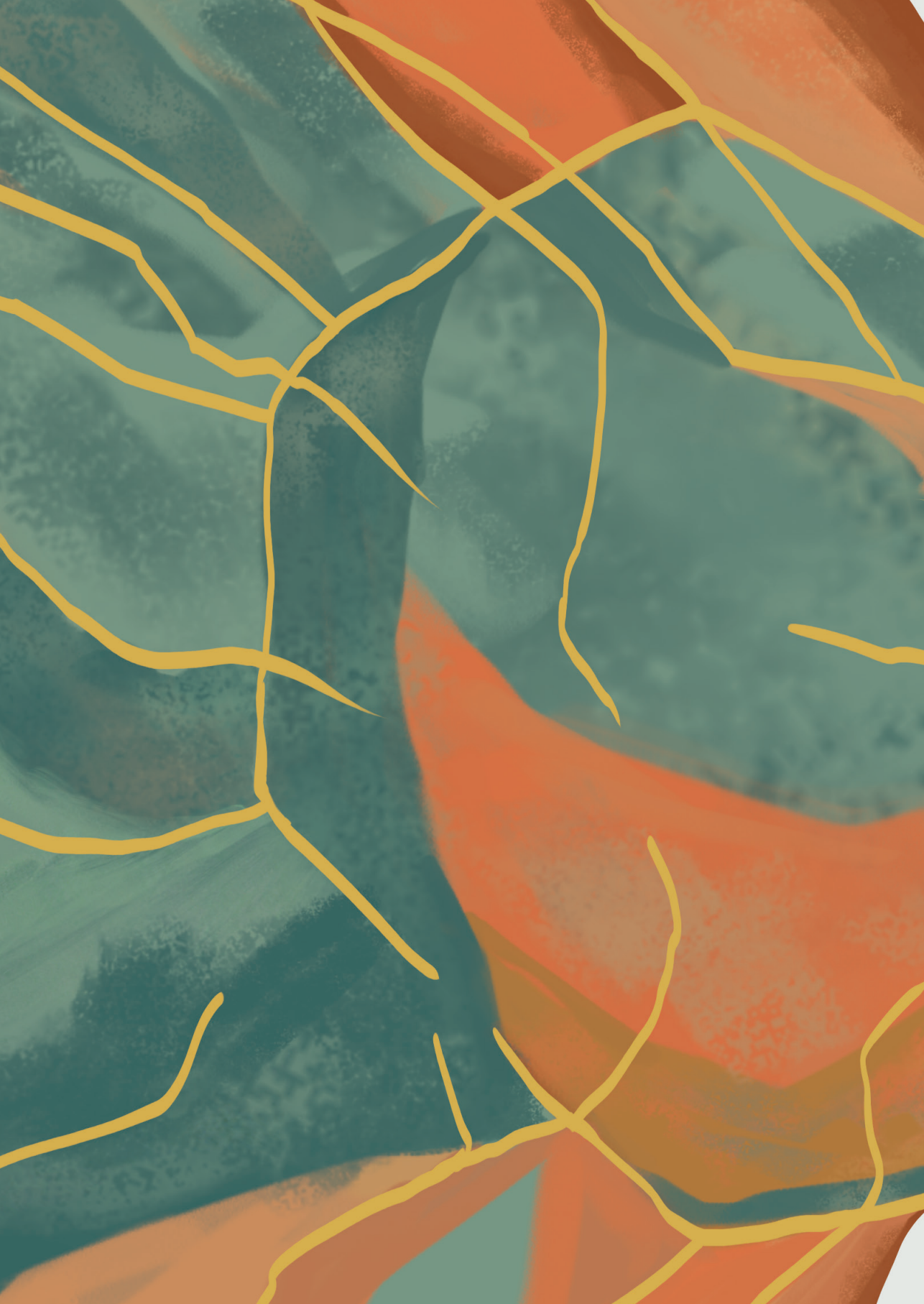
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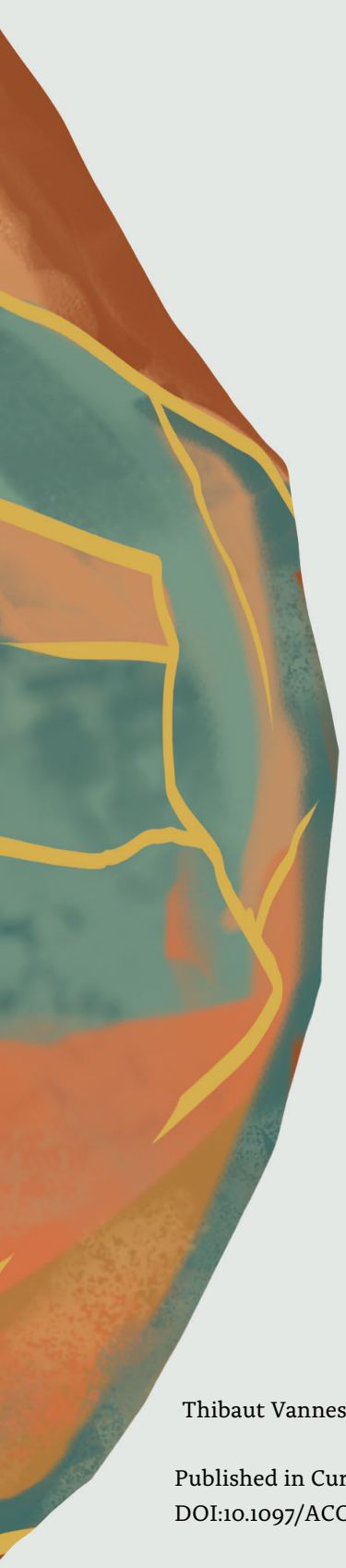
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CHAPTER 3

Pulsed radiofrequency in chronic pain

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Abstract

Purpose of the review

The increasing number of publications on pulsed radiofrequency (PRF) treatment of chronic pain reflects the interest for this technique. We summarize the literature for PRF in 5 indications: radicular pain, trigeminal neuralgia (TN), occipital neuralgia, shoulder and knee pain.

Recent findings

The efficacy and safety of PRF adjacent to the dorsal root ganglion was documented on cervical and on lumbar level. PRF has been used for the treatment of TN. The observed duration of effect is shorter than that of conventional RF but no neurological complications reported with PRF. PRF of the nervi occipitales is superior to steroid injections in occipital neuralgia. Several studies showed that PRF of the n. suprascapilaris may relief shoulder pain and can improves mobility of the shoulder joint. For the treatment of knee pain different nerves have been targeted for PRF treatment.

Summary

PRF treatment has progressively gained a place in the management of chronic pain syndromes. The concept is appealing because long-lasting effects are reported without complications. Future research is needed with high quality randomized controlled trials and identification of the optimal parameters of PRF in clinical practice.

Keywords

Knee pain, occipital neuralgia, pulsed radiofrequency, radicular pain, shoulder pain, trigeminal neuralgia

Key points

- No neurological complications reported in over 200 articles published.
- PRF adjacent to the dorsal root ganglion should be considered for the treatment of radicular pain.
- PRF for trigeminal neuralgia has a shorter duration of effect but a better safety profile than conventional radiofrequency.
- PRF of the nervi occipitales works better than steroid infiltrations for occipital neuralgia.
- PRF shows promising results in treating shoulder pain and chronic postoperative knee pain.

Introduction

The use of high frequency current at 500 kHz, called radiofrequency, is well introduced in pain management. When applied close to a sensory nerve, the heat generated in the cells at the electrode tip causes coagulation, which is believed to interrupt the pain conduction. The observation that the RF lesion adjacent to the dorsal root ganglion (DRG) causes only transient sensory loss in the relevant dermatome, while the relief of pain may be of much longer duration stimulated the development of a minimal neurodestructive administration mode for the electrical current. [1] Applying high-voltage radiofrequency current of 20 ms/500 ms allows the generated heat to be washed out, the maximum temperature is controlled not to exceed 42°C. The first study using pulsed radiofrequency (PRF) reports good pain relief in patients suffering lumbosacral radicular pain after application of PRF adjacent to the DRG. [1] Since this first publication there are more than 200 publications, including randomized controlled trials (RCTs), prospective, retrospective studies, case reports and about 30 basic science publications. The evolution of the number of publications on PRF is illustrated in figure 1. Thirty-seven percent of the publications are case reports, 12 % are retrospective studies, 13 % prospective studies, 13% are RCTs, 7 % are review articles and 18 % of the publications report on basic research. In this review, we summarize the evidence on five frequently studied indications: radicular pain, trigeminal neuralgia (TN), occipital neuralgia, shoulder and knee pain.



Figure 1 Evolution of the number of publications on pulsed radiofrequency per year.

Methods

In January 2017, we searched MEDLINE (Pubmed) for 'pulsed radiofrequency' and 'pain'. Searches were run for all available years, but limited to English language. Two authors independently screened the titles and abstracts for relevance. Full-text reports of the relevant papers were obtained.

Results

Using above mentioned search strategy we found a total of 212 articles, we analyzed 121 papers dealing with the selected indications. The selection procedure is clarified in figure 2.

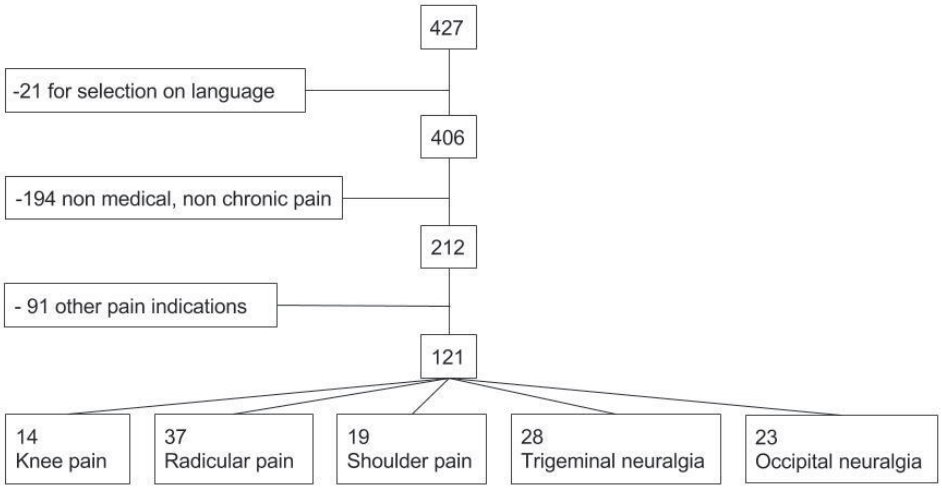


Figure 2 Selection of relevant literature on pulsed radiofrequency.

Radicular pain

Radicular pain is defined as pain radiating into the limb. Cervical radicular pain occurs in approximately one person in 1000. Lumbosacral radicular pain is more frequent with an annual prevalence between 9.9 and 25%. Although the pathophysiology is not fully understood, radicular pain is related to lesions that either directly compromise the DRG (mechanically) or indirectly compromise the spinal nerve and its roots by causing inflammation and/or ischemia of the axons. [2]

PRF was first compared to conventional RF at 42°C for patients with lumbosacral radicular pain. The global perceived effect was significantly better in the PRF group. [1]

These initial findings were confirmed in case reports, retrospective and prospective studies. [3-10, 11, 12] In all these studies, patients with various subdiagnoses of lumbosacral radicular pain could be included, and the treatment was not always limited to one intervention at one level.

In a prospective cohort study the effect of PRF adjacent to the lumbar DRG on pain and quality of life was assessed. Sixty-five patients were included with unilateral and monosegmental radiating pain down the leg, to the hallux (L5) or lateral side of the foot (S1), suggesting involvement of the corresponding lumbar spinal nerve and concordant with the MRI or computer tomography scan findings. [13] The radicular syndrome should have been present for at least 3 months, despite conservative treatment. The leg pain should be the primary complaint with an average pain score of at least 5 on a 10-point numerical rating scale (NRS). At 6 months' follow-up, the intention-to-treat analysis showed clinical success in 55.4% of the patients. The reduction in NRS and ODI was statistical significant compared to baseline. There has been one sham controlled feasibility study, with no significant difference in pain scores between the PRF and sham group at 3 months. [14] However, this study was flawed with possible selection bias and technical issues, rendering the conclusion unclear.

PRF adjacent to the cervical DRG was studied in observational studies [15, 16] and 1 RCT. The observational studies show more than 50% pain reduction in more than 60% of the patients. This effect appears to be sustained at 1 year follow up. In the RCT, PRF was shown to be more effective than placebo at 3 months' follow-up. Also 6 month post-treatment there was a positive trend in the PRF treatment but in this study the outcome fell short of statistical significance, due to baseline variations. [17].

PRF adjacent to the DRG reduces pain and improves disability in patients with radicular pain. No neurological complications were reported. PRF adjacent to the cervical DRG is recommended for the treatment of cervical radicular pain. [18] The use of PRF adjacent to the lumbar DRG can be considered for the treatment of lumbosacral radicular pain. [19]

Trigeminal neuralgia

TN, also called Tic Douloureux, is defined as sudden, usually unilateral, severe brief stabbing recurrent pain in the distribution of one or more branches of the fifth cranial nerve. It can be triggered by trivial sensations from trigger points located within the area of trigeminal innervation. [20] We distinguish idiopathic or classical and secondary trigeminal neuralgia.

PRF of the Gasserian ganglion could be an alternative to other interventional treatment options with less side effects; like the conventional ablative treatments that can cause anesthesia dolorosa or hypoesthesia. The initially published case reports on PRF of the Gasserian ganglion show contradictory outcomes. [21] The first RCT comparing PRF with radiofrequency found that only two out of 20 patients in the PRF group had pain

reduction compared with 19 out of 20 in the RF group 3 months after the procedure. [22] In the radiofrequency group 1 patient had anesthesia dolorosa and no complications were reported in the PRF group. A prospective observational study reports on 20 patients with trigeminal neuralgia treated with PRF of the Gasserian ganglion. At 1 year follow-up, seven patients had a favorable outcome. Patients who had unsatisfactory pain relief 2 weeks after treatment were switched to radiofrequency. [23] In a case series, patients with idiopathic TN and TN secondary to multiple sclerosis, were managed in a multidisciplinary setting, including neurology, neurosurgery, stomatology and anesthesiology/algology. They received complete information; including the potential side effects of radiofrequency and PRF and the possible shorter duration of effect of PRF compared to radiofrequency. In this way, the treatment was selected as a shared decision. Seventy-two patients, 75% with idiopathic TN and 25% with TN secondary to multiple sclerosis opted for the PRF treatment. At a mean follow-up period of 29 months ± 4.3 months; 34 patients (47%) had a good to excellent pain relief. The mean duration of pain relief was 20.1 ± 3.8 months. History of multiple sclerosis or surgery did not influence the response rate. No neurological or other complications were reported. [24]

With the aim to study the possibility to reduce the complication rate of radiofrequency, the combination of radiofrequency and PRF was studied in 3 RCT's [25-27]. Although two studies report a faster recovery from complications and a lower complication rate in the group with combined treatment, this was not confirmed in the third study. There was no difference in efficacy between the two treatment options.

One RCT compares high voltage with standard voltage PRF [28]. The high-voltage group (mean 71.5 V) had a significant higher short- and long-term success rate compared to the standard voltage group (mean 36.3 V) and no complications. Two case reports describe the safety of a PRF treatment up to 40 minutes, and suggest that a longer duration would improve outcome [29, 30].

PRF of the Gasserian ganglion was shown to provide pain relieve in about half of the patients. The duration of effect may be somewhat shorter than that of radiofrequency, however, a 20 months' pain relief is highly appreciated by the patients, and the repeat intervention seems to have comparable results as the first one. We observe an ongoing search for the optimal parameters, such as duration, voltage and frequency of the administered current.

The incidence of TN increases with age, and comorbidity is frequent in these patients. Therefore, we suggest providing full information on the advantages and potential disadvantages of the treatment options, resulting in a correct shared decision-making. No neurological complications were reported after PRF treatment of the Gasserian ganglion.

Occipital neuralgia

The International Headache Society defines occipital neuralgia as paroxysmal shooting or stabbing pain in the dermatomes of the nervus occipitalis major or nervus occipitalis minor. The pain originates in the suboccipital region and radiates over the vertex. Hypo- or dysesthesia in the affected area can accompany the pain. Pressure over the nervus occipitalis major or minor usually elicits the pain [31].

PRF of the n. occipitalis major and minor during 4 min was described in a case report that found 70% pain relief lasting 4 months. Repeated treatment after recurrence resulted again in 70% pain relief during 5 months [32]. A prospective trial showed > 50% pain relief in 68.4%, 57.9% and 52.6% of the patients respectively at 1, 2 and 6 months. The quality of life improved significantly and the need for medication decreased [33].

The efficacy of PRF of the nervi occipitales was compared with steroid injections in a multicenter, randomized, double-blind, comparative-effectiveness study. Patients included had occipital neuralgia, or migraine with occipital nerve tenderness. Forty-two patients received local anesthetic and NaCl 0.9% followed by three cycles of PRF treatment per targeted nerve. Thirty-nine patient received local anesthetic mixed with steroid and three cycles of sham PRF. At 6 weeks, the pain reduction was significantly greater in the PRF group compared with the steroid group, this persisted through the 6 months follow-up. Side effects were minor and transient in both groups [34].

The studies show a clinical effect of PRF of the nervi occipitales without serious side effects. The effect seems to last longer than that obtained with steroid infiltrations.

Shoulder pain

Shoulder pain is a common musculoskeletal problem [35]. It can be of various etiology including rotator cuff tear, adhesive capsulitis (frozen shoulder), glenohumeral osteoarthritis, post-traumatic pain and persistent pain following surgery. Four nerves (suprascapular, subscapular, subclavian and axillary nerves) innervate the shoulder, but the suprascapular nerve supplies up to 70% of the sensory innervation. [36] PRF of this nerve could be considered for frozen shoulder or capsulitis of the shoulder joint.

A RCT compared intra-articular corticosteroid injection versus PRF during 4 min to the suprascapular nerve in 50 patients with shoulder pain. There was a significant reduction in pain scores in both groups at 12 weeks, but the improvement rate was significantly higher in the corticosteroid injection group in terms of pain. No complications were observed in each group [37].

A second RCT of 22 patients compared the effect of PRF during 2 min to the suprascapular nerve versus a sham procedure. Only 13 of 22 patients completed the six months follow up. Dropout rate was higher in the sham group. A significant linear trend for improvement in NRS was observed within the PRF group, but not in the sham group. There were no complications [38].

A third RCT made the comparison between PRF of the suprascapular nerve and transcutaneous electrical nerve stimulation in 40 patients. Follow-up time was 12 weeks. They found no significant difference between both groups but both groups had improvement of Visual Analogue Scale (VAS) scores. No complications were mentioned [39].

Furthermore, there are four prospective observational studies describing the effect of PRF to the suprascapular nerve [40-43].

The studies suggest a pain relief after PRF treatment that last for 6 months. The effect of PRF is better than sham intervention and comparable to TENS. There is no consistency in the duration of PRF treatment, which ranges from 2 minutes to 8 min. Structured research into the optimal treatment duration should be performed.

Knee pain

Prevalence of chronic knee pain secondary to osteoarthritis is up to 12% above 60 years [44]. It is closely related to increasing age and obesity [45]. Six months after joint replacement about 50% of the patients still need analgesic medication [46]. Interventional pain treatment such as injection, and radiofrequency, targets the nerves innervating the knee joint and its surrounding structures, the relevant dorsal root ganglion or the nerve endings intra-articular. PRF of the sciatic nerve during 8 min was successful in 37 of the 47 procedures at 4 weeks follow-up [47].

A retrospective study of 115 patients applied PRF to the saphenous nerve for 8 min [48]. All patients showed improvement of their VAS score up to 6 months. A case series of 10 patients report the results of PRF to the nervus femoralis, the nervus saphenous,

the nervus peronaeus communis, the nervus tibialis and three plexuses (peripatellar, subsartorial and popliteal) [49]. Each nerve was treated for 8 min. At six months there was a reduction of more than 50% in mean NRS of ten patients. There were no complications.

PRF may be helpful in the treatment of chronic knee pain. It is, however, not clear which nerves should be targeted and how long PRF treatment should be administered. The best results are reported in 10 patients treated with PRF of the femoral, the saphenous, the common peroneal, the tibial and three plexuses (peripatellar, subsartorial and popliteal).

There are five studies (one RCT, two prospective, one retrospective and one case report) focusing on intra-articular PRF of the knee. The RCT of 70 patients compares three treatment groups [50]. Group 1 got ropivacaine and erythropoietin intra-articular injected, group 2 received ropivacaine and dextrose intra-articular and group 3 got treated with PRF intra-articular during 15 min. The mean VAS score at 12 weeks decreased the most in group 1 (3.5) versus group 2 (5.53) and 3 (5.5). They concluded that treatment with erythropoietin was more effective for osteoarthritis. One prospective study of 21 patients reports a significant improvement in VAS score at 12 weeks after PRF intra-articular during 10 min.[51] No adverse effects were mentioned. Furthermore, the use of intraarticular PRF is described in a retrospective study and a case report [52].

Intraarticular PRF seems to provide pain relief, but the injection of erythropoietin is more effective. The mode of action of this intraarticular PRF treatment is not clear.

There is only one retrospective study of 39 patients reporting about the addition of PRF on the dorsal root ganglion to TENS and exercise, for pain after a total knee arthroplasty [53]. When compared to a group of patients who only received TENS and exercise the VAS score (activity) and the DN4 scores were significantly better in the group were PRF was added.

A review assessed the role of radiofrequency treatment, ablative (radiofrequency and cooled radiofrequency) and non- ablative (PRF) in the treatment of chronic knee pain, either post-surgery or due to osteoarthritis [54]. They found that PRF of sensory nerves should be preferred for the treatment neuropathic pain, while avoiding the neuroma formation and deafferentation pain induced by ablative techniques.

Conclusions

PRF has opened new possibilities for the treatment of a variety of chronic pain syndromes, including neuropathic pain syndromes. Almost 20 years after the first report and more than 200 publications no complications are reported, making it an attractive treatment option. However, hard evidence is lacking for the majority of the indications, highlighting the importance of a shared decision with patients, based on risk/benefit profiles. For the future research there is need of high quality RCT's for several indications and identification of the optimal parameters for the application of PRF in clinical practice.

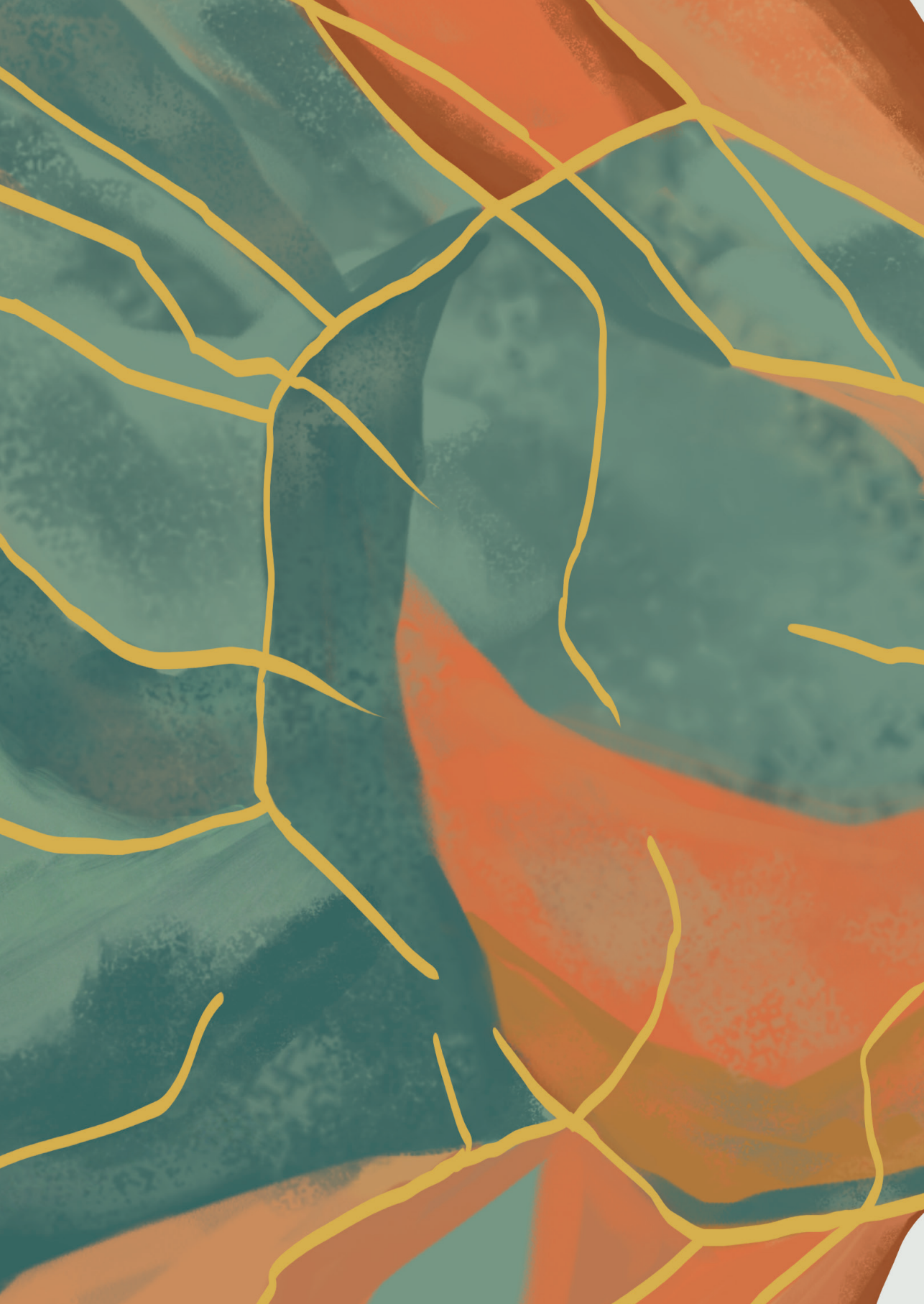
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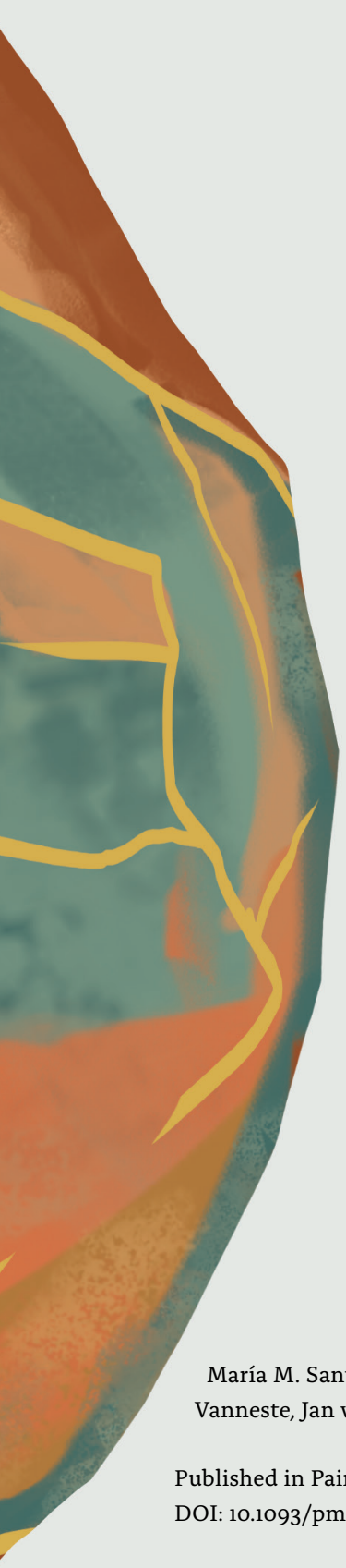
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CHAPTER 4

A randomized controlled trial to compare analgesia and functional improvement after continuous neuroablative and pulsed neuromodulative radiofrequency treatment of the genicular nerves in patients with knee osteoarthritis up to one year after the intervention.

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Abstract

Objectives.
To compare the analgesic and functional outcomes of continuous neuroablative radiofrequency (CNARF) and pulsed neuromodulative radiofrequency (PNMRF) treatment of genicular nerves up to 1 year after the intervention and to identify predictors associated with a successful outcome (defined as an at least 50% reduction in the preinterventional visual analog scale [VAS] rating) after genicular radiofrequency treatment.

Design.
A prospective randomized controlled trial.

Setting.
The Pain Department of the Jerez de la Frontera University Hospital, Cadiz, Spain, from January 2018 until May 2019.

Subjects.
Patients with grade 3–4 gonarthritis suffering from knee pain, with a VAS score ≥5 for >6 months.

Methods.
Eligible participants were randomly assigned to receive either CNARF or PNMRF of the superior medial, superior lateral, and inferior medial genicular nerves. The VAS and Western Ontario and McMaster Universities Osteoarthritis (WOMAC) scores were assessed before and at 1, 6, and 12 months after treatment. Medication use was quantified before and at 6 months after the intervention. Potential characteristics associated with the efficacy of radiofrequency intervention were explored by using multivariable statistical models.

Results.
A total of 188 participants were included. The magnitude and duration of beneficial effect and reduction in analgesic use were significantly greater in the CNARF group. Success at 6 months after radiofrequency treatment decreased with grade 4 gonarthritis; higher pre-interventional VAS score; and concomitant depression, anxiety disorder, and diabetes mellitus.

Conclusions.
Therapeutic efficacy and reduction in analgesic consumption were superior after CNARF. Treatment success at 6 months after radiofrequency intervention decreased with more severe gonarthritis; higher pre-interventional pain intensity; and concomitant depression, anxiety disorder, and diabetes mellitus.

Key Words
Randomized Controlled Trial; Osteoarthritis; Knee Pain; Radiofrequency; Outcome Assessment; Physical Function; Analgesic; Risk Factors

Introduction

Osteoarthritis is one of the most rapidly increasing major health conditions and a leading source of chronic pain, disability, and loss of health-related quality of life. Gonarthritis accounts for more than 80% of the total disease burden, and it becomes symptomatic in at least 10% to 16% of the adult population [1–3]. Although osteoarthritis is commonly referred to as a "wear-and-tear" disease, it is evident that not everyone develops osteoarthritis, and thus the disease is not necessarily an inevitable consequence of aging. Complex interactions among genetic, metabolic, biochemical, and biomechanical factors are thought to be important in disease progression [4,5]. The fact that the prevalence of gonarthritis has doubled in the past few generations suggests that recent changes in lifestyle, such as the adoption of the modern diet, increased sedentary behavior, and excessive adiposity, may have a major causative role [1]. As worldwide demographic transitions are expected to continue, the burden of gonarthritis and the socioeconomic costs associated with its management are likely to expand [6].

Because high-level evidence to recommend disease modifying interventions (such as intra-articular interleukin-1b and tumor necrosis factor inhibitors, growth factors, platelet-rich plasma, bone marrow aspirate concentrate, and mesenchymal stem cell–based therapies) is still unavailable [5], the management of gonarthritis focuses on symptom relief and functional restoration. This is performed by means of physiotherapy [7], systemic analgesia, and nonsteroidal anti-inflammatory drugs (NSAIDs) or by the injection of corticosteroids and hyaluronic acid directly into the affected joint [8, 9]. However, none of these approaches is efficient in achieving long-term analgesia, and the extensive use of NSAIDs or opioids might have serious side effects [9]. Although total knee arthroplasty effectively relieves pain and incapacity in a subset of patients with end-stage gonarthritis [10], around 14% to 53% continue to suffer from pain, and 7% to 51% report poor knee function postoperatively [11–14].

Both continuous neuroablative radiofrequency (CNARF) [15–25] and pulsed neuromodulative radiofrequency (PNMRF) treatment [26–30] of genicular nerves have proved successful in alleviating pain and improving disability in patients with gonarthritis who did not respond to conservative treatment and had contraindications to a surgical approach.

CNARF treatment uses high-frequency alternating current to induce thermal lesions. The thermal energy creates a predictable area of coagulative necrosis that is targeted to contain the nerves responsible for transmitting and/or modulating

pain sensation [31–33]. In PNMRF, thermal tissue injury may be minimized by using higher-voltage radiofrequency currents in a pulsatile manner. This allows time for the heat to dissipate, generally keeping the tissue temperature near the electrode below the neurodestructive range. The exact mechanism by which PNMRF provides clinical benefit is unclear. From a mechanistic point of view, pulsed radiofrequency treatment seems to primarily modulate signaling cascades in the C fibers while leaving nerve conduction in myelinated fibers intact [34–36]. As a minimally destructive alternative to CNARF, PNMRF treatment has attracted attention, as it could mitigate some concerns about potential side effects [34–37].

A number of prospective studies have compared the analgesic efficacy of CNARF with that of PNMRF for the treatment of painful conditions due to other causes [38–44] (Supplementary Data). Although the use of radiofrequency procedures to treat chronic knee pain has surged in the past decade, trials comparing beneficial effects induced by either CNRAF or PNMRF treatment are lacking. We therefore compared the ability of genicular CNARF, versus that of PNMRF, to reduce pain, functional impairment, and analgesic requirements in participants with advanced osteoarthritis of the knee. Because many questions remain about selection criteria and evidence for effectiveness, the ability to predict who will benefit from radiofrequency therapy is an important endeavor [45–47]. This subject has been reported in a retrospective study relating to cooled radiofrequency denervation of genicular nerves [48]. Considering that the factors affecting the efficacy of CNARF and PNMRF treatment remain to be prospectively defined, we explored the characteristics associated with the outcome of radiofrequency interventions.

Methods

Participant Recruitment

In this single-center, prospective, double-blind randomized controlled trial, patients suffering from pain caused by advanced gonarthritis were considered to receive radiofrequency treatment of genicular nerves. The research project was approved by the research ethics committee of the Regional Health Area of Cádiz, Spain, on January 26, 2017, and was registered in ClinicalTrials.gov (NCT03628482). The participants were recruited consecutively according to the order in which they consulted *the Pain* Management Department of the *University Hospital Campus Jerez de la Frontera*. Written, informed consent was obtained from all participants.

Eligible participants had suffered from chronic pain for more than 6 months, scoring at least 5 on a continuous visual analog scale (VAS) due to grade 3-4 gonarthritis, according to the Kellgren-Lawrence classification.[49] Pain could be dull, sharp, intermittent or constant, and typically flares-up with vigorous exercise. The pain proved to be resistant to conservative treatments including physiotherapy, oral analgesics, and intraarticular injection with hyaluronic acids or steroids.

Genicular radiofrequency treatment was applied as an alternative analgesic approach for the patients who refused knee arthroplasty or were judged by their surgeons as being ineligible for surgical treatment because of, for example, cardiovascular or other comorbidities. The exclusion criteria included acute knee pain associated with radicular neuropathy or intermittent claudication, connective tissue diseases, serious neurologic or psychiatric disorders, mental deterioration impeding adequate communication or collaboration, use of anticoagulant medications, presence of a pacemaker, prior electroacupuncture treatment, and intra-articular injection with steroids or hyaluronic acids within three months before to intervention.

Procedure

The targets for radiofrequency treatment included the superior lateral, the superior medial, and the inferior medial genicular nerves. Genicular nerve endings are tiny structures (Ø 1-1.5mm) [50,51] that are hardly perceptible by ultrasound. They can be localized because of their proximity to easily recognizable anatomical landmarks. [52-55] Ultrasound enables real-time imaging and soft tissue differentiation. The periosteum, ligaments, tendons, and blood vessels can be visualized, and direct stimulation or injury of these structures can be avoided. Furthermore, small

arteries supplying the knee joint can be used as an aid to identify the nerves sonographically [16,56]. Electrical stimulation, in combination with ultra-sound (dual guidance) facilitates nerve localization and can help coping with the topographical variation and intricacy of fibers supplying the knee. [21,22,24,25,28]

The technique was performed in an outpatient setting, under aseptic conditions, with basic monitoring (pulse oximetry and blood pressure) and was guided by ultrasound and neurostimulation. In the present study, no diagnostic nerve blocks were performed. Before initiating the procedure, any concerns of participants about the intervention were addressed. No sedation was used so that the participant could participate fully and accurately report the stimuli.

The participant was placed in supine position on the operating table, with the leg slightly flexed (20 degrees). Ultrasound scanning was performed on the medial surface of the thigh using a high-frequency (5-10 MHz) linear transducer placed lengthwise along the longitudinal femur axis to observe the junction between the femur shaft and its medial epicondyle. This point was marked on the skin indicating the insertion point of the introducer needle targeting the superior medial genicular branch. Then, the ultrasound probe was rotated 90 degrees to provide a transversal view, perpendicular to the longitudinal femur axis. An intradermal wheal of 1 to 2mL of 2% lidocaine was used for local anesthesia of skin and subcutaneous tissues.

With an in-plane approach a 20-gauge introducer cannula was advanced percutaneously to the area connecting the femur shaft with the medial epicondyle (epiphysis/diaphysis junction) at the middle of the measured anteroposterior depth of the femoral or tibial shaft. Then, the introduced cannula was directed slightly away from the corresponding bony landmark and positioned next to the periosteum, parallel to the assumed trajectory of the target nerve. Identical procedure was repeated at the medial tibia and the lateral femur to target the inferior medial and superior lateral genicular branches, respectively. [22] Subsequently, a radiofrequency probe from a pain management radiofrequency kit (CR-10P electrode Cosman 10 cm long and 23 gauge wide, with an active tip of 5 mm; Cosman Medical, Inc, Burlington, Massachusetts) was advanced through the introducer.

The radiofrequency electrode was positioned such that sensory stimulation (50 Hz) created paresthesia corresponding to the existing distribution of the participant's pain at less than 0.6V [18,26]. In order to avoid injuring motor nerves, absence of fasciculations in the corresponding area of the lower extremity was required when nerve stimulation at 2 Hz and 1.2 to 1.5 V was applied [20,22,28]. During stimulation

and lesioning, impedances were checked to ensure a complete electrical circuit, and these ranged from 300 to 700 ohm. Once the electrode position on each of the 3 targets was judged as correct, 2 mL of mepivacaine 2% was injected through each cannula to anesthetize the target nerve and the surrounding tissues. radiofrequency treatment was performed through the generator (Cosman G4 radiofrequency generator; Cosman Medical, Inc).

For CNARF ablation, the radiofrequency probe was inserted through the canula, and the electrode tip temperature was raised at 20 V to 80°C for 90 s. Neurotomy was achieved through lesions made parallel to the course of the nerve. PNMRF was carried out at 45V in 20 ms pulses every 0.5 s for 360 s at a temperature 42 °C with the needle tip positioned perpendicular, i.e., "end on," to the assumed trajectory *of the targeted nerve.* A total of three applications of either CNARF or PNMRF were performed, one for each genicular nerve. During the treatment, participants were continuously monitored for signs of discomfort. During the procedure the display of the radiofrequency generator was turned away from the participant's view. After both the CNARF and the PNMRF treatment, the needles were removed at 360 s after starting the radiofrequency current.

Evaluations
Participant demographics and quantifiable characteristics and comorbidities (including the Charlson comorbity index [57]), were assessed.

As the primary outcome, absolute VAS ratings were obtained. For the secondary and other outcomes, the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index was used, which summarizes pain (WOMAC A), stiffness (WOMAC B), and physical function (WOMAC C) scores [58]. Further outcomes included 1) health-related quality of life, obtained by using the 12-Item Short Form Health Survey (SF-12) physical and mental health summary scale scores [59]; 2) self-reported effective duration of analgesia, representing participants' positive response to treatment; 3) participants' satisfaction on a four-point Likert scale, in which they described their level of satisfaction by using a quantitative value (i.e., 1 [poor], 2 [average], 3 [good], and 4 [very good]); 4) medication consumption, which was monitored and quantified by using the Medication Quantification Scale version III (MQS III) ratings [60], as well as a dichotomous score to indicate whether or not (yes/no or 1/0) a participant was on a specific analgesic or class of medication (NSAIDs, tramadol, opioids, etc.); and 5) adverse effects, including abnormal proprioception, numbness, paresthesia, neuralgia, and motor weakness.

VAS, WOMAC, and SF-12 scores were assessed before the treatment and at 1 month, 6 months, and 12 months after the procedure. For each participant, the MQS III rating and the dichotomous score indicating the use of a specific class of medication (1/0) were obtained before the treatment and at 6 months after the radiofrequency intervention. Participant satisfaction was recorded at the end of the 12-month follow-up period.

Sample size calculation, Randomization, and Blinding

The sample size was calculated on the basis of the results of a two-arm pilot study that included 25 patients in each group [44] (Supplementary Data). Accordingly, a minimal clinically relevant distance between the VAS scores that needed to be detected was 1 VAS unit or 10 mm on a continuous VAS scale of 100 mm (similar to previous investigation studying gonarthritis pain [61]), and an equal variance corresponding to a standard deviation of 2 VAS units or 20 mm on a continuous VAS scale of 100 mm was assumed. In this case, 84 participants in each group (two-sided a=0.05 and b=0.1) would be sufficient to reliably detect a difference in the outcome. When a 25% post-randomization attrition rate, i.e., due to protocol violations, technical failures, etc., was taken into account, it was found that 105 participants per group were required.

Participants were assigned randomly by using a computer-generated randomization schedule to receive either CNARF or PNMRF treatment of the genicular nerves. The sequence generation was prepared by an external investigator not involved in the trial. The allocation sequence was concealed from personnel performing the interviews and the researcher enrolling and assessing participants in sequentially numbered, opaque, sealed, and stapled envelopes. Corresponding envelopes were opened only after the enrolled participants completed all baseline assessments, immediately before the intervention. Although the physician carrying out the intervention and the nurse operating the radiofrequency generator were aware of the arm to which each patient had been allocated, the outcome assessors were blinded to the allocation.

Statistical analyses

Comparisons of mean age, body mass index, the Charlson comorbidity index, and the MQS III scores [57] between the CNARF and PNMRF treatment groups were assessed by using the two-tailed t test for independent samples. Baseline participant characteristics (sex, grade of gonarthritis, previous total knee arthroplasty at the contralateral site, presence of comorbidities, and the ability to climb stairs) were compared between groups by using the Fisher exact test.

After data acquisition was complete, the VAS, WOMAC, and SF-12 scores were compared between the CNARF and PNMRF treatment groups at the four times of assessment (baseline and at 1 month, 6 months, and 12 months after the intervention) by using generalized estimating equations (GEEs). GEEs represent an extension of the generalized linear models (GLM), with the ability to model a wide variety of correlation patterns between the repeated measures [62]. For each of the investigated categories, the Holm-Sidak approach was used for post hoc pairwise comparison to test for differences in the mean VAS scores between (CNARF vs PNMRF) and within (over time) the treatment groups.

The effective duration of participants' positive response to treatment was compared between the CNARF and the PNMRF treatment arms by using Kaplan-Meier survival (time-to-event) analysis. Within this context, survival times represented the follow-up time from the radiofrequency intervention until the occurrence of the event of interest, i.e., "when the perceived beneficial effect of treatment becomes unsatisfactory." Participants who did not experience this particular event during follow-up had their survival times censored. The logrank test was used to test whether the survival distributions of the CNARF and PNMRF treatment groups were different.

Satisfaction scores in the CNARF and the PNMRF treatment groups were compared by using a multilevel mixed-effects ordered logistic regression. In the present investigation, the ordered categorical response represented a person's satisfaction, rated on a four-point Likert scale (1 [poor], 2 [average], 3 [good], and 4 [very good]) [63].

The MQS III ratings [57] before treatment and at 6 months after the intervention were compared by using the paired t test. The use of a specific analgesic or class of medication before therapy and at 6 months after the intervention was compared with the McNemars' test on paired proportions. MQS III ratings for a given time of assessment (before treatment or at 6 months after the intervention) were compared between the CNARF and the PNMRF treatment groups by using the two-tailed t test for independent samples. The use of a specific class of medication for a given time of assessment (before intervention or at 6 months after the intervention) was compared between the CNARF and the PNMRF treatment groups by using the Fisher exact test.

Global evaluation of therapy consisted of assessing the success rate of the treatment, defined as the proportion of patients with an at least 50% reduction of pretreatment VAS scores [VAS(50)] at each of the times of assessment, i.e., at 1, 6, and 12 months after intervention. From these proportions, the numbers that needed to be treated

could be calculated and compared. Success or failure of radiofrequency treatment was defined as whether or not a 50% or greater reduction in preintervention VAS rating [VAS(50)=1 or 0] could be obtained that persisted at least 6 months after the procedure.

Potential characteristics associated with the efficacy of radiofrequency interventions were explored by using multivariable statistical models. Possible covariables (also called effect modifiers or predictors) for inclusion were based on existing knowledge and clinical judgment. The associations of the following covariables with the outcome of intervention were analyzed: participants' age (years) and sex (males=0, females=1), body mass index ($m.kg^{-2}$), diabetes mellitus (Y/N or 1/0), arterial hypertension (Y/N or 1/0), depressive (Y/N or 1/0) and/or anxiety disorder (Y/N or 1/0), opioid use before intervention (Y/N or 1/0), VAS score before treatment, grade of gonarthritis (KL3=0, KL4=1), previous contralateral total knee arthroplasty (Y/N or 1/0), and modality of radiofrequency intervention (CNARF=0 and PNMRF=1). Covariables associated with the outcomes on univariable analysis ($P<0.25$) were included in a multivariable statistical model. We then sequentially excluded variables and terms from this initial multivariable model, using a stepwise backward-elimination procedure [64,65]. The aim was to seek the most parsimonious model (smallest number of independent variables) that still explained the outcome. Covariables that were correlated or highly collinear were excluded. The following outcomes were explored: 1) the proportion of participants with a successful outcome (≥50% reduction of pre-intervention VAS rating at 6 months after the intervention), using a logistic model; 2) the perceived duration of therapeutic effect, using a Cox proportional hazards model; 3) participant satisfaction, using a mixed-effects ordered logistic regression model [63]; and 4) the reduction in analgesic consumption, measured by the MQS III score.

Normality of distribution for the data sets with continuous variables was checked by visual inspection of the distribution and by using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Statistical significance was set at the 0.05 probability level. Data analysis was performed with Stata version 15 (StataCorp, College Station, TX).

Results

Results were reported in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines [66].

Between January 2018 and May 2019, we enrolled/assessed 234 participants eligible for radiofrequency treatment as a means of relieving the pain and disability caused by chronic osteoarthritis of the knee. Figure 1 shows that 18 of these participants were not randomized because of failure to meet the predetermined inclusion criteria, refusal to participate, or personal reasons. Of the 216 participants who were randomized, 28 participants were excluded, mainly because they were lost to follow-up or because of missing data sheets or procedural failures. Clinicians/data collectors and outcome adjudicators were unaware of the treatment the participant received. After the investigation, patients were not asked to which group (CNARF or PNMRF) they believed they had been randomized.

Pre-intervention demographics and quantifiable characteristics; comorbidities (Charlson comorbidity index [57]); pre-intervention VAS, WOMAC, and SF-12 scores; and medication use (MQS III scores [60]) were similar between the CNARF and PNMRF treatment groups (Tables 1–3).

Primary Outcome (VAS Scores)
There were significant differences in the mean VAS scores between the treatment groups and over time (Table 2 and Figures 2–4).

Secondary and Other Outcomes
The WOMAC Score
There were significant differences in the mean WOMAC A, WOMAC C, and WOMAC total scores between the treatment groups and over time. The mean WOMAC B scores were not different between treatment groups and were lower at 1 month after intervention within both treatment groups (Table 3 and Figure 5).

The SF-12 Ratings
There were significant differences in the mean SF-12 physical summary ratings between treatment groups and over time. The mean SF-12 summary scores did not significantly differ between treatment groups, but were significantly different at the various time points ($P<0.05–0.001$).

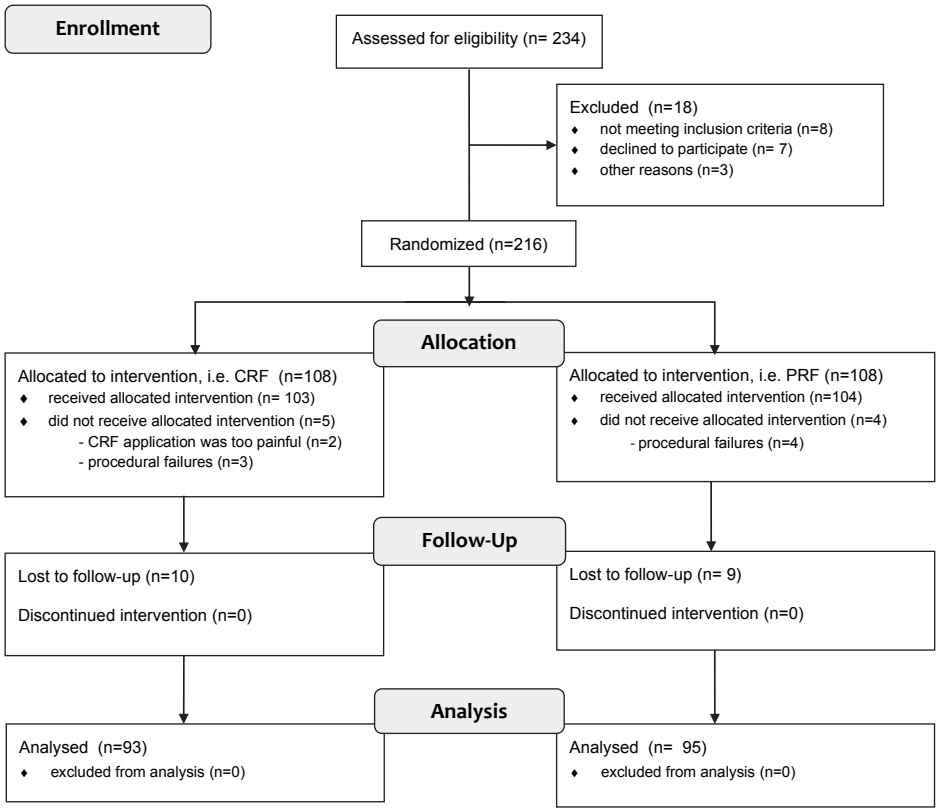


Figure 1 CONSORT flow diagram of the progress through the phases of a parallel randomized trial of two groups [66] (that is, enrollment, intervention allocation, follow-up, and data analyzed) receiving either continuous (CNARF) or pulsed radiofrequency (PNMRF) treatment of genicular nerves.

The Self-Reported Effective Duration of Analgesia

The effective durations of the therapeutic effect (defined as participants' positive response to treatment) for the CNARF and the PNMRF groups were compared by using Kaplan-Meier survival plots. Log-rank analysis demonstrated that the distributions of the survival functions of the CNARF and the PNMRF treatment groups were significantly different (chi^2 = 18.95, with degrees of freedom [df] = 1 or P<0.001), with mean survival times of 9.0 (95% confidence interval [CI]: 7.8–10.2) and 5.0 (95% CI: 3.2–6.8) months in the CNARF and the PNMRF groups, respectively (Figure 6).

Table 1 Participants' demographics and quantifiable characteristics

Patient characteristics	CNARF	PNMRF	p
Participants included	93/188	95/188	0.918
Males/Females (n)	12/81	16/79	0.580
Age (y)	73.1 [71.0-75.1]	74.1 [72.2-76.0]	0.447
BMI ($kg{\cdot}m^{-2}$)	30.1 [29.4-30.8]	30.9 [24.5-49.2]	0.150
Charlson Comorbity Index score	5.58 [5.21-5.95]	5.49 [5.15-5.83]	0.733
Grade of gonarthritis (3/4)	41/52	37/58	0.475
OA in other joints, different from treated knee	71/93	70/95	0.674
MQS III score	22.4 [20.9-23.8]	23.4 [21.7-25.2]	0.358
Previous TKA at contralateral side (n)	6/93	14/95	0.066
Climbs stairs (n)	40/93	30/95	0.105

Demographic data and participant characteristics in the continuous (CNARF) and the pulsed radiofrequency (PNMRF) treatment groups. BMI : body mass index ($kg{\cdot}m^{-2}$). Charlson Comorbidity Index quantifies an individual's burden of disease based on the presence of specific associated comorbidities [57]. Grade of gonarthritis: severity of gonarthritis graded according to the Kellgren-Lawrence scale [49]. MQS III: Medication Quantification Scale version III, instrument for quantifying medication regimen use in chronic pain populations [60]. TKA: total knee arthroplasty; climbs stairs: can climb and descending stairs without aid. Results are numbers (n) or mean [95%CI]. p: level of statistical significance.

The Participants' Satisfaction

Using a four-point Likert scale, the following scores were obtained: 4 (very good) in 62/93 versus 42/95 participants, 3 (good) in 22/93 versus 29/95 participants, 2 (average) in 7/93 versus 19/95 participants, and 1 (poor) in 2/93 versus 5/94 participants, for the CNARF versus PNMRF groups, respectively. Multilevel mixed-effects ordered logistic regression analysis demonstrated that participants in the CNARF group were more satisfied with the outcome of the intervention than were those in the PNMRF group (P=0.002).

Monitoring and Quantifying Medication Consumption

Participants' consumption of specific analgesics at 6 months after radiofrequency intervention was significantly less than that assessed before the treatment; i.e., NSAIDs were discontinued in about 50%, and both tramadol and opioids were abandoned in nearly 25% of participants who were using these medications before the treatment (P<0.001 for all). Significantly more patients discontinued NSAIDs and tramadol in the CNARF group than in the PNMRF group (P<0.010 for both). At 6 months after radiofrequency intervention, average MQS III rating was significantly lower to that assessed before treatment, with values for the whole population (n=188) (15.0 [95% CI: 13.9–16.0] at 6 months vs 22.9 [95% CI: 21.8–24.0] pre-intervention) (P<0.001), in the

CNARF group (n=93) (13.7 [95% CI: 12.2–15.2] at 6 months vs 22.4 [95% CI: 20.9–23.8] pre-intervention) (P<0.001), and in the PNMRF group (n=95) (16.2 [95% CI: 14.7–17.8] at 6 months vs 23.4 [95% CI: 21.7–25.2] pre-intervention) (P<0.001). At 6 months after radiofrequency intervention, the decrease of the MQS III rating in the CNARF group was higher than that obtained in the PNMRF group (P=0.023).

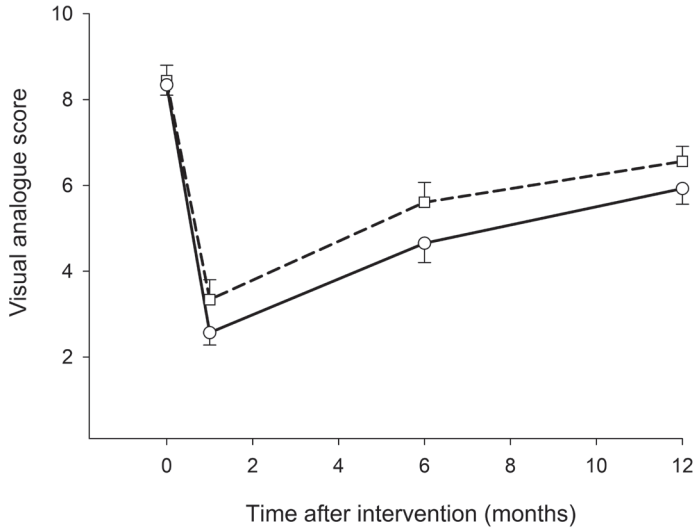


Figure 2 The visual analog scale (VAS) ratings (mean, 95% confidence interval) vs time were compared between the continuous neuroablative radiofrequency (CNARF; round symbols connected by solid lines) and the pulsed neuromodulative radiofrequency (PNMRF; square symbols connected by dotted lines) treatment arms at the four time points of assessment (baseline and at 1, 6, and 12 months after the intervention) by using generalized estimating equations. Post hoc pairwise comparisons of the VAS scores demonstrated that both the magnitude and the duration of analgesic effect with PNMRF were inferior to those obtained with CNARF. Asterisk and double asterisk indicate significant difference from the score obtained with PNMRF at the corresponding time of assessment (*P=0.015, **P<0.001).

Registration of Adverse Effects

The following adverse effects have been recorded: Pain upon application of radiofrequency current was reported in 15/93 versus 8/95 participants (P=0.107), and falls were reported in 2/93 versus 3/95 (P=0.668) participants, for the CNARF versus PNMRF groups, respectively. Abnormal proprioception, numbness, paresthesia, neuralgia, and motor weakness were not reported.

Table 2 Results of the visual analog scale ratings before and after treatment (primary outcome)

Parameter	RF modality	pre-intervention
VAS	CNARF (n=93)	8.36 [8.09 - 8.62]
	PNMRF (n=95)	8.45 [8.19 - 8.71]
	Difference between groups (p)	0.699
VAS(50)	CNARF (n=93)	-
	PNMRF (n=95)	-
	Difference between groups (p)	-
	NNT	-

Results of the visual analogue scale (VAS) ratings , assessed pre-treatment (baseline) and at 1 month, 6 months and 12 months after either continuous neuroablative (CNARF) or pulsed neuromodulative radiofrequency (PNMRF) treatment. VAS(50) represents the number of participants with at least 50% reduction of pre-intervention (baseline) VAS scores. Difference between groups (p): level of significance of the difference between the mean values of the treatment groups (CNARF versus PNMRF) obtained at the different times of assessment. NNT: the number of participants that need to be treated using CNARF for one of them to benefit (at least 50% reduction of pre-intervention VAS score) as compared to PNMRF.

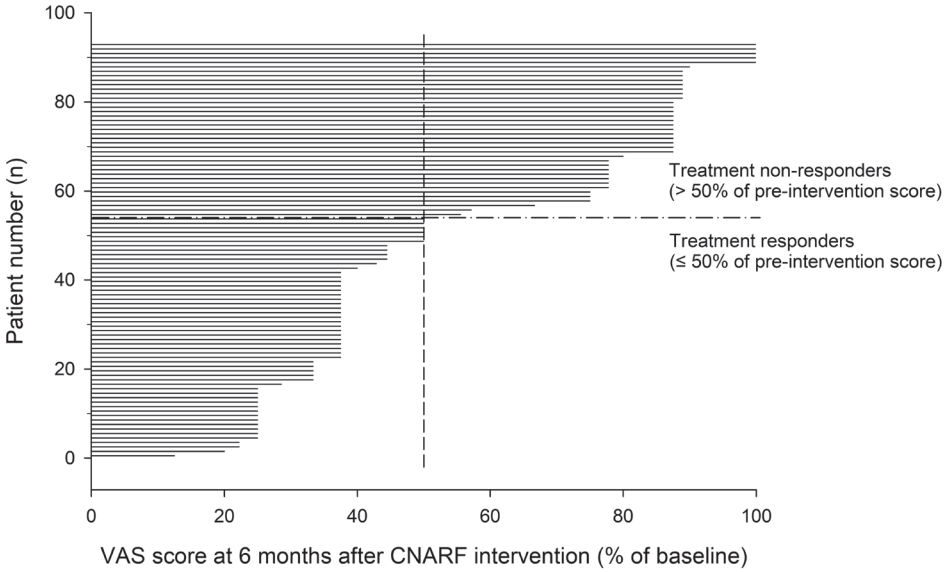


Figure 3 Visual analog scale (VAS) score 6 months after continuous neuroablative radiofrequency (CNARF) treatment for innervation to arthritic knee joints (% of pre-intervention rating). The dotted line represents a 50% reduction of the pre-intervention VAS score.

at 1 month	at 6 months	at 12 months
2.75 [2.46 – 3.03] §	4.68 [4.41 – 4.94] ¶	5.98 [5.72 – 6.24] ‡
3.40 [3.13 - 3.67] §	5.66 [5.39 – 5.92] ¶	6.59 [6.33 – 6.85] ‡
0.014	<0.001	0.016
87/93 [93.6 %] §	55/93 [59.1 %] ¶	32/93 (34.4 %) ‡
75/95 [79.0 %] §	26/95 [27.4 %] ¶	12/95 (12.6 %) ‡
0.004	<0.001	<0.001
6.40 [3.94 – 16.78]	3.15 [2.27 - 5.65]	4.59 [3.02-10.28]

Values are mean [95% CI] or proportion. §: significantly different from the scores obtained before (baseline) and at 6 and 12 months after RF intervention (p<0.001); ¶: significantly different from the scores assessed before (baseline) and at 1 month and 12 months after RF intervention (p<0.001); †: significantly different from the scores assessed before (baseline) and at 1 month after RF intervention (p<0.001); ‡: significantly different from the scores assessed before (baseline), at 1 month and 6 months after intervention (p<0.001). p: level of statistical significance.

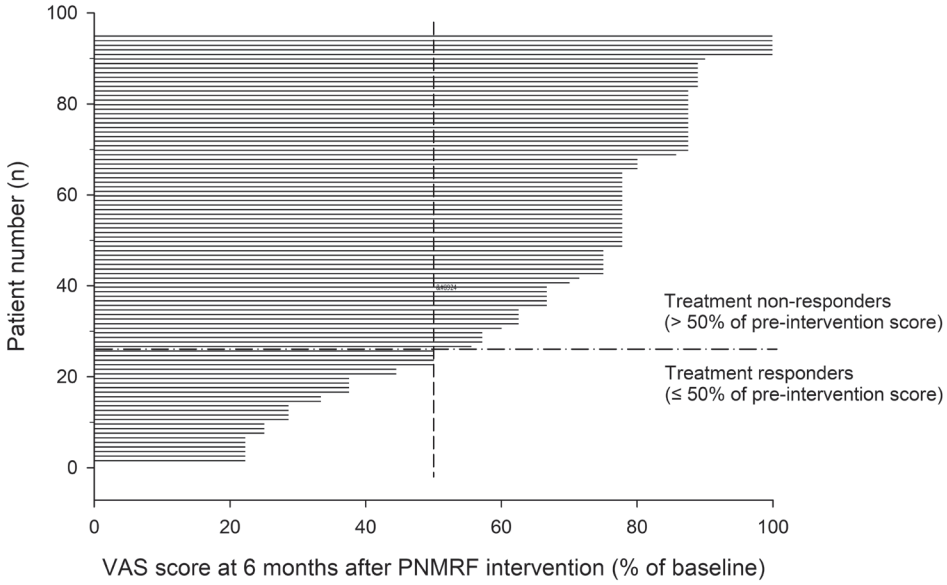


Figure 4 Visual analog scale (VAS) score 6 months after pulsed neuromodulative radiofrequency (PNMRF) treatment for innervation to arthritic knee joints (% of pre-intervention rating). The dotted line represents a 50% reduction of the pre-intervention VAS score.

Table 3 Results of the WOMAC and SF-12 scores before and after treatment

Parameter	RF modality	pre-intervention
WOMAC A	CNARF (n=93)	14.10 [13.62 - 14.57]
	PNMRF (n=95)	14.73 [14.25 - 15.20]
	Difference between groups (p)	0.170
WOMAC B	CNARF (n=93)	3.05 [2.95 – 3.16]
	PNMRF (n=95)	3.11 [3.00 – 3.21]
	Difference between groups (p)	0.746
WOMAC C	CNARF (n=93)	45.42 [44.26 – 46.58]
	PNMRF (n=95)	47.96 [46.80 – 49.10]
	Difference between groups (p)	0.077
WOMAC total	CNARF (n=93)	62.44 [59.72 – 65.15]
	PNMRF (n=95)	65.79 [63.72 - 67.86]
	Difference between groups (p)	0.085
SF12 physical summary	CNARF (n=93)	25.82 [24.56 – 27.08]
	PNMRF (n=95)	25.36 [24.11 – 26.62]
	Difference between groups (p)	0.614
SF12 mental summary	CNARF (n=93)	33.14 [31.94 – 34.33]
	PNMRF (n=95)	33.81 [32.62 – 35.00]
	Difference between groups (p)	0.436

Results of the Western Ontario and McMaster Universities Osteoarthrosis index (WOMAC), and Short Form Health Survey (SF12) scores, assessed pre-treatment (baseline) and at 1 month, 6 months and 12 months after either continuous (CNARF) or pulsed radiofrequency (PNMRF) treatment. WOMAC A, WOMAC B, WOMAC C and WOMAC total: scores for the pain, stiffness and function subscales and total scores of WOMAC index, respectively. Values are mean [95% CI]. Difference between groups (p): level of significance of the difference between the mean values of the treatment groups (CNARF versus PNMRF) obtained at the different times of assessment.

Identifying Predictors Associated with Outcome of Therapy

Success/Failure, Correlated to the Participant Characteristics Through Multivariable Logistic Regression The results of the logistic regression model estimating the relation between demographic and clinical characteristics and outcome are shown in Table 4. The likelihood of a successful outcome at 6 months decreased with gonarthritis being more severe (P<0.001) and pre-interventional VAS score being higher (P=0.001); PNMRF treatment (P=0.001); and concomitant anxiety disorder (P=0.004) and/or diabetes mellitus (P=0.046).

at 1 month	at 6 months	at 12 months
5.67 [5.19 - 6.14] §	8.19 [7.70 - 8.69] ¶	9.97 [9.32 – 10.61] †
7.01 [6.54 - 7.48] §	9.47 [8.92 – 10.00] ¶	11.51 [10.67 – 12.36] †
0.004	0.012	0.035
2.58 [2.48 – 2.68] §	2.73 [2.62 – 2.83]	2.87 [2.73 – 3.01]
2.64 [2.54 – 2.74] §	2.91 [2.79 – 3.02]	3.07 [2.89 – 3.25]
0.699	0.304	0.427
27.69 [26.53 – 28.85] §	32.21 [31.00 – 33.41] ¶	36.27 [34.69 – 37.84]†
31.18 [30.03 – 32.33] §	36.49 [35.17 – 37.81] ¶	41.21 [39.15 – 43.27]†
0.015	0.007	0.031
35.94 [33.23 – 38.64] §	43.08 [40.35 – 45.81] ¶	47.28 [44.10 – 50.47]†
40.83 [37.71 - 43.96] §	47.91 [45.85 – 52.15] ¶	53.47 [50.36 – 56.59]†
0.012	0.015	0.007
39.61 [38.36 – 40.85] §	34.54 [33.28 – 35.79] ¶	31.81 [30.56 – 33.06]†
37.67 [36.43 – 38.91] §	32.65 [31.08 – 33.89] ¶	30.16 [28.92 – 31.40]†
0.031	0.037	0.067
34.43 [33.24 – 35.61]	34.25 [33.82 – 35.03]	35.72 [35.11 – 36.33]†
34.13 [32.95 – 35.31]	34.35 [32.89 – 35.37]	34.85 [33.66 – 36.04]
0.730	0.773	0.310

§: significantly different from the mean scores assessed before (baseline) and at 6 and 12 months after RF intervention (p=0.005 - p<0.001); ¶: significantly different from the mean scores assessed before (baseline) and at 1 month and 12 months after RF intervention (p<0.001); †: significantly different from the scores assessed before (baseline) and at 1 month after RF intervention (p<0.001); ‡: significantly different from the mean scores assessed before (baseline), at 1 month and 6 months after intervention (p<0.001). p: level of statistical significance.

Perceived Beneficial Effect of Therapy

The perceived beneficial effect of therapy (participant's positive response to treatment) was shorter with gonarthritis being more severe (P=0.001) and pre-interventional VAS score being higher (P=0.006); PNMRF treatment (P<0.001); and concomitant depressive disorder (P=0.034).

Participant's Satisfaction

Participants' satisfaction at the end of the 12-month follow-up period decreases with gonarthritis being more severe (P=0.001); pre-interventional VAS score being higher (P<0.001); PNMRF treatment (P=0.021); and concomitant depressive disorder (P=0.002) and/or higher body mass index (P=0.038).

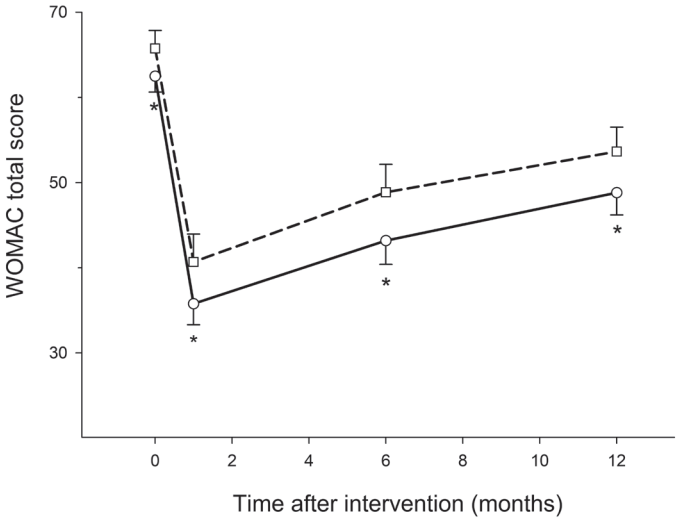


Figure 5 The total WOMAC score (mean, 95% confidence interval) vs time were compared between the continuous neuroablative radiofrequency (CNARF; round symbols connected by solid lines) and the pulsed neuromodulative radiofrequency (PNMRF; square symbols connected by dotted lines) treatment arms at the four time points of assessment (baseline and at 1, 6, and 12 months after the intervention) by using generalized estimating equations. Post hoc pairwise comparisons demonstrated that the total WOMAC scores during at least 6 months after radiofrequency intervention were higher with PNMRF, indicating worse pain/function. Asterisk indicates significant difference from the score obtained with PNMRF at the corresponding time of assessment (P=0.007–0.015).

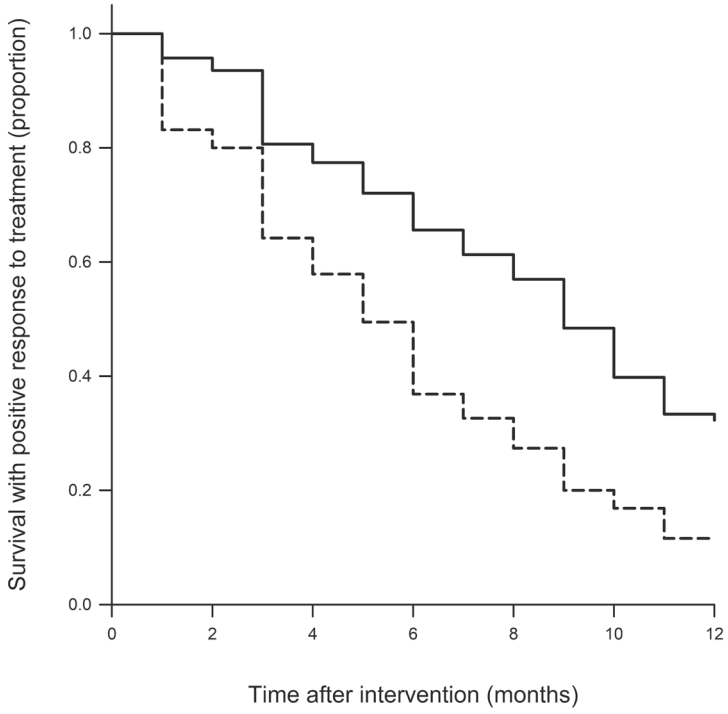


Figure 6 The effective duration of perceived beneficial effect of treatment. Proportion of participants surviving with positive response to treatment (proportion surviving) was compared between the continuous neuroablative radiofrequency (CNARF; solid line) and the pulsed neuromodulative radiofrequency (PNMRF; dotted line) treatment arms by using Kaplan-Meier survival (time-to-event) analysis. Log-rank analysis of these Kaplan-Meier survival plots demonstrates that the distributions of survival times of the CNARF and the PNMRF treatment groups are significantly different (chi2 = 18.95 with df = 1 or P<0.001).

Table 4 Covariables (predictor variables or effect modifiers) associated with successful intervention

Candidate covariables/effect modifiers
Age (yr)
Sex (Female=0; Male=1)
BMI ($kg \cdot m^{-2}$)
Diabetes (Y/N or 1/0)
Arterial hypertension (Y/N or 1/0)
Depressive illness (Y/N or 1/0)
Anxiety disorder (Y/N or 1/0)
Opioid use (Y/N or 1/0)
Pre-intervention VAS score
Grade of gonarthritis (KL3=0; KL4=1)
Previous contralateral TKA (Y/N or 1/0)
RF modality (CRF=0; PRF=1)

Covariables (predictor variables or effect modifiers), associated with successful intervention (≥50% reduction of pre-intervention VAS value). Candidate covariables associated with the outcomes on univariable analysis ($p < 0.25$) were included into a multivariable logistic model [64]. We then sequentially excluded covariables from this initial multivariable model, using a stepwise backward elimination procedure.

The Reduction in Drug Consumption

Reduction in medication use, as measured by the ΔMQS III score (difference in MQS III score before intervention versus MQS III score at 6 months after intervention), was negatively correlated with depressive disorder (P<0.001); opioid use before radiofrequency intervention (P=0.006); and PNMRF therapy (P=0.024).

Regression and collinearity diagnostics proved that the proposed models conformed to the assumptions of linear and logistic regression. All continuous variables were nearly normally distributed or could be converted to near-normality by applying an appropriate transformation [67–69].

Univariable data analysis			Adjusted multivariable data analysis		
OR	z	p	OR	z	p
0.97 [0.94-1.0]	-1.92	0.055	-	-	ns
0.56 [0.24 – 1.28]	-1.38	0.167	-	-	ns
0.91 [0.83 – 0.99]	-2.16	0.031	-	-	ns
0.44 [0.23 – 0.85]	-2.47	0.014	0.46 [0.21 – 0.99]	-2.00	0.046
0.57 [0.29 – 1.10]	-1.67	0.095	-	-	ns
0.49 [0.27 – 0.89]	-2.34	0.019	-	-	ns
0.35 [0.17 – 0.72]	-2.86	0.004	0.29 [0.13-0.68]	-2.86	0.004
0.41 [0.21 – 0.80]	-2.58	0.010	-	-	ns
0.38 [0.24 – 0.61]	-4.04	<0.0001	0.42 [0.25 – 0.70]	-3.32	0.001
0.26 [0.14 – 0.49]	-4.26	<0.0001	0.24 [0.12 – 0.48]	-3.95	<0.001
0.30 [0.11 – 0.86]	-2.24	0.025	-	-	ns
0.37 [0.20 – 0.68]	-3.32	0.001	0.31 [0.16 – 0.62]	-3.29	0.001

BMI: body mass index ($kg \cdot m^{-2}$); Grade of gonarthritis according to the Kellgren-Lawrence scale [49]: KL3= grade 3, KL4=grade 4. TKA: total knee arthroplasty. OR: odds ratio for a successful outcome. z: z score from odds ratio; a negative z-value indicates a negative association between a successful outcome and the covariable (predictor). p: level of significance; ns: not significant ($p \geq 0.05$).

Discussion

Principal findings and relation to existing knowledge.
In this single-center, prospective, randomized controlled trial, we found that both CNARF and PNMRF treatment of the genicular nerves significantly reduced pain, incapacity, and analgesic medication use in most participants with grade 3–4 gonarthritis whose pain was resistant to conservative treatments and who were considered ineligible for surgical intervention. Minimal complications and side effects were recorded, with no reports of abnormal proprioception, numbness, paresthesia, neuralgia, or motor weakness. NSAIDs were discontinued in about one half and both tramadol and opioids were abandoned in nearly one quarter of participants who had been using these medications before the treatment. Both therapeutic efficacy and reduction in analgesic use were superior after CNARF as compared with PNMRF.

Genicular radiofrequency intervention conferred a pain- and stiffness-free window, during which patients could undergo strength and endurance training without suffering the effort-induced pain exacerbation that had previously restricted their lifestyles [24]. By interrupting chronic peripheral nociceptive inputs, central amplification of pain signals [7, 70] can be reduced or prevented [25, 71]. These results are comparable to those previously reported on the use of either genicular CNARF [15–25] or PNMRF [26–30] to relieve pain and disability caused by osteoarthritis of the knee.

The positive treatment effects started to decay after 3 to 6 months, resulting in a mean effective therapeutic duration of about 9 months after CNARF and 5 months after PNMRF. One year after the intervention, 34% of patients in the CNARF group and 13% of patients in the PNMRF group still reported VAS scores with at least 50% improvement over pretreatment values. Furthermore, both the magnitude and the duration of effect (alleviation of pain and disability) were inferior after PNMRF as compared with CNARF, corroborating previous studies that focused on radiofrequency treatment of chronic pain from other causes [38–43, 72] (Supplementary Data).

In both treatment groups, analgesic efficacy, duration of the beneficial effect, and patient satisfaction decreased with 1) gonarthritis severity, 2) intensity of pre-interventional gonarthritis pain, and 3) concomitant depression or anxiety disorder. Furthermore, a greater propensity for radiofrequency treatment failure and patient discontent are associated with diabetes mellitus and/or higher body mass index.

Similar to previous investigations, higher pre-intervention pain levels, more severe osteoarthritic joint degeneration, and depressive illness were significant predictors of therapeutic failure [47, 48, 73, 74].

Concomitant diabetes mellitus is an important factor determining the intensity of pre-intervention pain because of its association with more severe synovitis, obesity, and neuropathic conditions [75]. Mental distress and psychiatric symptoms, including depression, anxiety, and anger, may decrease the effectiveness of analgesic therapy, regardless of the modality of treatment [74, 76–78].Although opioids could be withdrawn in about 25% of those who had been taking these substances before the intervention, their use might predispose to treatment failure and persistent analgesic requirement. Possible reasons include opioid-induced hyperalgesia/tolerance, nociceptive sensitization, association with mental disorders and secondary gain issues [45–47, 79].

The Use of Radiofrequency Therapy to Relieve Osteoarthritic Knee Pain

In CNARF, a constant high frequency (500 kHz) causes charged molecules to oscillate and finally generate heat, resulting in damage to all sizes of fibers in the nearby neural pathway. This involves an acute inflammatory response, including cell necrosis, collagen deposition, and scar formation, that occurs over 3 weeks after the procedure. The clinical picture shows complete interruption of the nerve. Functional, but not complete, reinnervation of the target site can occur over a period of months to years. The success of regeneration depends largely on the severity of the initial injury and the resultant degenerative changes. Studies have shown that axon regeneration sometimes deviates from the disrupted endoneurial tube; this may lead to neurinoma formation [31, 32].

Clinicians could avoid neurodestructive temperatures by using higher-voltage radiofrequency currents in a pulsatile manner (PNMRF). Although the mechanism of action has not been completely elucidated, laboratory reports suggest that PNMRF involves a genuine neurobiological phenomenon that alters pain signaling; some have described this as a neuromodulatory mechanism. Researchers' understanding of this procedure has advanced: Initially, the mechanism was a black box concept, but recent studies have reported changes in cellular ultrastructure, genetic expression, axonal firing frequency, synaptic transmission, and descending noradrenergic and serotonergic inhibitory control. From a mechanistic point of view, PNMRF seems primarily to modulate signaling cascades in small Ad and C fibers, while leaving myelinated fibers intact. PNMRF can be used to treat patients with nerve injury (neuropathic pain), in which inflicting further tissue damage is counterintuitive.

Unlike CNARF, which might be associated with neuritis-like reactions, neurinoma formation, motor deficits, and the risk of deafferentation pain, PNMRF seems to have few side effects [34, 80–82]. The effect of PNMRF on nociceptive transmission is more easily reversible and has a shorter duration than that obtained with CNARF, probably because it affects neuromodulation (i.e., transient inhibition of evoked synaptic activity) and confers only minimal structural changes [83].

Strengths and Weaknesses of the Study

The present study had some strengths over other studies. The present study was the first head-to-head comparison of the efficacy of both genicular radiofrequency treatment modalities in a randomized controlled trial.

Second, our randomized controlled trial involved adequate sample selection, sample size calculation, and appropriate controls, resulting in clear outcomes with small confidence intervals.

Third, it is important that clinicians be able to predict who will benefit from such a minimally invasive approach [45–47]. The predictors of successful genicular radiofrequency ablation were reported recently in the case of cooled radiofrequency treatment of the genicular nerves [48]. The most notable trend in that study was the negative association found between the degree/duration of gonarthritis and the outcome of the intervention.

However, certain methodological issues may have impacted the results. For instance, it was a retrospective study that used previously published data [84, 85], and thus it had inherent flaws, including post hoc selection of study variables, lack of predetermined sample size, expectation bias, and missing data.

Conversely, the present study had several limitations that warrant mentioning.

First, most of the participants had to continue taking medication to relieve the pain caused by degenerative changes in other joints or by contralateral total knee arthroplasty. This might have been a confounding factor, potentially distorting the outcomes.

Second, although the genicular nerves are one of the primary innervating branches that relay nociceptive information from the knee, additional innervations exist [52–55, 86]. Consequently, pain transmission may continue in spite of radiofrequency treatment.

Third, direct immunohistochemical observation of innervation in synovium samples taken from patients undergoing total knee replacement identified areas of considerable neuronal network destruction [79]. Spontaneous activity in damaged primary afferent nerves in the synovium of affected joints likely drives central sensitization, pain, and the development of neuropathic symptoms. However, a recent systematic review suggested that this neuropathic component contributes to knee joint pain in only about 20% of patients with gonarthritis [87, 88]. Accordingly, researchers must establish the scientific rationale behind the use of PNMRF in all patients with gonarthritis.

Fourth, in the present study, neurotomy was achieved by using single lesions (one lesion for each genicular nerve) that were made parallel to the course of the nerve. Most authors have applied CNARF by using 22-gauge radiofrequency cannulas with 10-mm active tips. Larger needles [88, 90] can generate larger lesions than the probes used in the present study (23-gauge/5 mm) [20, 22] or in the study by Ikeuchi et al. (22-gauge/5 mm) [19]. Although the heat lesion size produced by the smaller cannula was more limited, satisfactory clinical outcomes could be obtained [19, 20, 28, 29], perhaps because the genicular nerves have fairly consistent anatomy and because the radiofrequency probes were positioned accurately under ultrasound guidance and in combination with nerve stimulation. With these smaller probes and dual guidance (ultrasound and stimulation), we obtained CNARF success rates that were similar to those achieved earlier with a cooled radiofrequency intervention that used 18-gauge/4-mm electrodes, without nerve stimulation, and under fluoroscopic guidance [84, 85]. The effect of larger lesions on the duration of pain relief in individuals with a successful outcome is unclear [91]. Furthermore, greater-radiofrequency lesions may be more prone to causing collateral damage [92, 93].

Fifth, because of their potential to bias patient selection, no diagnostic blocks were used. Until now, no evidence-based algorithm has been established that can properly select which patients would benefit from genicular nerve radiofrequency treatment.

Contrary to facet-mediated pain, for which the diagnosis can be challenging because of the variety of potential pain generators in the spine, diagnostic uncertainty is far less likely when the knee is evaluated as a pain generator. In fact, it is unclear whether any diagnostic blocks of the genicular nerves are needed, given that they increase health care costs and the potential for complications as compared with immediate ablation.

Furthermore, a recent study was unable to show a difference in outcomes between patients randomized to receiving either a prior diagnostic or no diagnostic block at all [85]. When applying radiofrequency ablation, the distance between the needle and the nerve is of paramount importance. Therefore, even with suboptimal needle placement, a diagnostic block using 1.0 to 2.5mL of local anesthetics might be successful, even in cases where radiofrequency ablation with a similar needle placement would be unsuccessful [53].

Future studies on the radiofrequency treatment of the nerve supply to the knee should examine the roles of low-volume prognostic (i.e., genicular) blocks and intraarticular local anesthetic injections, which are frequently used to confirm a joint as the primary pain generator and thus predict the success of radiofrequency treatments [94].

Sixth, in the present study, we also included patients to be treated for osteoarthritis pain in the knee contralateral to the cognate joint to which previous knee replacement surgery had been applied. Osteoarthritis of the knee is often bilateral; 80% of patients with evidence of unilateral osteoarthritis of the knee develop bilateral disease within 12 years [95–97]. Furthermore, it is to be expected that, after previous knee replacement surgery, there will be a 30% to 45% chance that the other knee will need replacing within 10 to 15 years [98]. Interventional pain management could be explored as an alternative to assist, especially when the earlier contralateral knee arthroplasty outcome has been disappointing.

Seventh, the lack of patient feedback about the adequacy of blinding was identified as a weakness of the study [99].

Meaning of the Study: Implications for Clinicians and Policymakers

Meeting the needs of the tens of millions of patients suffering from gonarthritis pain requires access to a broad armamentarium of therapies for pain management [6]. As medications used to relieve gonarthritis pain can potentially exacerbate comorbid symptoms (e.g., gastrointestinal distress, cardiovascular toxicity, sedation, and depression), the dosage of analgesics that can be reasonably prescribed is limited [8, 9]. Despite the successful outcomes achieved by total knee replacement, up to 50% of patients continue to suffer from pain or reported poor knee function [11–14]. In the present study, genicular radiofrequency treatment was shown to be an alternative analgesic approach, allowing significant reduction of osteoarthritis pain medication use and thereby minimizing toxicity, drug interactions, and adverse events. Radiofrequency treatment, therefore, can help reduce opioid and opioid-like analgesic consumption in patients with advanced osteoarthritis of the knee,

thereby containing the rising toll of the harms that can result from the use of these medications. The predictors of the success or failure of genicular radiofrequency treatment, identified in our present trial, may inform an improved patient-selection paradigm for the procedure that is based on a wide range of demographic and clinical variables [45–48].

The annual rate of total knee replacement in the United States has doubled since 2000, especially in those 45 to 64 years of age [100]. Improvement of quality of life after knee replacement surgery was demonstrated to be lower for patients with fewer preoperative symptoms [101, 102]. A recent study concluded that access to knee joint replacement surgery should therefore be restricted to patients with more severe symptoms [101].

A minimally invasive radiofrequency intervention could allow total knee arthroplasty to be prevented or at least restricted to physically and mentally fit patients with more severely affected knee joint functioning. This is pertinent in the latter instance, as gains in postsurgical quality-of-life outcomes are significantly larger in cases with poorer preoperative functional status of the knee. Such a policy would reduce both morbidity and mortality [30] and make the practice of knee joint surgery more attractive and cost-effective than in its current use [101, 103].

Unanswered Questions and Future Research

Radiofrequency treatment of genicular nerves has proved successful in alleviating pain and improving disability in patients suffering from osteoarthritis of the knee. More research, however, is needed to optimize radiofrequency treatment of articular branches to the knee and better assess long-term outcomes. This can best be accomplished by large-scale, head-to-head trials comparing the relative merits of various radiofrequency modalities and treatments involving the genicular nerves, as well as other branches to the knee [94, 104].

Conclusion

The present prospective, single-center, randomized controlled trial is the first head-to-head comparison of the efficacy of genicular CNARF and PNMRF treatment to reduce pain, functional impairment, and analgesic requirement in patients with gonarthritis. In the present trial, we found that both CNARF and PNMRF treatment of the genicular nerves significantly reduced pain and incapacity in most participants with grade 3–4 gonarthritis whose pain was resistant to conservative treatments and who were considered ineligible for surgical intervention. Genicular radiofrequency treatment was shown to be an alternative analgesic approach, allowing significant reduction of pain medication use and thereby minimizing toxicity, drug interactions, and adverse events. Such an intervention, therefore, can help reduce opioid and opioid-like analgesic consumption in patients with advanced osteoarthritis of the knee, thereby containing the rising toll of the harm that can result from the use of these medications. Therapeutic efficacy, duration of beneficial effect, and reduction in analgesic consumption were superior after CNARF as compared with PNMRF. Treatment success at 6 months after radiofrequency intervention decreased with more severe gonarthritis; higher pre-interventional pain intensity; and concomitant depression, anxiety disorder, and diabetes mellitus.

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Supplementary Data

Supplementary Data may be found online at http://pain-medicine.oxfordjournals.org.

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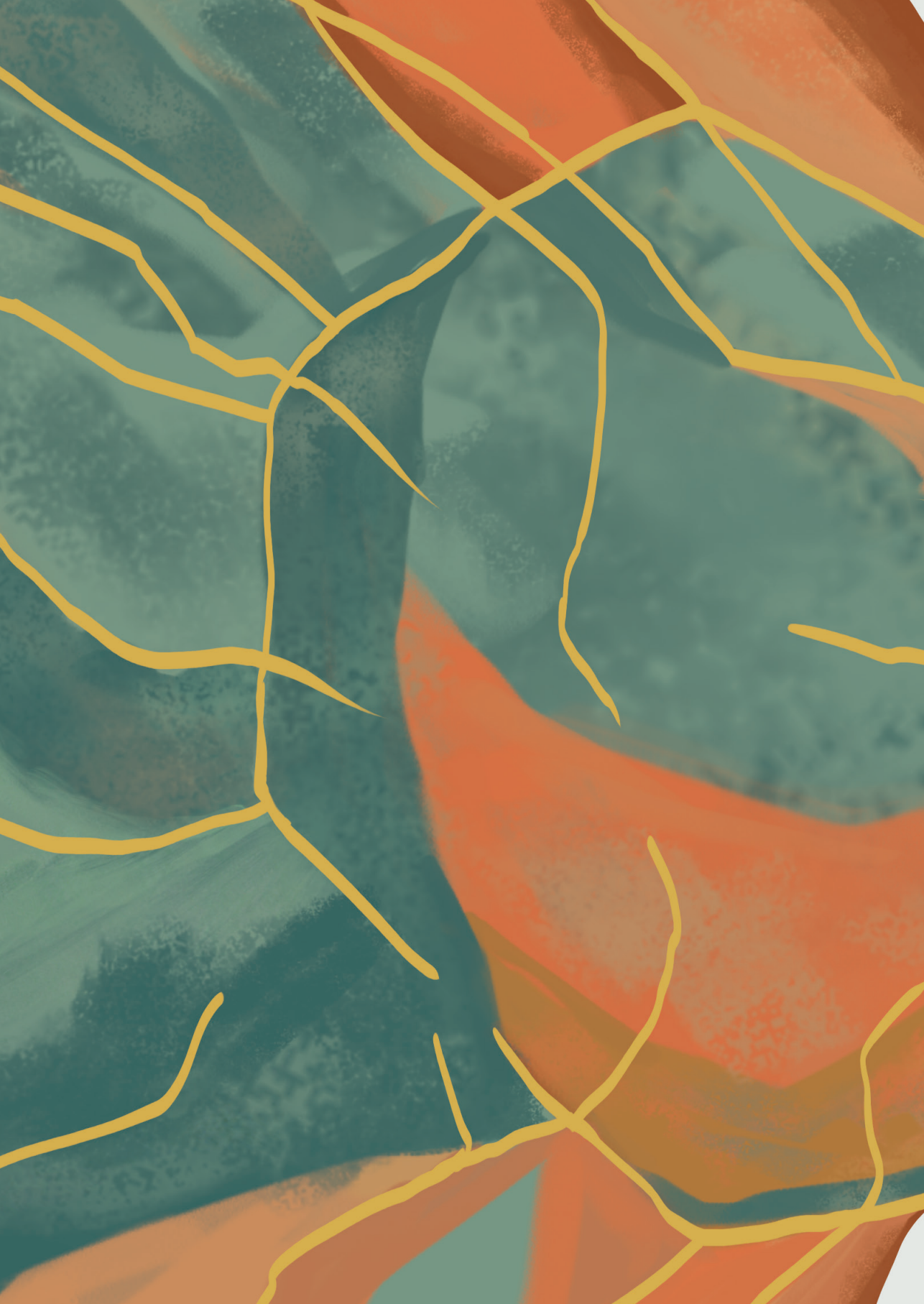
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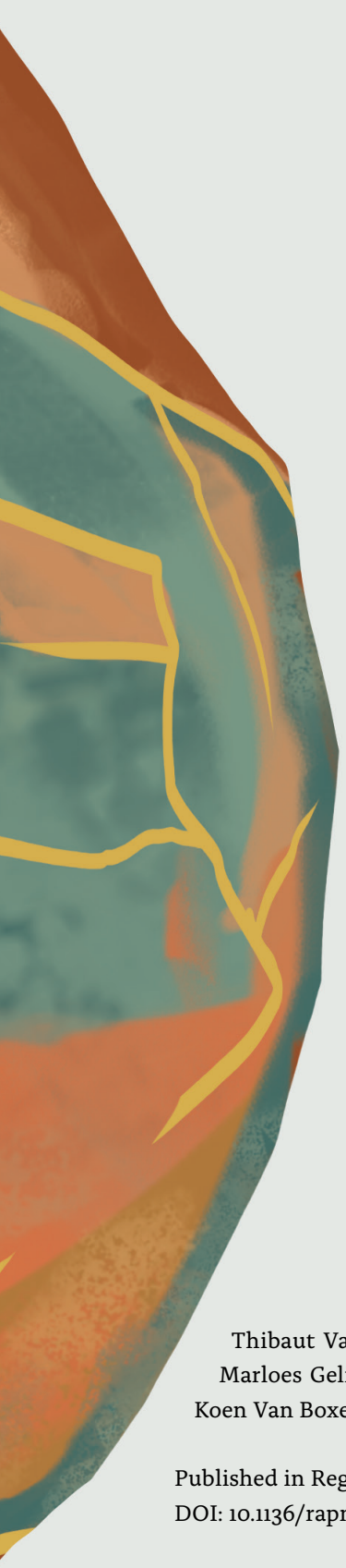
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CHAPTER 5

Comparison of cooled versus conventional radiofrequency treatment of the genicular nerves for chronic knee pain:

a multicenter non-inferiority randomized pilot trial (COCOGEN trial)

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Abstract

Background
Radiofrequency (RF) of the genicular nerves has the potential to reduce chronic knee pain due to osteoarthritis (OA) or persistent post-surgical pain (PPSP), however a direct comparison between the two main modalities used, conventional and cooled, is lacking.

Methods
This double blind, non-inferiority, pilot, randomised controlled trial compared the effects of cooled and conventional RF in chronic knee pain patients suffering from OA or PPSP after total knee arthroplasty. Patients were randomized following a 1:1 rate. The primary outcome was the proportion of patients with ≥50% pain reduction at 3 months post intervention. Other outcomes were knee pain, functionality, quality of life, emotional health, and adverse events up to 6 months post intervention. Conventional RF was tested for non-inferiority to cooled RF in reducing knee pain at 3 months follow-up.

Results
Forty-nine of 70 patients were included, of which 47 completed 3-month follow-up. The primary outcome was achieved in 4 of 23 patients treated with conventional RF (17%) versus in 8 of 24 with cooled (33%) (p=0,21). Results from the non-inferiority comparison were inconclusive in relation to the non-inferiority margin. There was no statistically significant difference between secondary outcomes. There were no serious adverse events.

Conclusions
Conventional and Cooled radiofrequency of the genicular nerves were shown to reduce chronic knee pain due to osteoarthritis and persistent post-surgical pain. This pilot study did not demonstrate statistically significant differences in the proportion of patients experiencing ≥50% pain reduction between techniques. The non-inferiority analysis was inconclusive. These results warrant further research.

Trial registration number NCT03865849

Introduction

Chronic knee pain is most often caused by osteoarthritis (OA) of the knee, a degenerative process that affects joint cartilage and the subchondral bone.[1] OA causes pain, stiffness and loss of function leading to psychological and sleeping disorders, and a diminished quality of life. Worldwide, the prevalence of knee OA is increasing reflecting the aging population and the increasing prevalence of obesity, a well-known risk factor.[2] Non-surgical treatment options, including pharmacological therapy, physiotherapy and lifestyle changes, are often insufficient and frequently associated with side effects. Consequently, many OA patients undergo a total knee arthroplasty (TKA).[3]

Unfortunately, a TKA is not a guarantee of success, given that the incidence of persistent postsurgical pain (PPSP) and functional limitation after TKA is as high as 53%.[4] Patients suffering from OA that have exhausted conservative treatments and are not surgical candidates (eg, due to comorbidities or very young age) and PPSP patients only have few therapeutical options.[5] Radiofrequency (RF) treatment of the genicular nerves might be a viable treatment option.

RF treatment of the genicular nerves is a minimally invasive treatment that reduces pain by interrupting the conduction of nociceptive stimuli through the application of a radiofrequent current adjacent to the responsible nerves. Recent systematic reviews indicate that RF is a safe and effective treatment in patients with OA of the knee, and to a lesser extent, in PPSP patients after TKA. [6–8] Two RF modalities, conventional and cooled RF, are commonly used to target the superomedial, the superolateral and the inferomedial genicular nerve. Prior studies suggest a higher success rate and a longer effect of cooled compared with conventional RF due to an increased lesion size, however, until present, no direct comparative studies have been performed in an randomised controlled trial (RCT).[6,9] This knowledge gap warrants further comparative studies. This is the first prospective study to directly compare the effectiveness of conventional and cooled RF in patients with chronic knee pain due to OA or PPSP after TKA. The primary goal was to provide an estimate of clinical treatment effects (pain, physical functioning, mental health, medication use, quality of life and adverse events, (AE)). A pilot design was chosen for the following reasons. First, to assess the feasibility of conducting a sufficiently powered randomized controlled trial in the future. Second, to evaluate the study design and thirdly to calculate a sample size more accurately. We hypothesize that in both patient groups (OA and PPSP), knee pain relief after conventional RF treatment is not inferior to cooled RF. In this article, only the effectivity outcomes will be discussed.

Methods

Trial Design

The COCOGEN trial is a prospective, double-blind, randomized, non-inferiority, pilot trial conducted in three participating centers (Hospital Oost-Limburg, Belgium; Maastricht UMC+, The Netherlands; Rijnstate, The Netherlands). Total follow-up time was 6 months. Patients were enrolled from February 10, 2020 to April 28, 2021.

Randomization, allocation, and blinding

Participants were randomly allocated to one of two parallel groups, conventional or cooled RF, with an allocation ratio of 1:1, and variable block size of 2 or 4 after stratification per etiology of pain (OA and PPSP) using the online CASTOR EDC application. The study was double-blinded: both the patient and the outcome assessor were blinded to treatment allocation. The treating pain physician was unblinded. The blinding of patients was tested approximately 30min after the treatment by asking the patient which intervention they thought they received with the following possible answers: 'Conventional RF', 'Cooled RF', and 'I don't know'. All patients were systematically unblinded 6 months after treatment.

Participants

Patients were recruited by their treating pain physician. Adult subjects were included if they suffered from moderate to severe (Numeric Rating Scale (NRS) >4) chronic anterior knee pain (> 12 months) due to OA or PPSP after TKA that was unresponsive to conventional treatments (physiotherapy, analgesics, or intra-articular infiltrations). For OA patients, a radiologic confirmation of Kellgren-Lawrence (KL) grades II–IV on X-ray or MRI was required.[10] For PPSP after TKA patients, a negative orthopedic workout was required. [11] Informed consent was obtained in all patients before participation. Exclusion criteria were: body mass index >40kg/m2 ; chronic widespread pain; untreated psychosocial disease; radicular pain in index leg; local or systemic infection (bacteremia); uncontrolled immune suppression; uncontrolled coagulopathy (defined as supratherapeutic dose of anticoagulation medication); currently implanted with a defibrillator, neuromodulator or other electrical devices; allergies to products used during the intervention; evidence of inflammatory arthritis or an inflammatory systemic disease responsible for knee pain; intra-articular injections (eg, steroids, hyaluronic acid, platelet enriched plasma) in the index knee during the 3 months prior to start study; previous conventional or cooled RF of the index knee; pregnant, nursing or planning to become pregnant before the treatment; participation in another clinical trial/investigation within 30 days prior to signing informed consent and patients who refused to comply to protocol procedure.

Study Procedures and Data Collection

The study data were collected from the medical patient record, questionnaires, and functionality tests at baseline, 1, 3 and 6 months after the procedure in an online patient case report form in the Castor data management tool. Data collection at baseline included: demographic data, NRS, KL grade of OA, results of goniometry, and results of the timed-up-and-go test (TUG). Data collected at the follow-up visits were: NRS, Oxford knee score (OKS), patient's self-reported impression of change measured by the Patient's Global Impression of Change (PGIC), health related quality of life expressed in EuroQol-5 Dimension- 3 Level (EQ-5D-3L), mental health measured by Hospital Anxiety and Depression Scale (HADS) and in the Pain Catastrophizing Scale (PCS), medication use measured by the change in Medication Quantification Scale III (MQS III), knee functionality measured using goniometry and the TUG test, and AE. The OKS, HADS, PCS and functionality tests were only collected at the 3-month and 6-month follow-up visit. The NRS score at each time point was calculated as the mean score of the previous 4days, collected using a pain diary.

Intervention

An RF treatment of the superomedial, superolateral, and inferomedial genicular nerves was performed in a standardized manner in both treatment groups using a Halyard/ Coolief RF generator. [12] A prognostic block prior to the treatment was not performed as a recent study showed no benefit of prior prognostic blocks. [13] All patients were monitored. No sedation was used. Patients were positioned in a supine position on a fluoroscopy table with the index knee flexed 10°–15°. The procedure was performed under sterile conditions. For each nerve, the needle was placed guided by ultrasound in the proximity of the genicular nerve at the junction of the shaft and condyle of the femur and tibia. After identifying the target point, the skin and subcutaneous tissues were anesthetized with 1mL lidocaine 2% at estimated entry point. The needle was advanced using an anterior to posterior 'in plane' approach until contact is made with the bony cortex at the center between anterior and posterior of the femur and tibia. If ultrasound guided needle tip position was final a control fluoroscopy image was made to confirm the final needle tip position in AP and lateral view. A sensory threshold (50 Hz) of ≤0.5V and an absent response to motor stimulation (2Hz) of 1.0V was obtained for each genicular nerve. Consequently, 1mL of lidocaine 2% was injected at each genicular nerve before RF treatment. The conventional RF was performed using for each nerve a 100mm, 18-gage, straight RF introducer and a 10mm active tip RF probe set at a temperature of 80°C the tip for 90s. The cooled RF was performed with a 100mm long, 17-gage, straight RF introducer and a 4mm active tip, 18-gage cooled RF probe generating a temperature of 60°C at the tip of the probe for 150s.

Outcomes

Endpoints were chosen following the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidelines. [14] The primary endpoint is the proportion of patients with a pain reduction of at least 50% at 3months postintervention. Pain intensity is expressed using the 11-point NRS. The NRS is a unidimensional, subjective measurement of pain intensity, expressed by the patient as a number between 0 and 10, ranging from no pain to maximal pain. A pain dairy containing 3 NRS recordings per day for 4days prior to each visit during the active hours of the day was collected. The NRS was not specified to be evaluated in rest or in movement, thus aiming to reflect the pain the patient experienced during normal daily activities. We used a threshold of 50% pain decrease, despite the IMMPACT guidelines recommending a threshold of 30%. We chose for 50% as this threshold is most often used in the clinic, as well in previous studies, making comparisons later on easier. In addition, we also collected data on at least 30% pain reduction. The secondary endpoints were NRS, OKS, PGIC, EQ-5D-3L, HADS, PCS, MQS III, goniometry, TUG test, and AEs. [15–23] PGIC was measured using a 7-point Likert scale ranging from '0' meaning 'Much worse' to 7 meaning 'Extremely improved'. Patients scoring 6 and 7 were considered having a significant improvement. Success of blinding was also tested as mentioned previously.

Statistical methods

The rule-of-thumb of Julious suggested including 12 patients per group in case of a pilot study, so that preliminary data on effect sizes, measures of spread, and feasibility can be obtained.[24] As this study is stratified by indication (OA and PPSP after TKA), we aimed to include a total of 48 patients.

The clinical outcomes were analyzed according to the intention-to-treat principle. Patient baseline characteristics were described for both knee pain groups separately and stratified by treatment allocation using mean and SD for continuous variables, and count and percentage for categorical variables.

The primary outcome, the proportion of patients achieving treatment success at 3 months after treatment, was computed as percentage and was tested between groups using Pearson's $\chi 2$ test. To test for non-inferiority, mean NRS change from baseline and between group difference in change score, including 95% CI, were calculated at 3 months. The lower bound of the 95% CI of the difference was compared with the non-inferiority limit of 0.75 NRS points. [25,26] Other secondary study parameters were reported as mean or percentage difference including 95% CI. All hypothesis testing was considered explorative.

Results

Participants
Seventy patients were screened for eligibility, of which 49 were included. One additional patient was included due to a small lag in registration in the database as the last two patients were recruited approximately at the same time in different centers. Figure 1 depicts the Consolidated Standards of Reporting Trials flow chart of participants during the trial. Three patients dropped out, one of which received a TKA. There were further no missing data for the primary endpoint and there were no cross overs between the groups. Table 1 presents the baseline patient characteristics.

The primary outcome
There were more patients who achieved the primary endpoint after a cooled RF in comparison with conventional RF as described in table 2. Similarly, a higher percentage of patients reached ≥50% pain reduction after a cooled RF in comparison with conventional RF at all other time points. However, these differences were not statistically significant at each time point.

The ORs of ≥50% pain reduction after a cooled versus conventional RF treatment were 1.46 (95% CI 0.44 to 4.87), 2.38 (95% CI 0.60 to 9.38) and 2.7 (95% CI 0.69 to 10.55), respectively at 1, 3 and 6 months after treatment in the whole group, independent of the indication.

The differences between the proportion of patients with ≥50% pain reduction after an RF treatment (conventional and cooled combined) between OA and PPSP were also not statistically significant at each time point, although absolute numbers where at each time point higher in the OA group.

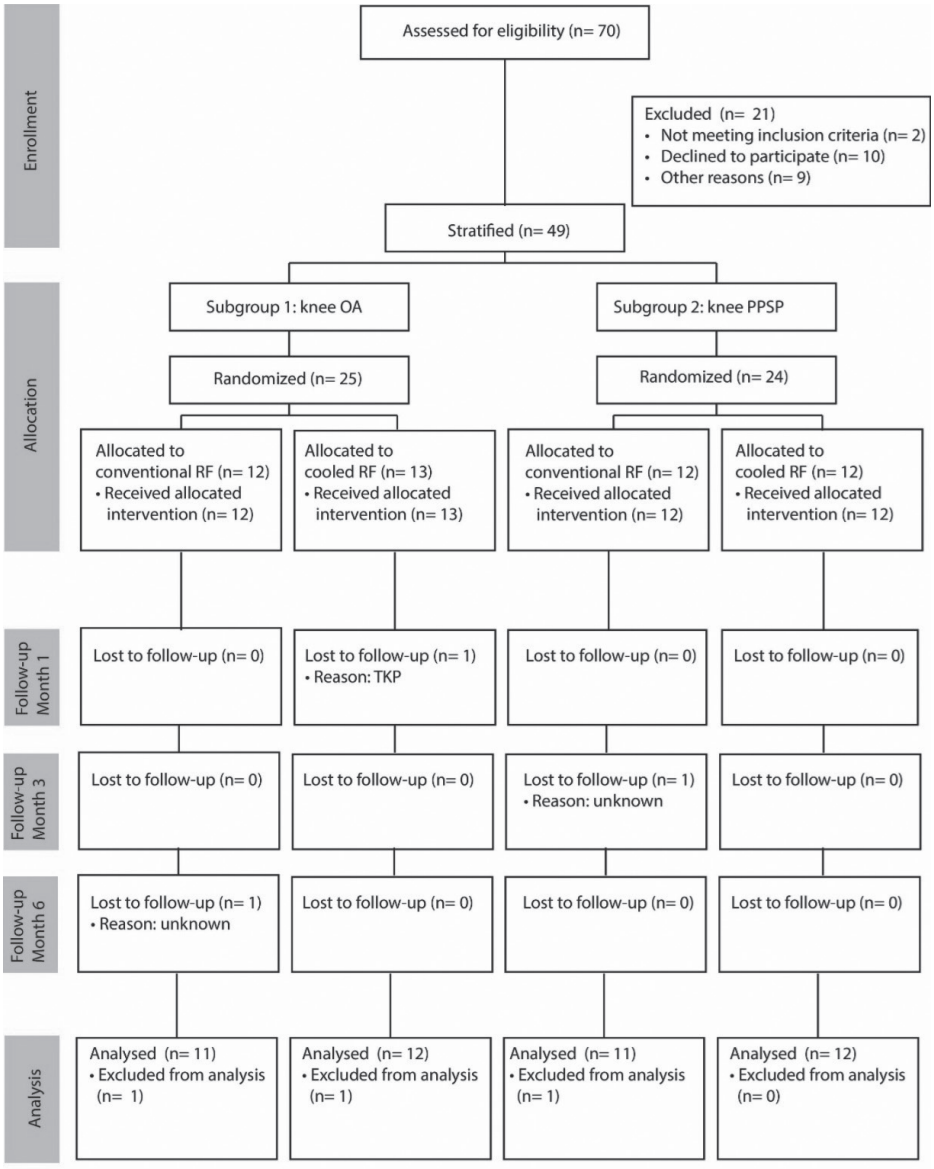


Figure 1 Participant flow chart during the study. All allocated participants received the planned treatment and were analyzed according to the intention-to-treat principle. OA, osteoarthritis; PPSP, persistent postsurgical pain; TKP, total knee prothesis; RF, radiofrequency.

Table 1 Baseline demographic characteristics of patients per stratification group.

OA	**Conventional RF**	**Cooled RF**
Sample size, n (%)	12 (48)	13 (52)
Sex, n (%)		
Male	1 (8)	7 (54)
Female	11 (92)	6 (46)
Mean age (SD) in years	62.0 (14.4)	62.0 (13.1)
Mean grade of OA (SD)	31.0 (0.8)	3.2 (0.9)
Mean BMI (SD) in kg/m^2	32.6 (4.9)	29.1 (4.0)
Mean NRS score (SD)	6.4 (1.4)	5.3 (2.1)
Mean OKS score (SD)	16.3 (5.6)	21.5 (7.4)
Mean EQ-5D-3L score (SD)	0.4 (0.29)	0.4 (0.3)
Mean MQS III score (SD)	9.1 (5.9)	8.1 (6.4)
Mean PCS score (SD)	22.6 (13.0)	23.5 (11.8)
Mean HADS depression subscale (SD)	5.6 (3.8)	8.5 (4.8)
Mean HADS anxiety subscale (SD)	6.6 (5.2)	9.1 (5.0)
Goniometry		
Mean knee flexion (SD) in degrees	65.8 (16.8)	69.1 (24.2)
Mean knee extension (SD) in degrees	168.0 (7.7)	162.9 (9.7)
Mean Timed up-and-go test score (SD) in seconds	14.0 (4.8)	14.5 (5.5)
PPSP after TKA	**Conventional RF**	**Cooled RF**
Sample size, n (%)	12 (50)	12 (50)
Sex, n (%)		
Male	2 (17)	4 (33)
Female	10 (83)	8 (67)
Mean age (SD) in years	65.0 (11.8)	65 (8.8)
Mean BMI (SD) in kg/m^2	28.8 (5.2)	28.2 (5.6)
Mean NRS score (SD)	6.0 (1.8)	6.9 (1.2)
Mean OKS score (SD)	20.8 (6.5)	17.1 (5.4)
Mean EQ-5D-3L score (SD)	0.4 (0.3)	0.5 (0.34)
Mean MQS III score (SD)	6.3 (6.8)	10.0 (6.5)
Mean PCS score (SD)	24.9 (9.0)	24.1 (9.7)
Mean HADS depression subscale (SD)	8.3 (4.1)	6.1 (5.2)
Mean HADS anxiety subscale (SD)	8.8 (3.2)	7.2 (4.6)
Goniometry		
Mean knee flexion (SD) in degrees	59.4 (16.1)	67.8 (17.5)
Mean knee extension (SD) in degrees	165.2 (9.7)	164.9 (7.3)
Mean Timed up-and-go test score (SD) in seconds	14.6 (3.4)	14.8 (3.7)

Values are reported as means (SD) unless specified otherwise. BMI, body mass index; EQ-5D-3L, EuroQol-5 Dimension- 3 Level; HADS, Hospital Anxiety and Depression Scale; MQS III, Medication Quantification Scale III; NRS, Numerical Rating Scale; OA, osteoarthritis; OKS, Oxford Knee Score; PCS, Pain Catastrophizing Scale; PPSP, persistent postsurgical pain; TKA, total knee arthroplasty.

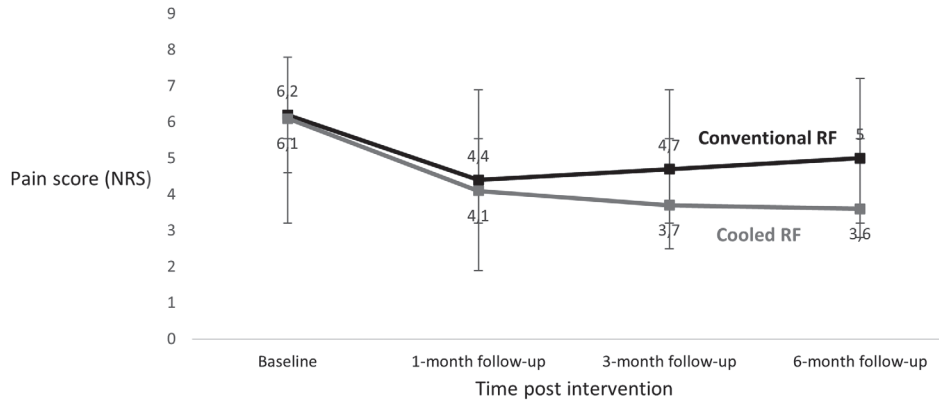
Table 2 Percentage of patients with ≥30% and ≥50% pain reduction after conventional and cooled RF treatment.

≥50% pain reduction compared to baseline	**OA**		
	Conv RF, n (%)	**Cooled RF**, n (%)	**P value***†
1 month	5/12 (41.7)	6/12 (50)	1.00
3 months	3/12 (25)	4/12 (33.3)	1.00
6 months	3/11 (27.3)	4/12 (33.3)	1.00
≥30% pain reduction compared to baseline	**OA**		
	Conv RF,n (%)	**Cooled RF,**n (%)	**P value***†
1 month	6/12 (50)	7/12 (58.3)	0.68
3 months	5/12 (41.7)	8/12 (66.7)	0.22
6 months	4/11 (36.4)	5/12 (41.7)	1.00

*P value compares conventional RF versus cooled RF procedure in the OA group.

†Pearson's χ2 test used to compare proportions.

‡P value compares conventional RF versus cooled RF procedure in the PPSP group.



Abbreviations: NRS, Numeric Rating Scale; RF, Radiofrequency treatment.
Lines represent the standard deviation.

Figure 2 Mean NRS at each time point compared between conventional and cooled RF in the whole group.

PPSP			Whole group		
Conv RF, n (%)	**Cooled RF,** n (%)	**P value**† ‡	**Conv RF,** n (%)	**Cooled RF,** n (%)	**P value**† §
2/12 (16.7)	3/12 (25)	1.00	7/24 (29.2)	9/24 (37.5)	0.54
1/11 (9.1)	4/12 (33.3)	0.32	4/23 (17.4)	8/24 (33.3)	0.21
1/11 (9.1)	5/12 (41.7)	0.16	4/22 (18.2)	9/24 (37.5)	0.15
PPSP			**Whole group**		
Conv RF,n (%)	**Cooled RF,**n (%)	**P value**† ‡	**Conv RF,**n (%)	**Cooled RF,**n (%)	**P value**† §
4/12 (33.3)	6/12 (50)	0.41	10/24 (41.7)	13/24 (54.2)	0.39
2/11 (18.2)	6/12 (50)	0.19	7/23 (30.4)	14/24 (58.3)	0.05
1/11 (9.1)	5/12 (41.7)	0.16	5/22 (22.7)	10/24 (41.7)	0.17

§P value compares conventional RF versus cooled RF procedure in the whole population.
OA, osteoarthritis; PPSP, persistent postsurgical pain; RF, radiofrequency ablation

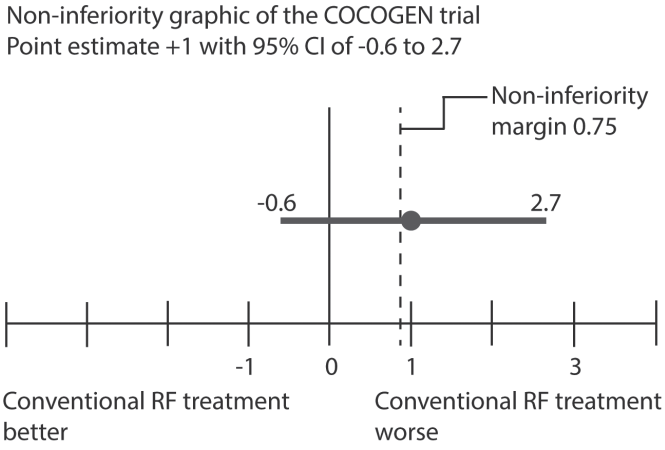


Figure 3 Non-inferiority graphic. RF, radiofrequency ablation.

Table 3 The evolution of secondary outcomes at different timepoints compared between conventional and cooled RF treatment of the genicular nerves.

	Baseline	
	Conv. RF	Cooled RF
Mean NRS (SD)	6.2 (1.6)	6.1 (1.8)
Patients with significant improvement in PGIC, n (%)	-/24	-/25
Mean OKS score (SD)	18.1 (6.1)	19.8 (7.2)
Mean EQ-5D-3L score (SD)	0.4 (0.3)	0.5 (0.3)
Mean HADS depression subscale (SD)	7.0 (4.2)	7.0 (5.2)
Mean HADS fear subscale (SD)	7.7 (4.5)	8.0 (4.8)
Mean PCS score (SD)	24.2 (11.0)	23.5 (10.9)
Mean MQS III score (SD)	7.7 (6.4)	9.1 (6.4)
Goniometry: Mean knee Flexion (SD) in degrees	62.5 (16.6)	79.8 (37.6)
Goniometry: Mean knee Extension (SD) in degrees	167.1 (8.7)	152.7 (32.2)
Timed up-and-go test score (SD) in seconds	14.1 (4.2)	14.6 (4.7)

*P value compares conventional RF versus cooled RF procedure.

†Pearson's χ2 test used to compare proportions and paired t-test used to compare means.

‡P value of mean paired difference between baseline and follow-up NRS.

Secondary outcomes

Numerical Rating Scale

At each time point, the mean NRS score of the OA subgroup, PPSP subgroup and the whole population decreased in a statistically significant manner ($p<0.05$) compared with baseline after both conventional and cooled RF treatment (figure 2). The mean pain reduction (ΔNRS) (95% CI) at 3 months compared with baseline was −2.0 (−3.2 to −0.9) for OA, −2.0 (−2.8 to −1.1) for PPSP and −2.0 (−2.7 to −1.3) for the whole population. In patients treated with cooled RF, the mean pain reduction (ΔNRS) (95% CI) at 3 months compared with baseline was −2.2 (−4.2 to −0.1) for OA, −2.5 (−3.8 to −1.2) for PPSP and −2.3 (−3.5 to −1.2) for the whole population. In patients treated with conventional RF, the mean pain reduction (ΔNRS) (95% CI) at 3 months compared with baseline was −1.9 (−3.3 to −0.5) for OA, −1.5 (−2.6 to −0.3) for PPSP and −1.7 (−2.5 to −0.8) for the whole population. The mean ΔNRS of the OA and PPSP subgroup was statistically significant at each follow-up point compared with baseline, but the mean ΔNRS was not significantly different between the OA and PPSP subgroups at each follow-up moment. When analyzing both the OA an PPSP population together, at each follow-up point, the ΔNRS of cooled RF compared with baseline was not significantly

1 month FU			3 months FU			6 months FU		
Conv. RF	Cooled RF	P value * †	Conv. RF	Cooled RF	P value * †	Conv. RF	Cooled RF	P value * †
4.4 (2.5)	4.1 (2.3)	0.79[c]	4.7 (2.2)	3.7 (2.3)	0.36‡	5.0 (2.2)	3.6 (2.2)	0.13‡
8/24 (33.3)	11/24 (45.8)	0.38	9/23 (39.1)	10/24 (45.5)	0.67	5/22 (22.7)	9/24 (37.5)	0.28
-	-		26.3 (9.1)	28.9 (9.6)	0.36	25.0 (9.6)	27.0 (8.7)	0.47
0.6 (0.3)	0.6 (0.3)	0.87	0.6 (0.3)	0.6 (0.2)	0.47	0.6 (0.3)	0.6 (0.28)	0.62
-	-		6.2 (5.2)	5.1 (5.1)	0.47	7.0 (4.9)	5.46 (4.8)	0.31
-	-		6.1 (4.4)	5.27 (3.7)	0.49	6.38 (4.6)	6.0 (4.7)	0.79
-	-		22.2 (12.5)	18.1 (11.4)	0.26	23.1 (13.7)	18.0 (12.4)	0.20
6.3 (6.0)	6.2 (5.6)	0.95	6.8 (6.2)	5.2 (4.5)	0.31	5.0 (5.2)	6.2 (5.0)	0.40
-	-		61.6 (18.1)	63.5 (17.4)	0.71	65.6 (21.2)	64.9 (17.3)	0.91
-	-		168.4 (7.2)	166.8 (12.3)	0.61	169.1 (6.3)	165.1 (11.6)	0.18
-	-		13.9 (7.2)	12.0 (3.9)	0.28	11.8 (5.5)	10.9 (2.8)	0.49

Conv, conventional; EQ-5D-3L, EuroQol-5 Dimension-3 Level; HADS, Hospital Anxiety and Depression Scale; MQS III, Medication Quantification Scale III; NRS, Numeric Rating Scale; OA, osteoarthritis; OKS, Oxford Knee Score; PCS, Pain Catastrophizing Scale; PGIC, Patient's Global Impression of Change; PPSP, persistent postsurgical pain; RF, radiofrequency ablation; TKA, total knee arthroplasty.

different to the ΔNRS of conventional RF compared with baseline. There was, however, an increase of the ΔNRS over time in the whole cooled RF group compared with a decrease in the whole conventional RF group.

The non-inferiority outcome

The non-inferiority comparison between conventional and cooled RF was performed on the combined OA and PPSP population due to the limited number of patients included in this trial. The point estimate difference in NRS was 1 at 3 months but as the 95% CI (–0.6 to 2.7) includes the non-inferiority margin of 0.75, it is inconclusive at this point (figure 3).

Patient's Global Impression of Change, OKS, EQ-5D-3L, HADS, PCS, MQSIII, Goniometry, and TUG test. Table 3 describes the evolution of the secondary outcomes at different timepoints compared between conventional and cooled RF treatment of the genicular nerves in the whole population.

Adverse events

There were no serious AE. There were no significant differences in prevalence of AE between conventional and cooled RF, respectively, 5 and 6 cases. After conventional RF, five patients reported a transient increase in pain. After cooled RF, three patients developed a subcutaneous hematoma which resolved spontaneously, one patient developed infrapatellar hypoesthesia, and two patients reported a transient increase in pain.

Blinding

Data from two participants were missing. Thirty-nine patients (83%) reported that they did not know which treatment they received. Five patients (11%) guessed the wrong allocation and three (6%) guessed right.

Discussion

As this is a pilot trial with inherent low statistical power, the primary goal was to estimate and compare the treatment effect size of conventional and cooled RF of the genicular nerves. This study showed that the proportion of patients with at least 50% pain reduction was higher, although not significantly, after a cooled RF treatment of the genicular nerves in comparison with a conventional RF treatment in patients with chronic knee pain due to OA, PPSP and the whole population at each time point up to 6months after the procedure. Mainly, in the PPSP group cooled RF led to higher proportion of patients with ≥50% pain reduction in comparison with conventional RF. The differences were not statistically significant reflecting among others the insufficient sample size of this pilot trial. Despite this, we found a statistically significant pain reduction after both conventional and cooled RF treatment of the genicular nerves up to 6 months postprocedure. The point estimate of the difference in mean pain reduction from baseline between conventional and cooled RF at 3months was one which could indicate inferiority of conventional RF, nevertheless, these results are inconclusive as the 95% CI included the non-inferiority margin of 0.75. At 6months, the mean pain reduction of the patients treated with cooled RF was 2.5 point, which is above the clinically relevant margin of 2 points according to the IMMPACT guidelines. This was not the case with conventional RF. The proportion of patients with ≥50% pain reduction and the absolute pain reduction, although both higher in the OA group, did not differ statistically significant between OA or PPSP. Most secondary outcomes improved in time after both conventional and cooled RF. We found no statistically significant difference in secondary outcomes between both RF treatments. There were no serious AE reported, indicating that both RF modalities are safe. Results of the blinding analysis also indicate that the blinding process was adequate. In a large retrospective study by Kapural et al cooled RF also resulted in a higher chance of treatment success and a longer duration of effect in comparison with conventional RF in OA patients.[27]

When comparing the findings of this trial with the literature, we remark that treatment success in this study is lower. Earlier studies demonstrate treatment success (proportion ≥50% pain reduction) of a conventional RF between 32% and 59% at 3months and after a cooled RF between 61% and 74% at 6months.[12,13,27,28] First, this difference could be explained by the fact that no prognostic block was used in this trial. We did not include a prognostic block as we considered that its possible benefit did not outweigh the risks. The possible benefit is a better patient selection and by this better treatment outcomes. However, the randomized controlled trial by McCormick et al showed that a prognostic block with 1mL of local anesthetic and a 50% threshold

did not lead to improved pain and knee function outcomes in comparison with not performing a prognostic block.[13] At the moment, there are no prospective studies showing a better outcome with the use of prognostic genicular nerves blocks prior to RF. The main drawback of using prognostic blocks, is that patients with a false-negative block are refused a potentially safe and effective treatment. Furthermore, there are also other downsides and risks associated with the use of prognostic blocks such as an increased cost, patient discomfort and especially in the group of patients post-TKA the risk of infection. Moody et al reported two cases of patients with PPSP suffering a knee infection after a prognostic genicular nerve block. [30] Also, there are other studies where investigators have decided to not perform a prognostic block. [31-33] Second, most published studies include only OA patients, whereas in this study both OA and PPSP patients were included. To our knowledge, this is the first RCT that investigated the effects of cooled RF in PPSP patients. In operated patients, anatomy can be even more variable and causes of pain can be plural resulting in diminished treatment success. As this study found an effect size of the primary endpoint of 18.7% and 37.5%, respectively, for conventional and cooled RF at 6 months in the whole population, it is of utmost importance that future studies also include a sham procedure to evaluate the possible placebo effect.

The prevalence of knee OA is rising and subsequently also the prevalence of total knee replacement and that of PPSP after TKA. As these conditions have a high impact on the patients' health-related quality of life and a high societal cost, there is a need for minimally invasive alternative treatments.[27] As cooled RF is associated with a higher product cost it is important to deter - mine not only its effectiveness but also the cost-effectiveness. [34]

This study has several limitations. First, as this is a pilot trial sample size is, inherent to the design, too low to draw conclusions. Nevertheless, as this is the first trial to directly compare conventional and cooled RF of the genicular nerves in an RCT, results remain important to guide future research. Second, there was no prognostic block used prior to the RF treatment in both OA and PPSP patients which could have influenced our results. Third, this study was designed to target only three genicular nerves. In the literature, there is an ongoing discussion on possible strategies to increase treatment success, for example, by targeting more nerves or targeting nerves at different locations as cadaveric studies demonstrate significant anatomical variability. [35-36] Fonkoue et al performed a study that compared an injection of 5 vs 3 nerves with LA and steroid in OA patients with a follow-up of 12 months.[37] They found in both groups a significant reduction in pain intensity but only a significant greater pain reduction in the group with 5 nerves 1-hour post - operative. All the other time points showed no significant

difference. Furthermore, the study performed by Chen et al targeted four nerves with cooled RF and found that 71% of patients report ≥50% pain reduction at 6 months. [38] These results are comparable (74.1% of patients reported ≥50% pain reduction) with the study of Davis et al with a similar design with the exception that they only targeted three genicular nerves.[39] The retrospective analysis of Chen et al found that targeting more than three nerves increased treatment success (Global Perceived Effect >30%) from 57.5% (126/219) to 80% (36/45), although there are inherent limitations due to the retrospective design.[40] The editorial of Kim and Cohen advocates that ablation of up to ten genicular nerves could improve outcomes of this treatment.[36] However, this hypothesis is also based in ex vivo studies and prospective clinical trials on patients comparing the number of genicular nerves targeted are lacking. It is at this time unknown whether denervation of all nerves, which innervate the anterior knee, is necessary for adequate analgesia.[36] On the other hand, increasing the number of lesions, also increase the risk of complications, therefore each intervention should be a balance between possible clinical benefits and risk of complications. At the time this study was conducted, most studies performed an RF treatment of the genicular nerves on three nerves. Nevertheless, targeting more than three nerves theoretically could lead to better outcomes and should be focus of future research.

Conclusions

In conclusion, both conventional and cooled RF of the genicular nerves reduced pain in the OA and PPSP population. The explorative results of this pilot study showed that a not statistically significant higher proportion of patient experienced ≥50% pain reduction from baseline after cooled RF compared with conventional RF. The non-inferiority analysis was inconclusive. Further research in the form of a powered comparative RCT is warranted.

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Contributors

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Competing interests

None declared.

Patient consent for publication

Not applicable.

Ethics approval

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Provenance and peer review

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Data availability statement

Data are available on reasonable request.

Supplemental material

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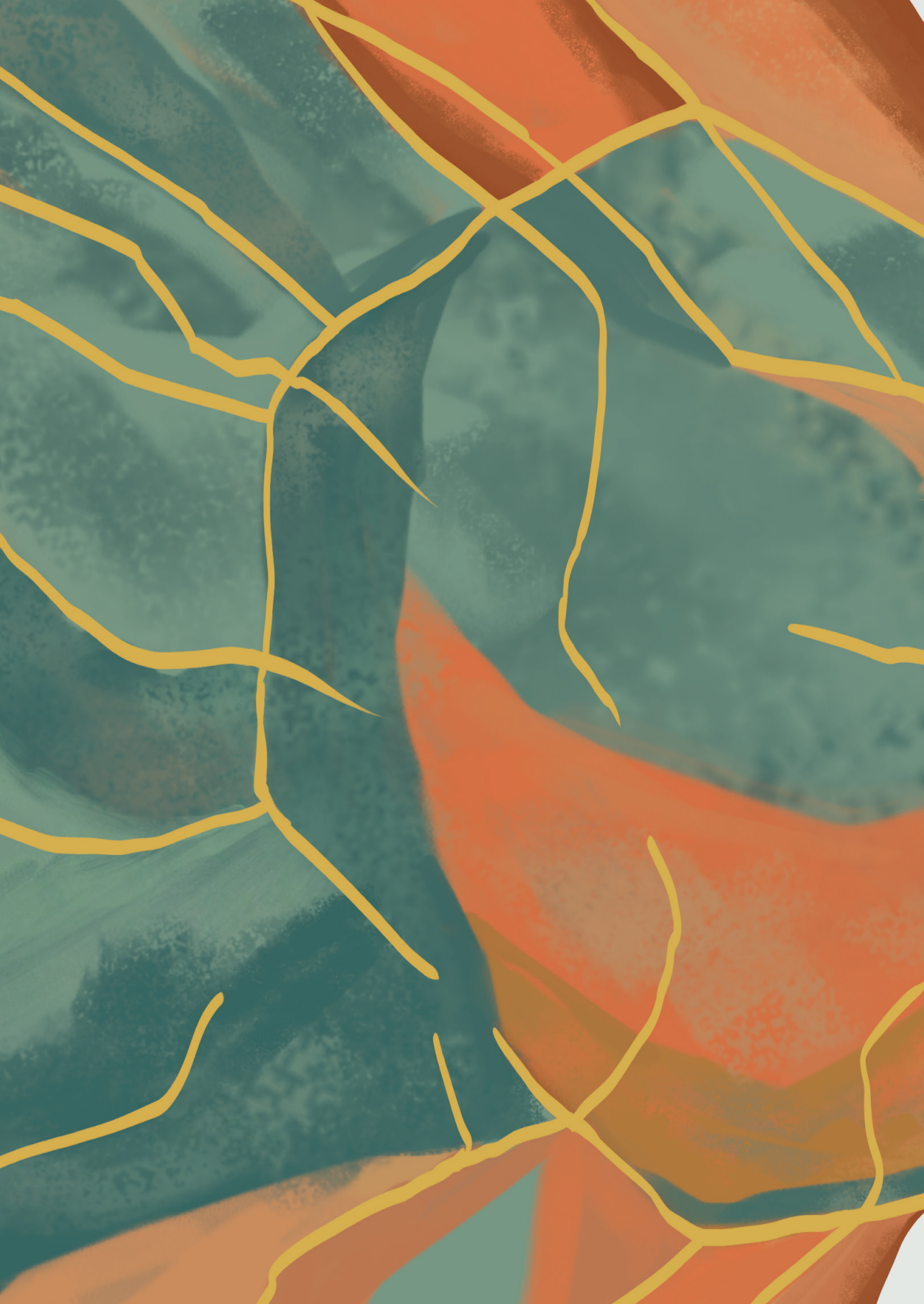
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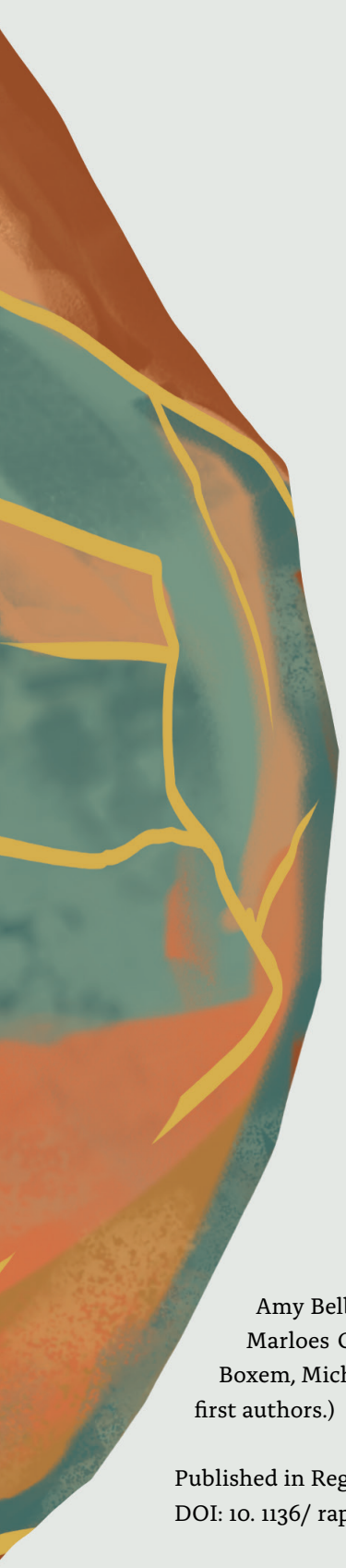
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CHAPTER 6

Cooled Versus Conventional Radiofrequency Treatment of the Genicular Nerves for Chronic Knee Pain:

12-month and cost-effectiveness results from the multicenter COCOGEN Trial

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Abstract

Background

Radiofrequency treatment (RF) of the genicular nerves reduces chronic knee pain in patients with osteoarthritis (OA) or persistent post-surgical pain (PPSP) after total knee arthroplasty (TKA). The objective of this study is to compare long term outcomes of cooled and conventional RF and perform an economic evaluation.

Methods

The COCOGEN trial is a double blind, non-inferiority, pilot, randomised controlled trial that compared the effects up to 12 months of cooled and conventional RF in chronic knee pain patients suffering from OA or PPSP after TKA following a 1:1 randomisation rate. Outcomes were knee pain, functionality, quality of life, emotional health, medication use and adverse events. A trial-based economic evaluation was performed with a 12-month societal perspective. Herein, the primary outcome was the incremental costs per Quality Adjusted Life Year (QALY).

Results

41 of the 49 included patients completed the 12 months follow-up. One patient in the PPSP cooled RF group had substantial missing data at 12 months follow-up. The proportion of patients with ≥50% pain reduction at 12 months was 22.2% (4/18) in patients treated with conventional RF versus 22.7% (5/22) in patients treated with cooled RF ($p>0.05$). There was a statistically significant difference between the mean absolute NRS at 12 months after cooled RF in comparison with conventional RF in patients with PPSP ($p = 0.02$). Differences between other outcomes were not statistically significant. The health economic analysis indicated that cooled RF resulted in less costs and improved QALYs compared with conventional RF in PPSP, but not in OA. There were no serious adverse events.

Conclusions

Both RF treatments demonstrated in approximately 22% of patients a ≥ 50% pain reduction at 12 months. In patients with PPSP, contrary to OA, cooled RF seems to be more effective than conventional RF. Additionally, cooled RF has in patients with PPSP, opposed to OA, greater effectiveness at lower costs compared with conventional RF.

Trial registration number NCT03865849

Introduction

Osteoarthritis (OA) of the knee is a degenerative disease of the cartilage and subchondral bone which leads to pain, loss of function and potentially a lower quality of life and financial burden. [1-4] When conservative therapy fails to treat these symptoms, a total knee arthroplasty (TKA) is the last resort. However, not everyone is a suitable candidate for such a procedure because of comorbidities or young age. Patients with comorbidities have a higher peri-operative risk and postoperative revalidation can be difficult. Young patients have worse outcomes with a higher risk of revision. [5] Furthermore, up to 53% of patients develop persistent post-surgical pain (PPSP) after a TKA, forming a second cause of chronic knee pain. [6, 7]

Chronic pain has a high impact on a patient's quality of life and is associated with a high socioeconomic cost. [3, 4] Recently, radiofrequency (RF) treatment of the genicular nerves emerged as a minimally invasive treatment for chronic knee pain. By blocking nociceptive pain signals from the knee, through applying a RF current in proximity of the genicular nerves, a patient with knee OA or PPSP after TKA can obtain pain relief and improvement of knee function. [8, 9] In addition to the conventional RF treatment, a newer modality, cooled RF has been developed to create a bigger lesion size aimed to further improve the success rate and prolong the effect. [10] In a previous publication, both after a conventional and cooled RF treatment of the genicular nerves a reduction of chronic knee pain in the osteoarthritis and persistent postsurgical pain after TKA population up to six months was described. [11] While this pilot trial was intrinsically underpowered, cooled RF resulted in a non-significant higher probability of pain reduction compared with conventional RF in the whole study population and in both subgroups (OA and PPSP). In the PPSP group, the discrepancy between treatment success of cooled RF versus conventional RF was higher when compared with the OA group. In another recent trial, cooled RF did not result in significantly higher long-term benefits when compared with conventional RF in patients with OA. [12] Other previous trials also indicate that RF of the genicular nerves leads to improved quality of life in patients with knee OA. [13-15] Whether cooled RF treatment is cost-effective compared with conventional RF in patients with therapy resistant OA or PPSP, is yet unknown.

In this manuscript we present the 12-month clinical effectiveness results and the cost-effectiveness analysis of cooled versus conventional RF in therapy-resistant chronic knee pain due to OA and PPSP. The analysis is a part of the COCOGEN pilot randomized controlled trial, of which the 6-month effectiveness results are published in a separate paper. [11] We hypothesized that at 12 months in both patient groups (OA and PPSP), knee pain after conventional RF treatment is not inferior to cooled RF and that cooled RF is cost-effective compared with conventional RF.

Methods

Trial Design

The COCOGEN trial was a randomised controlled, non-inferiority, pilot trial conducted in three participating centres (Hospital Oost-Limburg, Belgium; Maastricht UMC+, The Netherlands; and Rijnstate, The Netherlands). Patients were followed up to 12 months after treatment. Ethical approval was granted from the ethical committees of Hospital Oost-Limburg (19/0038U) and Maastricht UMC+ (NL69877.068.19/METC 19-031). The study was registered at ClinicalTrials.gov on 7 March 2019 (NCT03865849). Patients were enrolled between 10 February 2020 and 28 April 2021.

Participants, Randomization, and Blinding

Adult patients suffering from long term (> 12 months) chronic anterior knee pain due to OA and PPSP after TKA that were unresponsive to conventional treatments (physiotherapy, analgesics, or intra-articular infiltrations) were included in the trial (Supplement S1). After stratification per aetiology of pain (OA and PPSP), participants were randomized into two treatment groups, the conventional and cooled RF group, with an allocation ratio of 1:1, and variable block size of 2 or 4 in the online CASTOR EDC application. In this double-blinded trial, both the patient and the outcome assessor were unaware of the patient's treatment allocation up to 6 months. After a systematic unblinding at 6-months patients were followed up until 12 months after treatment. Patients were encouraged to continue other conservative care throughout the trial.

Intervention

Participants received RF treatment of the superomedial, superolateral and inferomedial genicular nerves using a Halyard/Coolief RF generator. [16] No prognostic block prior to the treatment was used. Patients were not sedated, hemodynamically monitored, and positioned in a supine position on a fluoroscopy table with the index knee flexed 10-15°. The RF needle placement was guided by ultrasound and final position was controlled using fluoroscopy. The target point was the mentioned genicular nerves at the junction of the shaft and condyle of the femur and tibia. The subcutaneous tissue was anesthetized with 1 ml lidocaine 2% at each entry point before introduction of the RF needle. After obtaining a sensory threshold (50 Hz) of ≤ 0.5V and an absent response to motor stimulation (2 Hz) of 1.0 V, 1 ml of lidocaine 2% was injected at each genicular nerve. Each of the three nerves was treated with conventional RF using a 100 mm, 18-gage, straight RF introducer and one 10 mm active tip RF probe set at a temperature of 80°C for 90 seconds or with cooled RF using a 100 mm long, 17-gage, straight RF introducer and one 4 mm active tip, 18-gage cooled RF probe generating a temperature of 60°C at the tip of the probe for 150 seconds.

Study end points and Data Collection
Participants were assessed at baseline, 1, 3, 6 and 12 months after the procedure. Data was collected from the medical patient record, questionnaires, and functionality tests in an online patient case report form in the Castor data management tool.

The primary endpoint of the COCOGEN trial was the proportion of patients with ≥50% pain reduction at 3 months. We previously reported that 4 of 23 patients treated with conventional RF (17%) vs in 8 of 24 with cooled (33%) (p=0,21) reached the primary endpoint at 3 months. [11]

The clinical outcomes at 12-month follow-up were the following: Numerical Rating scale (NRS), Oxford knee score (OKS), patient's self-reported impression of change measured by the Patient's Global Impression of Change (PGIC), health-related quality of life expressed in Euroqol 5-Dimensions 3-Levels (EQ5-5D-3L), mental health measured by Hospital Anxiety and Depression Scale (HADS) and by the Pain Catastrophizing Scale (PCS), medication use assessed by the Medication Quantification Scale III (MQS III), adverse events and incidence of a TKA. [17-23] The NRS score at each timepoint was the mean score of the previous 4 days except for the 12 months follow-up. At 12 months patients were asked to report the NRS in rest and during movement. We reported the mean of these two.

Statistical methods
As COCOGEN is a pilot RCT, the rule of thumb of Julious was used to include 12 patients per treatment group mounting to a total of 48 patients. [24] This rule of thumb ensures enough participants to estimate treatment effects and measures of variance, but may not ensure sufficiently high power for null-hypothesis testing. The effectiveness outcomes were analyzed following the per-protocol principle as this is more conservative for testing non-inferiority hypothesis. To test for non-inferiority, mean NRS difference between groups, including 95% CI, were calculated at 12 months. The lower bound of the 95% CI of the difference was compared with the non-inferiority limit of 0.75 NRS points. [25, 26] The analysis of the outcomes was exploratory due to the pilot nature of the trial. The proportion of patients achieving treatment success was calculated as percentage. The difference between groups was computed, including 95% confidence interval, and Pearson's chi-squared test was used for the comparison between the treatment groups. We reported the secondary study parameters as mean or percentage difference including 95% confidence interval. The mean NRS at 12 months was calculated as the average score of the reported NRS during rest and during movement.

The economic evaluation

The economic evaluation was designed and analyzed to conform with the Dutch guidelines for health economic evaluation (HEA). [27] A cost-effectiveness analysis was performed for patients with OA and PPSP separately. The base case analysis was performed from a societal perspective and a time horizon of 12 months.

Health outcomes

The quality-adjusted life years (QALY) was chosen as the measure of benefit of the cooled and conventional RF intervention. The QALY is the preferred health outcome in economic evaluations and is a combined measure of health-related quality of life (HRQoL) and survival.[28] HRQoL was measured by the EQ-5D-3L. [29] The EQ-5D-3L is a patient-reported generic measure of HRQoL comprising five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels reflecting the severity of the impact of the patient experiences. The patient's responses were converted to utility scores using the Dutch social tariff. [30] Subsequently, QALYs were calculated using the area under the curve of the time in which a certain health state was, multiplied by the utility score of this health state. The EQ-5D was completed electronically at 1, 3, 6 and 12 months after treatment.

Resource use and costs

Resource use was classified in four main categories: RF intervention costs, health care resource use, costs for patients and family, and productivity costs. The cost of the RF interventions was calculated as the sum of the cost of a day hospitalisation, the costs of the used material and the cost of the medical personnel. Health care resource utilisation included health care related visits (e.g., general practitioner, physiotherapist, dietician), visits to other allied professionals (e.g., social worker), use of home care (home nursing care and family care), inpatient hospitalisations, and emergency department visits. Patient and family costs included out-of-pocket expenses made by the patient (e.g., for medication, braces) and informal care costs. Costs due to lost productivity included costs due to short- and long-term absence from paid and unpaid work.

Data on other health care utilisation, patient and family costs and costs due to loss of productivity were collected electronically using an adapted version of the iMTA Medical Consumption Questionnaire (MCQ) and the Productivity Cost Questionnaire (PCQ) at baseline, 3-, 6- and 12-months. [31, 32] The recall period for the PCQ and MCQ questionnaires was 4 weeks and 3 months respectively. The iMTA MCQ is a validated generic instrument for measuring resource use and includes questions on healthcare use e.g., consultation with health care professionals (medical doctor, general practitioner physiotherapist),

interventions, hospitalisations, and informal care and out of pocket expenses. The costs of healthcare use were calculated by multiplying the resource use by the price per unit of resource using Dutch reference prices. [27] The unit price in Euro for each cost category can be found in the supplementary file (Supplement S2). The reference year to which all costs have been adjusted for the analysis is 2021. As the follow-up period did not exceed 12 months, no discount rate was applied. Costs of medication use were calculated only based on the information the patients reported in the MCQ questionnaire and not linked to the MQS III score. The iMTA PCQ is designed and validated to assess productivity loss, by quantifying the hours of lost paid and unpaid work. Productivity costs were calculated using the friction cost method. [27]

Statistical analysis of HEA

Missing PCQ data were imputed based on paid work status at previous measurement and earlier/later responses (e.g., if a respondent did not have paid work at baseline and the PCQ was missing at 3 months, 0 costs were imputed). Other missing cost and effect data were imputed using multiple imputation using the mice package for R. [33] The imputation model included randomization, age, sex, and cost variables at other time points. Less than 5% of data was missing, hence 10 imputed datasets were generated.[34, 35] Since the MCQ and PCQ were not administered at 9-month follow-up, the mean costs of 6 and 12 months were used to calculate the total 12 months costs for each respondent. Each of the imputed datasets was analyzed separately and results were pooled using Rubin's rules.

Mean health care and societal costs and QALYs for the OA and PPSP subgroups acquired over the one-year study period were reported using descriptive statistics. [36] The mean differences in costs and effects between cooled and conventional RF were estimated using linear regression models, adjusted for baseline differences and confounders, where appropriate. [37] To address the uncertainty surrounding the differences in costs and effects, non-parametric bootstrapping with 5000 replications was used to estimate their 95% confidence intervals.[38] If appropriate, the deterministic incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in mean costs by the difference in mean QALYs between cooled and conventional RF. Non-parametric bootstrapping was used to plot the joint distribution of the difference in costs and QALYs in a cost-effectiveness plane, further exploring uncertainty. Finally, cost-effectiveness acceptability curves show the probability of the cooled RF being cost-effective compared with conventional RF for a range of ceiling ratios for a QALY. Ceiling ratios reflect the maximum price health policymakers are willing to pay for an additional QALY. In the Netherlands, the Council for Public Health and Health Care proposes an informal ceiling ratio between €20.000 and €80.000 per QALY, depending on the burden of disease. [39]

To assess the robustness of results, in addition to the base case analysis of the economic evaluation, additional analyses were performed: (1) an analysis from a health care perspective in which costs due to productivity loss and patient and family costs were excluded, and (2) an analysis with a short-term perspective (6 months). All analyses were performed in R Studio. The reporting of this economic evaluation follows the Consolidated Health Economic Evaluation Reporting Standards guidelines. [40]

Results

Participants

41 of the 49 included patients reported 12 months outcomes (10 in the OA conventional RF group, 11 in the OA cooled RF group, 8 in the PPSP conventional RF group and 12 in the PPSP cooled RF group). Figure 1 depicts the Consolidated Standards of Reporting Trials flow chart of participants during the trial up to 12 months. In the OA group 21 of 25 patients (84%) completed the study versus while 20 of 24 patients (83%) of the PPSP group completed the study. One patient in the PPSP cooled RF group had substantial missing data at 12 months follow-up, including the NRS. Between 6 and 12 months five additional patients dropped out. All randomized patients received the allocated treatment. There were no crossovers between the treatment arms. Baseline patient characteristics were presented in the previous publication. [11]

Effectiveness analysis

The evolution of the clinical outcomes during the 12-month follow-up is presented in Figure 2.

Percentage of pain reduction

At 12 months, the percentage of patients that reached ≥ 50% pain reduction compared with baseline was 22.2% (4/18) after a conventional RF, and 22.7% (5/22) after cooled RF (Table 1). In both OA and PPSP populations, the difference in percentage of patients that reached ≥ 50% pain reduction between cooled and conventional RF was not statistically significant. When using the recommended cut-off of ≥ 30% pain reduction by the IMMPACT guidelines, only the difference between conventional and cooled RF in the PPSP group was statistically significant (p=0.045). The other differences were not statistically significant.

Numerical Rating Scale

Whole population: cooled versus conventional RF

The mean pain reduction (ΔNRS) (95% CI) of all patients treated with cooled RF at 12 months compared with baseline was −1.4 (-2.5 to -0.7). This change over time was statistically significant (p = 0.018). The mean ΔNRS (95% CI) of all patients treated with conventional RF was −0.8 (-2.3 to 0.7). This change over time was not statistically significant (p = 0.29). The mean absolute NRS at 12 months did not differ significantly (p = 0.30) between cooled and conventional RF. The non-inferiority comparison between conventional and cooled RF was performed in the whole population due to the limited small sample size of this trial. The point estimate difference in NRS was 0.9 at 12 months with 95% CI (-0.8 to 2.6). This includes the non-inferiority margin of 0.75 making it inconclusive at this point (Figure 3).

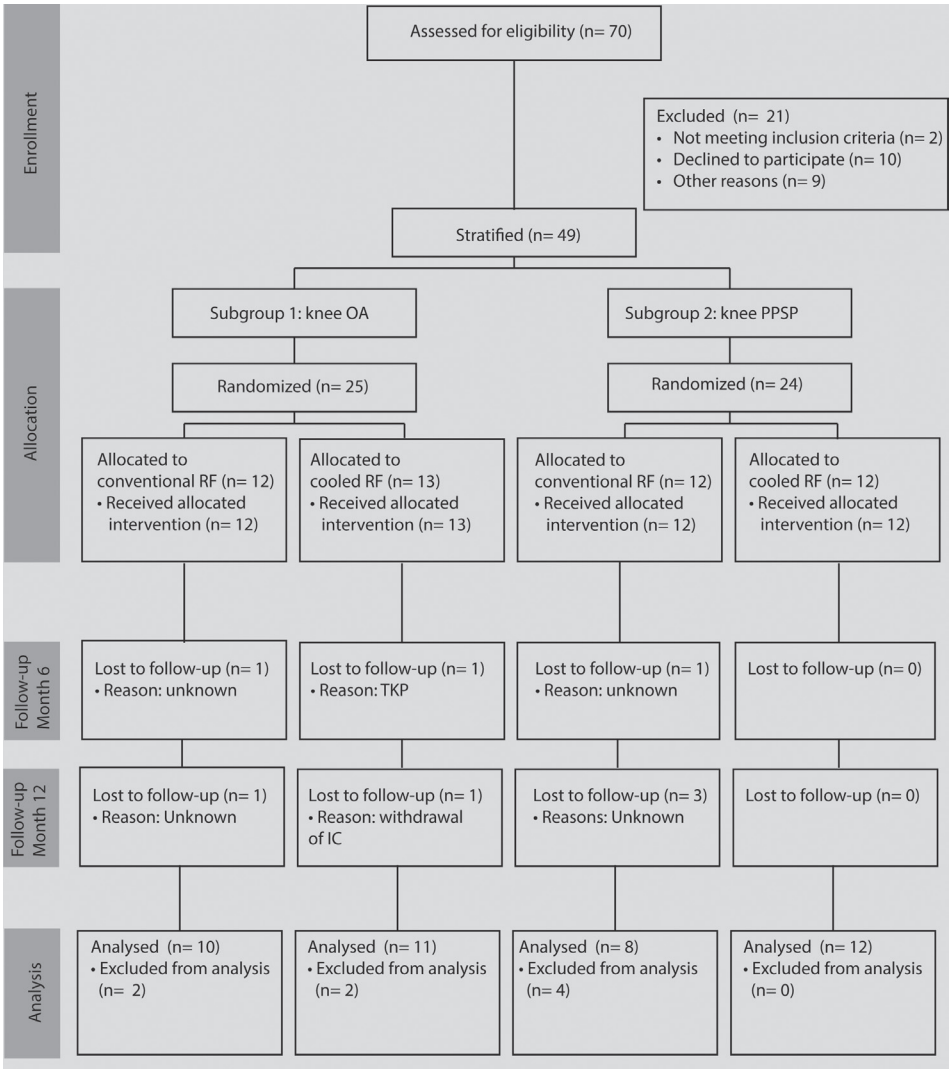


Figure 1 The Consolidated Standard of Reporting Trials flow chart of participants during the trial up to 12 months. IC, informed consent; OA, osteoarthritis; PPSP, persistent postsurgical pain; RF, radiofrequency, TKP, Total Knee Prothesis.

Table 1 The percentage of patients with ≥30% and ≥50% pain reduction after conventional and cooled RF at 12-months follow-up timepoints in each patient subgroup.

≥50% pain reduction compared with baseline	OA		
	Conv RF, n (%)	**Cooled RF**, n (%)	**P value***,†
6 months	3/11 (27.3)	4/12 (33.3)	1.00
12 month	4/10 (40)	3/11 (27.3)	0.66
≥30% pain reduction compared with baseline	**OA**		
	Conv RF,n (%)	**Cooled RF,**n (%)	**P value***,†
6 months	4/11 (36.4)	5/12 (41.7)	1.00
12 months	4/10 (40)	4/11 (36)	1.00

*P value compares conventional RF with cooled RF procedure.
†Pearson's $\chi 2$ test used to compare proportions.

Whole population: PPSP versus OA

The mean NRS of patients with PPSP decreased from 6.4 at baseline to 6.1 at 12 months. In these patients, the mean ΔNRS (95% CI) at 12 months compared with baseline was -0.6 (-1.8 to 0.6). This change over time was not statistically significant (p = 0.30). The mean NRS of patients with OA decreased from 5.8 at baseline to 4.2 at 12 months. In these patients, the mean ΔNRS (95% CI) at 12 months compared with baseline was -1.6 (-2.9 to -0.2). This change over time was statistically significant (p = 0.024). The mean absolute NRS at 12 months did not differ significantly (p ≥ 0.05) between patients with PPSP and OA.

Patients with PPSP: cooled versus conventional RF

In patients with PPSP treated with cooled RF, the mean ΔNRS (95% CI) at 12 months compared with baseline was -1.7 (-3.2 to -0.3). This change over time was statistically significant (p = 0.03). In patients with PPSP treated with conventional RF, the mean ΔNRS (95% CI) at 12 months compared with baseline was 0.9 (-0.9 to 2.7). This change over time was not statistically significant (p = 0.27). The mean absolute NRS at 12 months did differ significantly between conventional and cooled RF in patients with PPSP (p = 0.02).

Patients with OA: cooled versus conventional RF

In patients with OA treated with cooled RF, the mean ΔNRS (95% CI) at 12 months compared with baseline was -1 (-3 to 0.9). This change over time was not statistically significant (p = 0.26). In patients with OA treated with conventional RF, the mean ΔNRS (95% CI) at 12 months compared with baseline was -2.1 (-4.3 to 0). This change over time was statistically significant (p = 0.05). The mean absolute NRS at 12 months did not differ significantly between conventional and cooled RF in patients with OA (p = 0.41).

Other outcomes

In figure 2 we present the evolution of the other clinical effectiveness outcomes. The mean PGIC, OKS, EQ5-5D-3L, HADS depression subscale, HADS anxiety subscale, PCS, and MQS III of the conventional RF and cooled RF group were not statistically significantly different at 12 months follow-up. Mean scores of the other outcomes in the whole population at 12 months are presented per allocated RF treatment in online Supplementary S3.

Two patients with OA (one in the OA cooled RF group and one in OA conventional) underwent a TKA procedure between 6 and 12 months follow-up. One additional patient with PPSP treated with conventional RF was treated with corticosteroids and capsaicin patch in the index knee between the 6 and 12 months follow-up. No patient with PPSP underwent a revision or other surgical reintervention of the total knee prothesis.

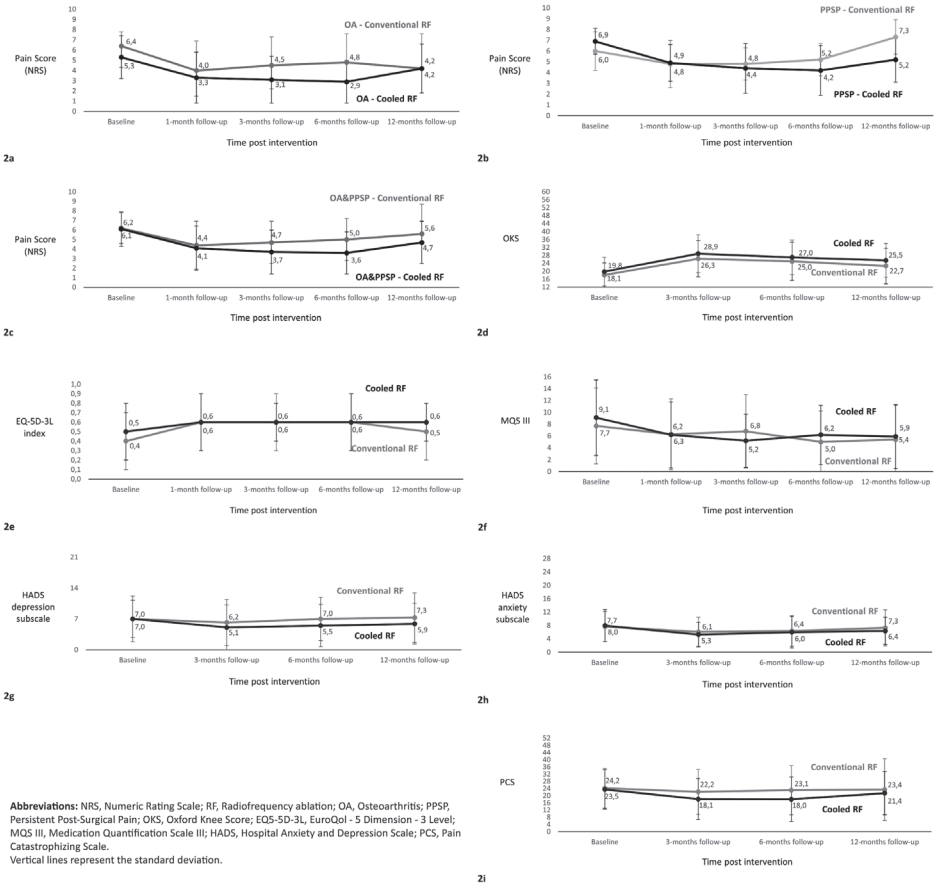
Safety analysis

There were no adverse events reported that were possibly or definitively related to the procedure at the 12 months of follow-up. The infrapatellar hypoesthesia reported after a cooled RF at 6 months did not persist at 12 months.

Health-economic analysis

Participants

23 patients were included and analyzed in the PPSP subgroup and 24 in the OA group. The distribution of included patients in Belgium and the Netherlands was, respectively, 32 and 15. One patient with OA treated with cooled RF and one patient with PPSP treated with conventional RF were excluded from the analysis as no data was collected on resource use and costs at any of the follow-up moments. We present in online supplemental file S4 the baseline patient characteristics of the analyzed population.



Abbreviations: NRS, Numeric Rating Scale; RF, Radiofrequency ablation; OA, Osteoarthritis; PPSP, Persistent Post-Surgical Pain; OKS, Oxford Knee Score; EQ5-5D-3L, EuroQol - 5 Dimension - 3 Level; MQS III, Medication Quantification Scale III; HADS, Hospital Anxiety and Depression Scale; PCS, Pain Catastrophizing Scale.
Vertical lines represent the standard deviation.

Figure 2 Evolution of the clinical outcomes during the 12-month follow-up of the COCOGEN trial. Vertical lines represent the standard deviation. NRS, numerical rating scale; RF, radiofrequency; OA, osteoarthritis; PPSP, persistent postsurgical pain; OKS, Oxford knee score; EQ-5D- 3L, EuroQol 5-dimension 3-level; MQS III, Medication Quantification Scale III; HADS, Hospital Anxiety and Depression Scale; PCS, Pain Catastrophizing Scale.

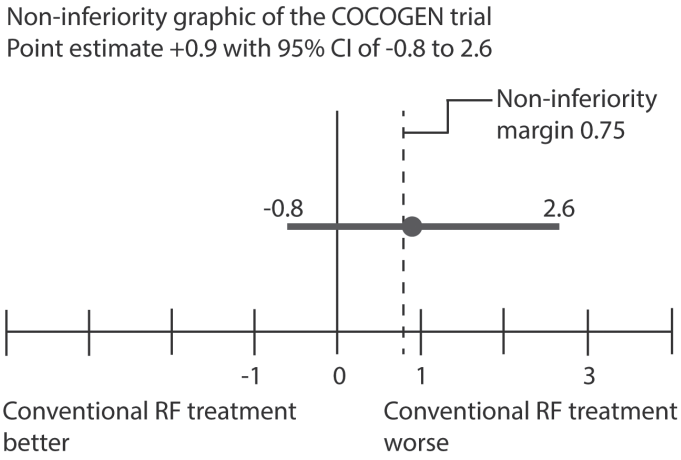


Figure 3 Non-inferiority graphic of the COCOGEN trial.

Health care use

Costs from societal perspective for each subgroup at 12 months are outlined in Table 2. In PPSP, the two highest contributors to the considerably higher societal costs in the conventional RF group compared with cooled RF were the health care costs and the costs for patients and family (i.e., out of pocket expenses and informal care costs). In the OA group, all three categories (health care costs, costs for patients and family and productivity costs) contributed to the higher total societal costs of the cooled RF group compared with conventional RF.

Cost-utility analysis

In the PPSP group at 12 months after treatment, the difference between the mean QALYs estimated between cooled RF and conventional RF favoured cooled RF. At 12 months the patients with PPSP treated with cooled RF had fewer total costs with a higher gain in QALYs compared with the conventional RF group. Hence, cooled RF is the dominant treatment and no ICER was calculated. In the OA group at 12 months after treatment, the difference in QALY between the cooled and conventional RF groups favoured conventional RF (Table 2). At 12 months, the patients with OA who were treated with cooled RF had more total costs with a lower gain in QALYs compared with the conventional RF group. As a result, cooled RF is inferior to conventional RF.

The bootstrapped estimates of incremental costs and QALYs are aggregated in the cost-effectiveness plane and represent uncertainty surrounding the cost and effect differences (Figure 4). The majority of the data points in patients with PPSP cover the southeast quadrant indicating that when taking statistical uncertainty into account, cooled RF generates more health gains at lower costs, while most of the data points in the OA population cover the northwest quadrant indicating that cooled RF generally generates poorer health outcomes at higher costs. As a results, in PPSP, cooled RF is highly likely to be cost-effective, while in OA, cooled RF has a very low probability of being cost-effective in comparison with conventional RF at any willingness-to-pay threshold as visualised in the cost-effectiveness acceptability curves (Figure 5).

Sensitivity analysis

The cost-utility analysis from the healthcare perspective (i.e., excluding productivity costs and costs to patient and family) in the OA population showed that the difference in costs between cooled and conventional RF is substantially lower at 12 months compared with the societal perspective (Table 2). Similarly, the cost-saving potential of cooled RF in the PPSP population is lower. However, the final results of the analyses (i.e., whether the treatment was likely to be cost-effective) were unchanged.

The results from the 6-month analysis are available in online supplemental file S5 and are congruent to the conclusions reached during the 12-month analysis.

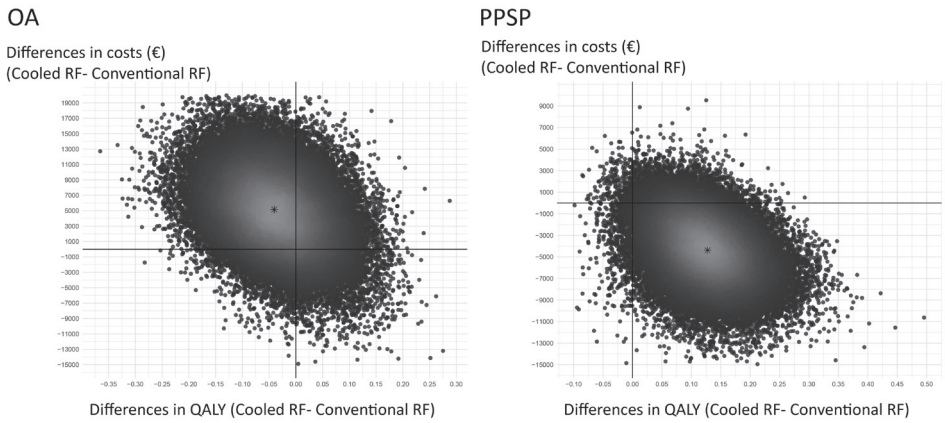


Figure 4 The incremental cost-effectiveness planes for the osteoarthritis and persistent postsurgical pain population representing the cost difference (€) and differences in quality-adjusted life year estimated using EuroQol 5-dimension 3-level between cooled and conventional radiofrequency at the 12-month time point. OA, osteoarthritis; PPSP, persistent postsurgical pain; RF, radiofrequency ablation; QALY, quality-adjusted life year.

Table 2 Effectiveness outcomes and costs (€) presented per subgroup (OA and PPSP) and per RF modality after multiple imputation, based on 10 imputed datasets.

Outcomes for the OA group at 12 months after treatment		
Outcomes	Mean (SE)	
	Conventional RF	Cooled RF
QALY	0.604 (0.004)	0.558 (0.002)
Total Health care related costs	3405 (64)	4528 (125)
Costs for patients and family	1018 (44)	3391 (85)
Productivity costs/loss	3881 (0) †	6254 (0) †
Total Societal costs	8303 (60)	14173 (159)
Outcomes for the PPSP group at 12 months after treatment		
Outcomes	Mean (SE)	
	Conventional RF	Cooled RF
QALY	0.516 (0.002)	0.690 (0)
Total Health care related costs	4313 (216)	2499 (62)
Costs for patients and family	2894 (67)	666 (30)
Productivity loss	3270 (0) [a]	2286 (0) [a]
Total Societal costs	10477 (204)	5451 (62)

Costs for each category were summed and the mean difference was calculated. The sample size analyzed per subgroup was as follows: OA conventional RF (n=12), OA cooled RF (n=12), PPSP conventional RF (n=11), PPSP cooled RF (n=12).

*The uncertainty expressed in 95% CI around the mean costs and effects in each subgroup is calculated using non-parametric bootstrap simulations with 5000 replications. Measurements are adjusted for baseline differences in EQ-5D index and costs (healthcare costs, patient and family costs, productivity costs, and total societal costs, respectively).

	Unadjusted mean difference (95% CI) *	Adjusted mean difference (95% CI)*
	-0.046 (-0.227 to 0.134)	-0.040 (-0.187 to 0.106)
	1123 (-2126 to 4372)	371 (-2627 to 3369)
	2373 (-600 to 5346)	876 (-839 to 2590)
	2373 (-5266 to 10012)	2494 (-5544 to 10531)
	5860 (-3313 to 15052)	5145 (-4485 to 14776)

	Unadjusted mean difference (95% CI) *	Adjusted mean difference (95% CI) *
	0.174 (0.014 to 0.334)	0.128 (0.008 to 0.247)
	-1814 (-4711 to 1083)	-1961 (-4848 to 925)
	-2228 (-4518 to 62)	-2002 (-4268 to 258)
	-984 (-4258 to 2290)	-366 (-3680 to 2948)
	-5026 (-11022 to 970)	-4376 (-10124 to 1372)

†These values have a SE of 0 since missing data in productivity costs were imputed separately before the multiple imputation procedure. OA, osteoarthritis; PPSP, persistent postsurgical pain; QALY, quality-adjusted life year; RF, radiofrequency.

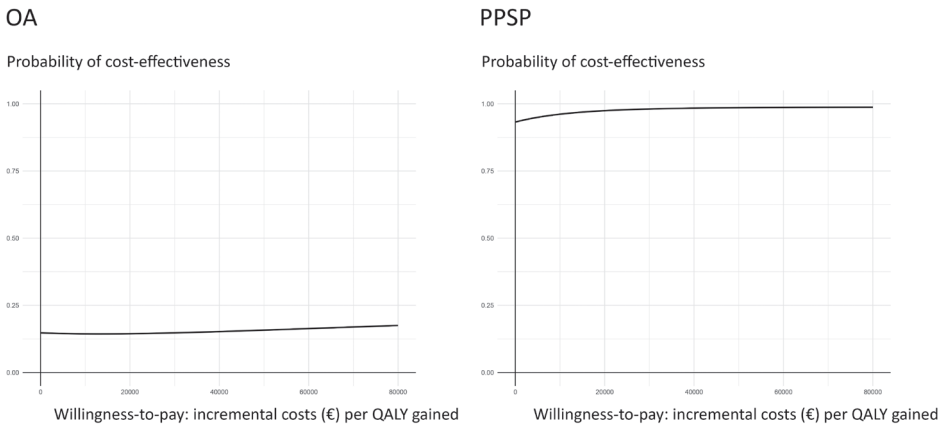


Figure 5 The cost-utility acceptability curve for cooled radiofrequency (RF) compared with conventional RF in the osteoarthritis and persistent postsurgical pain population at 12 months. OA, osteoarthritis; PPSP, persistent postsurgical pain; RF, radiofrequency; QALY, quality-adjusted life year.

Discussion

The 12-month data of the COCOGEN trial revealed no difference in treatment success (around 22%) between cooled and conventional RF in patients with chronic knee pain when treatment success is defined as pain reduction of ≥ 50%. In the OA and PPSP group separately, treatment success was not significantly different between the two RF modalities. In patients with OA, treatment success was higher (33.3%) than in the PPSP group (10.5%). Remarkably, in patients with OA, treatment success was higher at 12 months compared with 6 months possibly reflecting an artifact from the small sample size of this trial or a more fluctuating course of pain in patients with OA. In patients with PPSP, treatment success diminished at 12 months in comparison with the 6-months results. When treatment success was defined as ≥ 30% pain reduction, there was also no significant difference between a conventional RF (22.2%) or a cooled RF (40.9%) in the whole population. In each population separately, the difference was more pronounced in the PPSP group. While there was no significant difference between conventional or cooled RF in patients with OA, this difference was statistically significant in patients with PPSP (0% treatment success after conventional RF, whereas 45% treatment success after cooled RF). Furthermore, only in patients with PPSP, there was a statistically significant reduction of the absolute NRS score after cooled RF (1.7 point decrease), whereas this was not the case after conventional RF (0.9 point increase). A possible explanation could be that in PPSP, patients' anatomy is changed due to the total knee replacement in comparison with patients with OA probably resulting in more anatomical variability. Therefore, cooled RF, which creates a bigger lesion, could be more effective than conventional RF in PPSP. Another possible explanation could be that in the different populations the etiology of pain is different. In a postoperative state, it seems logical that neuropathic pain dominates over nociceptive pain. [8, 41, 42] Other alternative strategies to improve treatment success include targeting more than three genicular nerves. At the moment, most studies target three nerves as originally described by Choi et al. but the optimal number of nerves to target should be further identified. [16, 43, 44]

In the cost-effectiveness analysis of the COCOGEN trial, we found that in the PPSP group, cooled RF resulted in a small gain in QALYs at 12 months compared with conventional RF. This was accompanied by a cost-saving potential when cooled RF was performed compared with conventional RF. In the OA group, however, cooled RF resulted in lower QALYs at 12 months and higher costs compared with conventional RF. The high societal costs in the OA group receiving cooled RF may be explained by their poorer health (i.e., quality of life) post-treatment, compared with conventional RF, and this may lead to a higher level of care use and productivity loss, and thus

higher societal costs. Despite the limited number of patients included in this analysis, the findings of this trial indicate that cooled RF is likely to be cost-effective in the PPSP population but not in the OA population at decision-making thresholds used in the Netherlands.

Similar to the findings of other trials in the OA population, the NRS in the COCOGEN trial changed in a statistically significant manner when compared with baseline after cooled RF up to 12 months; however, the effect of cooled RF did not lead to a significant increase in the OKS score. [45, 46] Our findings are also in line with the results of the study of Santana et al. where the effectiveness of the conventional RF seemed to diminish at 12 months resulting in higher NRS scores.13 Our data reflected a similar evolution after cooled RF, even though these differ from the results from Davis et al. where treatment effect remained stable up to 12 months. [45]

A single trial by Qudsi-Sinclair et al. reported long-term data of conventional RF in patients with PPSP up to 12 months. [47] The NRS change in the trial by Qudsi-Sinclair and the COCOGEN trial were congruent. The NRS decrease from baseline after conventional RF in the COCOGEN trial and in the trial of Qudsi-Sinclair et al. is followed by a progressive increase in NRS from 6 to 12 months.

To date, a single economic evaluation has been published on RF of the genicular nerves. Desai et al. performed a trial-based cost-effectiveness analysis comparing cooled RF to intra-articular steroid injections in patients with OA which strongly favored cooled RF. [15] When compared with Desai et al., the OA population in our trial has similar baseline OKS scores and an equivalent EQ-5D index. In contrast to Desai et al., however, we found that the improvement in EQ-5D utility after cooled RF was much smaller in OA and that health care costs, costs to patient and family, and productivity losses were higher, resulting in a high likelihood that cooled RF is not cost-effective in OA compared with conventional RF. These two trials have several methodological differences: Desai et al. included health care costs only and used a mapping analysis to calculate EQ-5D utility based on the OKS. Generally, the disease-specific OKS is more sensitive to health changes in the OA population than the generic EQ-5D, which may explain the larger QALY gain.

No adverse events developed after both a conventional or a cooled RF at 12 months supporting the long-term safety of both treatments. Secondary outcomes including quality of life (EQ-5D-3L), emotional health (HADS and PCS), and medication use did not change in a statistically significant manner between cooled and conventional RF up to 12 months.

Currently, there is an increase in research on RF of the genicular nerves and growing evidence that different RF modalities are effective. A comparison of the long-term effects of these interventions in relation to their costs is becoming imperative for the incorporation of this intervention in chronic knee pain decision-making algorithms to guide the optimal allocation of the available healthcare resources. As mentioned previously there is a limited number of trials that evaluate 12 months or longer follow-up of patients undergoing RF of the genicular nerves, and there are no prospective trials comparing cooled to conventional RF up to 12 months published until present. [13, 45-48]

One of the main strengths of this trial is that it is designed in a pragmatic manner increasing the external validity of the results. Furthermore, this is the first published health economic analysis from societal perspective comparing cooled and conventional RF in patients with therapy-resistant chronic knee pain. Despite this, no decisive conclusion can be derived based on these results due to the intrinsically small sample size of this pilot trial. This was evident in the effectiveness outcomes and subsequently in the health economic analysis resulting in increased uncertainty surrounding the outcomes. While bootstrap analyses can overcome some statistical uncertainty, results must be interpreted with caution due to the very small number of patients in each subgroup (OA and PPSPS) and highly skewed nature of cost data. A second limitation of this study was the systematic unblinding after 6 months of follow-up, which may have had an influence on subjective outcome measures taken after unblinding. Thirdly, the COCOGEN study was performed in Belgium and The Netherlands– encompassing two different health systems. There may be some differences in access to first-line and second line care; however, cost prices are similar in both countries. Moreover, results are presented from both the societal and health care perspective, in line with Dutch and Belgian guidelines, respectively. Fourthly, in this trial we did not include all costs of analgesics. Since we did not see meaningful differences in medication use on the Medication Quantification Scale Version III score, we do not expect this to have influenced the trial findings. Inclusion of all costs of analgesics is however recommended in a future trial.

The COCOGEN trial was primarily designed as a pilot trial to guide further research. Future studies should be sufficiently powered for between-group comparisons with inclusion of a sham procedure and a long follow-up to prove effectiveness of the current technique and should include the collection of resource use and quality of life data to perform a cost-effectiveness analysis. At the moment, the COGENIUS trial (NCT05407610) is being conducted. [49] This is a powered trial that aims to compare conventional and cooled RF with a sham procedure in OA and PPSP with two years follow up.

Conclusions

In conclusion, the COCOGEN study showed that RF of the genicular nerves is safe and can result in ≥ 50% pain reduction in approximately 22% of patients with chronic knee pain at 12 months. In patients with PPSP, contrary to OA, cooled RF seems to be more effective and cost-effective than conventional RF. Larger powered trials with inclusion of a sham procedure and long follow up should be conducted to support these finding.

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Contributors

Both AB and TV are co-first authors. TV acts as guarantor of overall content. All authors have contributed substantially to the manuscript and agree with the content.

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Competing interests

None declared.

Patient consent for publication

Not applicable.

Ethics approval

This study involves human participants. Ethical approval was granted from the ethical committees of Hospital Oost-Limburg (19/0038U) and Maastricht UMC+ (NL69877.068.19/METC 19-031). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data are available on reasonable request.

Supplemental material

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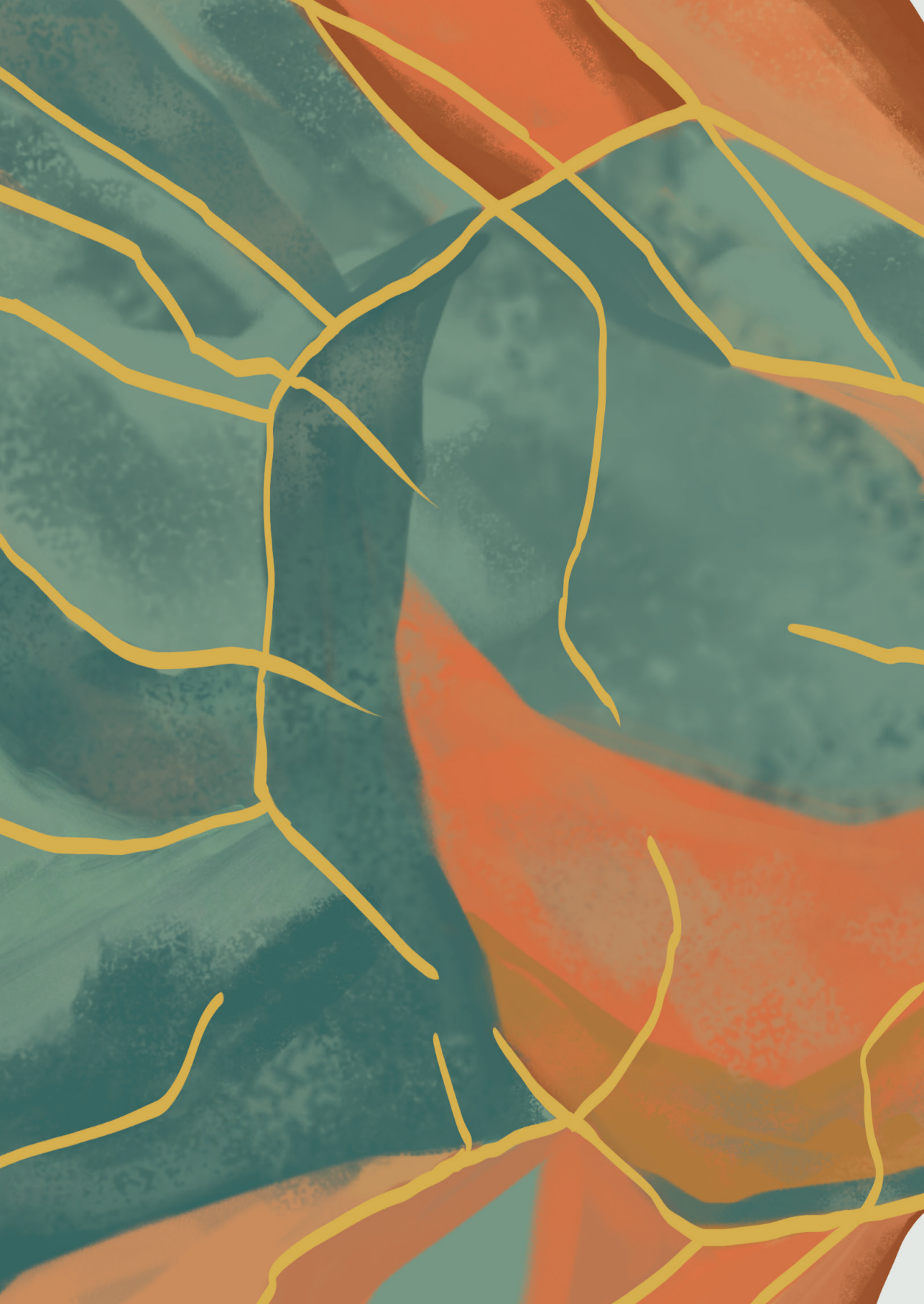
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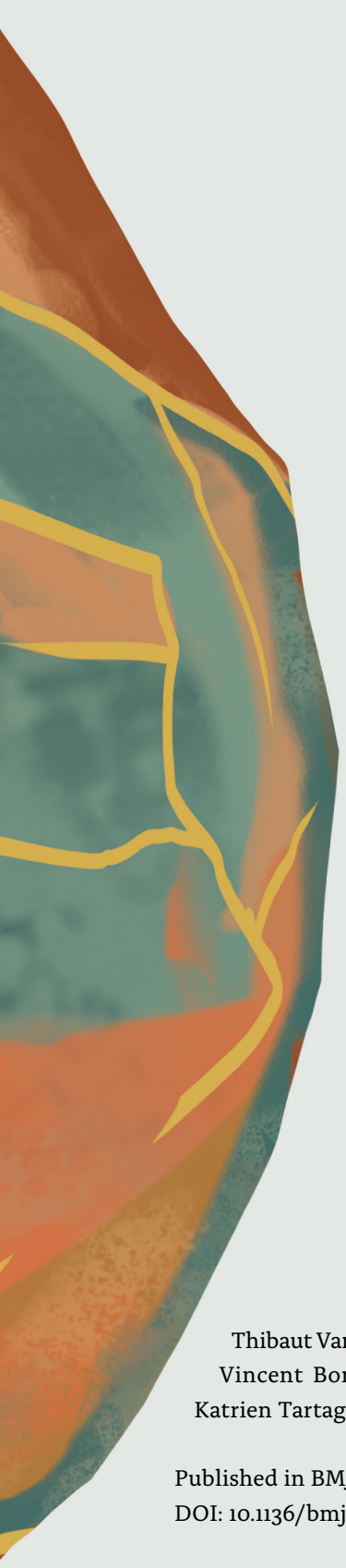
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CHAPTER 7

Comparison of conventional and cooled radiofrequency treatment of the genicular nerves versus sham procedure for patients with chronic knee pain:

protocol for a multicentre, double blind, randomised controlled trial. (COGENIUS)

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Abstract

Introduction

The prevalence of chronic knee pain is increasing. Osteoarthritis (OA) and persistent postoperative pain (PPSP) are two important causes of knee pain. Chronic knee pain is primarily treated with medications, physiotherapy, life-style changes and intra-articular infiltrations. A radiofrequency treatment (RF) of the genicular nerves is a therapeutical option for refractory knee pain. This study investigates the effectiveness and cost-effectiveness of conventional and cooled RF in patients suffering from chronic, therapy resistant, moderate to severe knee pain due to OA and PPSP.

Methods and analysis

The COGENIUS trial is a double-blinded, randomised controlled trial with two-year follow-up. Patients and outcome assessors are blinded. Patients will be recruited and treated in Belgium and the Netherlands. All PPSP after a total knee prothesis and OA patients (grade 2-4) will undergo a run-in period of 1-3 months where conservative treatment will be optimised. After the run-in period, 200 patient per group will be randomised to conventional RF, cooled RF or a sham procedure following a 2:2:1 ratio. The analysis will include a comparison of the effectiveness of each RF treatment with the sham procedure and secondarily between conventional and cooled RF. All comparisons will be made for each indication separately. The primary outcome is the Western Ontario and McMaster Universities Osteoarthritis Index score at 6 months. Other outcomes include knee pain, physical functionality, health-related quality of life, emotional health, medication use, healthcare and societal cost and adverse events up to 24 months post-intervention.

Ethics and dissemination

Ethics approval was obtained from the Ethics Committee of the University of Antwerp (Number Project ID 3069 - Edge 002190 - BUN B3002022000025), the Ethics committee of Maastricht University (Number NL80503.068.22 - METC22-023) and the Ethics committee of all participating hospitals. Results of the study will be published in international peer-reviewed journals.

Trial registration number NCT05407610

Strengths and limitations of this study

1. The COGENIUS trial is a powered, double-blind, multicentre, randomised controlled trial.
2. Both cooled and conventional radiofrequency treatments will be compared to a sham procedure.
3. Another strength is that a cost-effectiveness analysis will be performed.
4. All patients will undergo a run-in period of 1-3 months where all recommended conservative treatments for chronic knee pain will be optimised.
5. A limitation of the trial is that the follow-up is limited to 2 years after treatment.

Introduction

Chronic knee pain, defined as knee pain that persists or recurs for more than 3 months, is an increasing cause of pain and disability worldwide. (1–4) The main cause of chronic knee pain is osteoarthritis (OA) of the knee. (4,5) Therapy resistant knee pain after a surgical intervention on the knee, otherwise named persistent postsurgical pain (PPSP), is another important cause of chronic knee pain. (6,7)

Knee OA is a progressive degenerative disease, commonly diagnosed in adults over 50 years of age, that leads to pain, stiffness, and loss of function of the joint.(8) The lifetime prevalence of OA is increasing due to the aging of the population and an increase in obesity, which are well-known risk factors. (8–10) Due to lack of disease-modifying drugs, the cornerstone of care for OA is conservative treatment. (9,11–13) This includes non-pharmacological care (education, lifestyle changes, exercise programs, weight management), pharmacological care (non-steroidal anti-inflammatory drugs, paracetamol, duloxetine) and/or intra-articular (IA) infiltrations with corticosteroids or hyaluronic acid. (12,13) Unfortunately, conservative care for knee OA is often insufficient or associated with side effects. Around 50% of patients who are first diagnosed with symptomatic knee OA is estimated to eventually undergo a total knee arthroplasty (TKA) in their lifetime.(14) Despite being an effective procedure, up to 20% of patients after primary TKA express dissatisfaction and experience moderate to severe PPSP. (6,7,15,16) Similar to OA, treatment of PPSP is symptomatic and limited to non-interventional conservative care. (6,7) The disease burden of patients with knee OA pain and PPSP refractory to conservative care is high and leads to sleeping disorders, psychological distress, and a diminished quality of life. (17–19)

This underlines the need for improvement in treatment strategies for OA and PPSP. Growing research on a radiofrequency (RF) treatment of the genicular nerves, points to the potential of this treatment for patients with therapy resistant OA and PPSP. (20,21) A RF treatment blocks the transmission of painful stimuli from the sensory genicular nerves of the knee to the central nervous system by means of a thermal lesion created using RF current. (20,21) Since the first report on RF of the genicular nerves by Choi et al. in 2011, the procedure has evolved to target the genicular nerves more accurately. Furthermore, different RF modalities have been introduced to clinical practice aiming to increase the effectivity of the treatment. (20,22,23) Conventional and cooled RF are the two most used RF modalities. Recent systematic reviews report that conventional RF treatment of the genicular nerves is an effective, well-tolerated and safe procedure in knee OA. (24–27) At the moment, literature on RF for knee PPSP is scarcer. (28) Furthermore, retrospective and pilot studies indicate a possible larger

effectivity of cooled RF compared to conventional RF on knee pain. However, these have not been directly compared in powered prospective studies in both the OA and PPSP population. (29,30) Comparison of RF to a sham procedure is only tested in the relative small study of Choi et al. (31) Confirmation of superiority of RF treatment over a sham procedure in a larger trial is essential for the incorporation of a RF treatment in the clinical treatment algorithm for chronic knee pain.

To address to above-mentioned research questions, we aim to conduct a powered, randomised controlled trial that compares the effectivity of cooled RF versus conventional RF versus a sham procedure in patients with chronic knee pain because of therapy resistant OA or PPSP after a TKA. Our hypothesis is that cooled RF is superior to conventional RF and that both RF treatments are superior to a sham procedure in both populations at 6 months after intervention. Other objectives are to further determine the effects of the cooled RF versus conventional RF versus sham procedure up to 24 months in terms of pain reduction, physical functioning, medication use, other patient-reported outcomes and side effects of the performed interventions, and the cost-effectiveness.

Methods and analysis

Study design

The COGENIUS study is a three-arm, pragmatic, prospective, multicentre, double-blind (participant- and assessor-blinded), randomised sham-controlled trial of estimated 4 years' duration. Four hundred patients with chronic moderate to severe anterior knee pain refractory to conventional treatments, 200 with knee OA and 200 with PPSP, will be included and followed up for a period of 24 months. Participants will be recruited and treated in 13 hospitals in Belgium and 2 hospitals in the Netherlands. Each patient will undergo a run-in period of 1-3 months to guarantee that conservative treatment is maximally carried out in all patients. Stratified per group (OA and PPSP), participants who fulfil the inclusion criteria after the run-in period will be randomly allocated to a conventional RF intervention, a cooled RF intervention or a sham procedure following a 2:2:1 ratio. Patients will be encouraged to continue usual care during the study. During follow-up, patients will not be actively offered a repeat intervention. However, a repeat RF intervention will be allowed after the completion of the primary endpoint at 6 months as part of usual care. Figure 1 depicts the schematic flow of the patients in the COGENIUS trial. The study will follow the Standard Protocol Items Recommendations for Interventional Trials and the Consolidated Standards of Reporting Trials. (32,33) Design of the COGENIUS trial was preceded by a pilot trial, the COCOGEN study, comparing cooled to conventional RF in the OA and PPSP population. (29)

Participants and recruitment

Potential participants for the study will be identified by pain physicians in hospital centres after primary identification and referral from general practitioners, rheumatologists, orthopaedic surgeons, rehabilitation physicians, and other pain physicians. The recruiting physicians will be informed about the study by means of information leaflets and scientific meetings. The potential participants will be screened by a researcher based on the inclusion and exclusion criteria presented in Table 1. Before inclusion in this trial, PPSP patients are required to have undergone a negative orthopaedic work-up. This constitutes an orthopaedic visit where mechanical prosthetic problems, joint infection, inflammatory or allergic response to implanted material, and nerve damage are excluded. All assessments necessary for inclusion are performed as standard of care. After the acquirement of the informed consent (see supplementary documents 1 -3), the eligible patients will be enrolled in the run-in period.

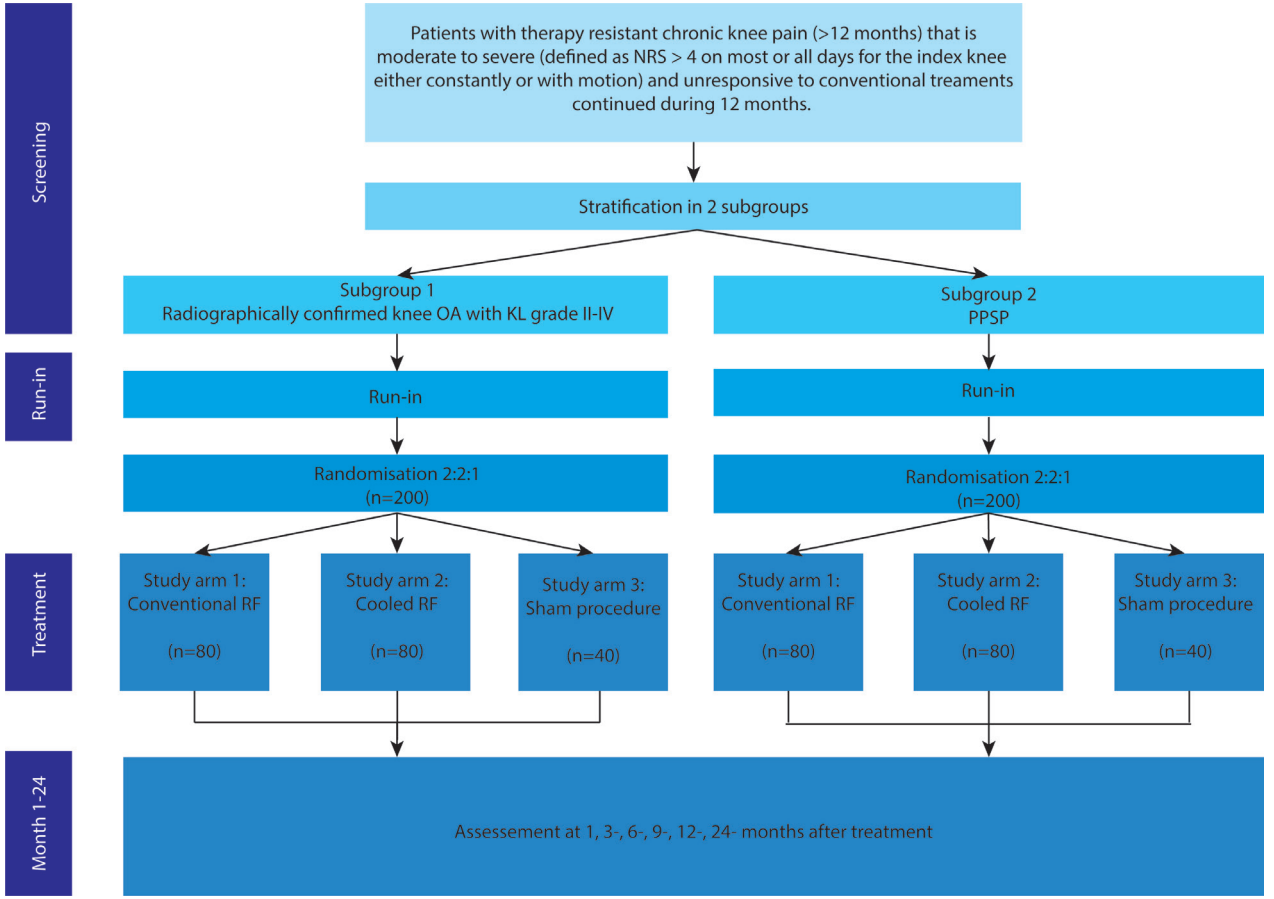


Figure 1 Schematic flow of the design of the randomised study comparing cooled RF to conventional RF to a sham procedure. KL, Kellgren-Lawrence; NRS, Numerical Rating Scale; OA, osteoarthritis; PPSP, osteoarthritis; RF, radiofrequency.

Table 1 The inclusion and exclusion criteria used in the COGENIUS trial.

Inclusion criteria	**Exclusion criteria**
Adult patients (Age ≥ 18 years old).	Local or systemic infection (bacteraemia).
Chronic anterior knee pain (> 12 months) that is moderate to severe (defined as NRS > 4 on most or all days for the index knee either constantly or with motion at time of screening and, an average NRS score reported in the patient diary >4 at the end of the run-in period).	Evidence of inflammatory arthritis or an inflammatory systemic disease responsible for knee pain.
Unresponsive to conventional treatments ongoing for at least 12 months prior to inclusion	Intra-articular injections (steroids, hyaluronic acid, platelet enriched plasma, …) in the index knee during the 3 months prior to procedure.
Only for knee OA patients: Radiologic confirmation of osteoarthritis of Kellgren-Lawrence grade 2 (mild), 3 (moderate) or 4 (severe)	Pregnant, nursing or planning to become pregnant
Only for patients with PPSP after TKA: a negative orthopaedic work-up.	Previous diagnosis of Chronic widespread pain. Patients with unstable psychosocial disorder. Allergies to lidocaine, propofol, chlorhexidine. Uncontrolled coagulopathy. Uncontrolled immune suppression. Patient is currently implanted with a neurostimulator. Current radicular pain in index leg. Previous conventional or cooled radiofrequency of the index knee. Bilateral knee pain Patients who have a planned TKA in the near future Patients who are unwilling or mentally incapable to participate Participating in another clinical trial

NRS, Numerical Rating Scale; OA, osteoarthritis; PPSP, persistent postsurgical pain; TKA, total knee arthroplasty.

The run-in period

A run-in period of approximately 1- 3 months depending on the specific needs of the patient is planned to optimise the conservative care of the patients enrolled in the trial.

The run-in period includes education on OA or PPSP, physiotherapy following a standardised physiotherapy prescription, dietary weight management with possible referral to a dietician, self-efficacy and self-management programs in patient organisations, use of gait aids and optimisation of the pharmacological treatment. All patients will be required to have undergone treatment with the following medication for the knee pain before or during the run-in period if not medically contraindicated: topical & oral NSAIDs, paracetamol, tramadol, and duloxetine. At the end of the run-in period, the success of conservative treatment will be evaluated. The participant will proceed to the randomisation and study intervention phase if the mean NRS of the participant is >4 during the 4 days prior to the run-in evaluation contact. Baseline measurements will be gathered by a researcher.

Randomisation
Patients will be randomised on the day of study intervention through the CASTOR EDC application after stratification following the aetiology of pain into the OA or PPSP group. CASTOR is a web-based software designed for randomisation and data collection during clinical trials that protects the privacy of the participants, conforming to all applicable medical data privacy laws and regulations (GCP, 21 CFR Part 11, EU Annex 11, the European Data Protection Directive, ISO9001, and ISO27001/NEN7510). Patients will be assigned in a 2:2:1 ratio to receive either conventional RF intervention of the genicular nerves, cooled RF intervention of the genicular nerves or sham procedure.

Blinding
The COGENIUS study is designed as a double-blind study: the participants and the outcome assessor will be blinded to the intervention group. The intervention team (pain physician performing the RF/sham intervention and the assisting nurse) will be the only persons that are aware of the allocation group. Special attention was given to the uniformisation of the procedure during the administration of the three study interventions. Therefore, all three interventions will be performed in the same operating room, using similar monitoring and patient positioning, similar vertical drape to hinder the vision of the patient, the communication with the participant will be similar, the length of procedure and the auditory information the participant will hear, will also be similar. Patients will not be systematically unblinded. Unblinding will be possible in case of a valid safety reason or after the termination of the study at 24 months postprocedure.

The blinding of each patient enrolled in this study will be tested at 1 month after randomisation. Patients will be asked to provide their "best guess" of the intervention allocation and to provide the confidence level of their guess (a five-point scale ranging

from “Not at all” to “Extremely”). The success of blinding will be measured using a blinding index that ranges from –1 to 1 and measures the intervention-specific proportion of unblinded subjects considering the confidence in the guess. (33,34)

Interventions
All patients will be placed in a supine position on a fluoroscopy table with the index knee flexed and will be monitored with pulse oximetry. Sedation with propofol can be administered if considered necessary so that the patient is comfortable but and able to communicate and report the stimulation during the procedure adequately.

No diagnostic block is performed prior to the study intervention. The superomedial (SMG), the superolateral (SLGN) and the inferomedial (IMGN) genicular nerve will be targeted under sterile conditions using a high frequency linear ultrasound probe as depicted in Figure 2. (35)

For the SMGN, the transducer is placed in a coronal orientation over the medial side of the femur at the junction between the epiphysis and diaphysis of the femur. In case of visualisation of the SM genicular artery at this level just above the bony cortex, the RF cannula will be placed directly next to this artery, otherwise the target is just anteriorly to the adductor tubercle at the posterior side of the femur. After the out-of-plane entry point is determined, the skin and soft tissues are anesthetised with 1 ml lidocaine 2%. The cannula is inserted subcutaneously and the transducer is turned 90° into the transverse plane. The cannula is advanced anterior to posterior ‘in plane’ until contact is made with the bony cortex at the posterior half of the femur. A RF electrode is introduced in the cannula.

For the IMGN, the transducer is placed in a coronal orientation over the medial side of the distal knee to visualise the junction of the tibial medial epiphysis and diaphysis, the inferomedial genicular artery and the medial collateral ligament. In case the IM genicular artery is visualised below the medial collateral ligament and above the bony cortex, the RF cannula is targeted next to this artery, otherwise the physician will aim at the junction between the epiphysis and diaphysis under the medial collateral ligament. After the out-of-plane entry point of the needle is determined, the skin and soft tissues are anesthetised with 1 ml lidocaine 2%. The cannula is inserted subcutaneously, and the transducer is turned 90° into the transverse plane. The cannula is advanced anterior to posterior ‘in plane’ until contact is made with the bony cortex at the centre of the tibia. A RF electrode is introduced in the cannula.

For the SLGN, the transducer is placed in a coronal orientation over the lateral side of the proximal knee at the junction between the epiphysis and diaphysis. In case the SL genicular artery is visible, the RF cannula is aimed next to the artery, otherwise the posterior side of the junction between the epiphysis and diaphysis of the femur is the target point. The transducer is centred to this target point and consecutively turned 45° into an oblique view. After the 'in plane' entry point of the needle is determined, the skin and soft tissue are anesthetised with 1 ml lidocaine 2%. The RF cannula is inserted and advanced using an 'in plane' approach in the oblique plane until contact is made with the posterior side of the bony cortex of the femur. A RF electrode is introduced in the cannula.

After all three cannulas are positioned, their proximity to the genicular nerves is tested using sensory stimulation (50 Hz). Paraesthesia should be present at a threshold of less than 0.5 V. Additionally, motoric stimulation (2 Hz) should confirm the absence of fasciculations below 1 V. Before study treatment, the position of the cannulas is controlled using fluoroscopy. First, an AP view is made, and the needle tip should be at the junction between the diaphysis and the epiphysis in proximity of the bony cortex. Second, a lateral view is made where the needle tip should be within the two middle quarters of the tibia width for the inferomedial genicular nerve and within the posterior half of the femur width for the superomedial and superolateral genicular nerve. After confirmation of needle position 1 ml of lidocaine 2% is injected close to each genicular nerve with the exception of the sham procedure.

Conventional RF of the genicular nerves
A 100 mm long, 18G straight RF introducer and an electrode with a 10 mm active tip is used during conventional RF to apply 80°C at the tip during 90 seconds for each genicular nerve.

Cooled RF of the genicular nerves
A 100 mm long, 17G straight RF introducer and an 18 G cooled electrode with a 4 mm active tip is used during cooled RF to apply 60°C at the tip and on average 80°C in the targeted tissue during 150 seconds for each genicular nerve.

The sham procedure
Each genicular nerve will be similarly targeted with an 18-gauge introducer using ultrasound. Subcutaneous local anaesthetic (1 mL lidocaine 2% per entry point) will be administered before introducer. Probe placement and sensory and motor testing will be applied similar as above mentioned. The interventional team will simulate the acquisition of fluoroscopic images and also the RF treatment by using a recording of the sound of the working RF generator.

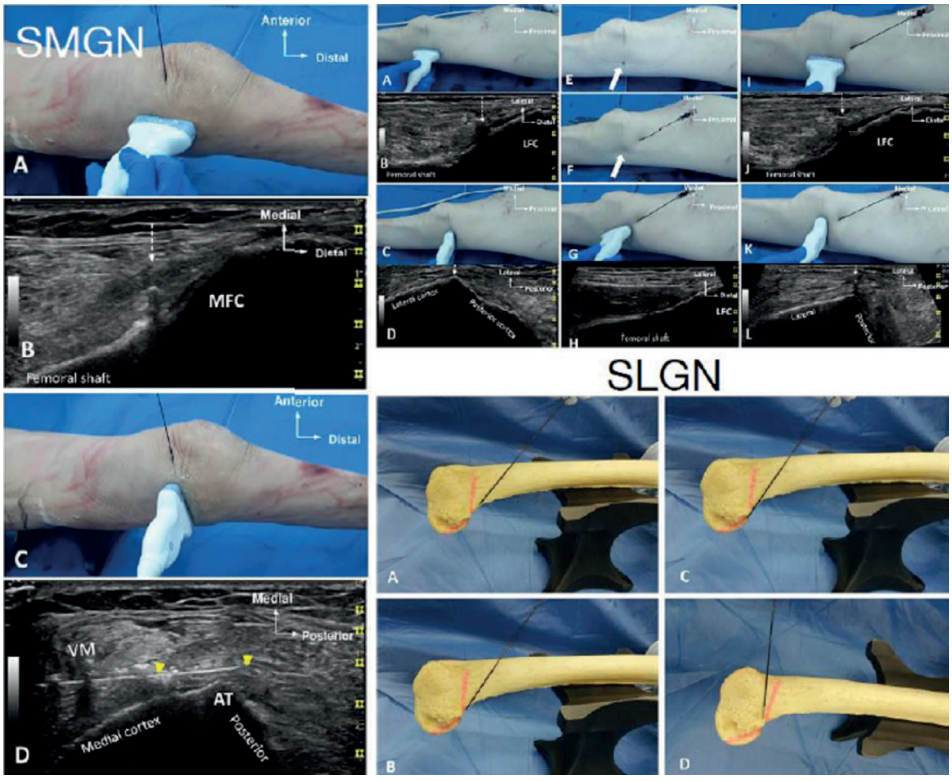


Figure 2 The ultrasound approach to target the SMGN and the SLGN. The procedure to target the IMGN is similar to the SMGN. The RF needle is marked with yellow arrows. The target point is marked with white arrows. (35) I%GN, inferomedial genicular nerve; RF, radiofrequency; SMGN, superomedial genicular nerve; SLGN, superolateral genicular nerve.

Outcome measures

The chosen primary and secondary outcomes are chosen based on the OMERACT-OARSI and IMMPACT core outcome guidelines. (36,37)

Primary outcome measures

The primary outcome is the total Western Ontario and McMaster Universities Osteoarthritis Index score (WOMAC) at 6 months postintervention. (38) The WOMAC score is derived from a self-administered OA-specific validated questionnaire on pain, stiffness, and physical functioning of the knee joint and ranges between 0 to 96 points with 96 indicating the highest possible disease burden. Per stratification, the WOMAC score of each RF groups will be compared to the score of the sham group and the WOMAC score of the cooled RF will be compared to the conventional RF group.

Secondary outcome measures

The secondary outcomes of the study are as follows: (1) the WOMAC score at 1-month, 3-month, 12-month and 24-month postintervention; (2) pain intensity assessed by the mean NRS (range 0-10) of the 4 days prior to each visit; (3) the proportion of patients with a pain reduction of at least 50% assessed by the NRS compared to baseline; (4) health-related quality of life assessed by the EuroQoL-5D-5L (EQ-5D-5L); (5) physical functioning assessed by goniometry by using the CJOrtho app, 'timed up and go' test and 6-min walk test; (6) mental health status assessed by the Hospital Anxiety and Depression Scale (HADS) and Pain Catastrophizing Scale (PCS); (7) Patient Global Impression of Change (PGIC); (8) patient's satisfaction assessed by 7-point Likert scale; (9) medication use measured by the Medication Quantification Scale III (MQS III); (10) opioid dependence and (11) the incidence of related adverse events (AE). (39–45) All the secondary outcomes will be measured and analysed at 1-month, 3-month, 6-month, 12-month and 24-month post-intervention. Extra information will be gathered on the EQ-5D-5L, MQS III, opioid dependence and related AE at 9 months after intervention for the health economic analysis. We defined certain AE of interest that will be systematically questioned. There are the following: postoperative pain (transient neuritis), infection, damage to collateral tissue (nervous tissue: e.g., deafferentation dysesthesia, paralysis; blood vessel: e.g., bruising or haematoma; ligaments: e.g., pes anserine damage; skin: for example, superficial burns), failure of technique and allergy.

Additionally, in order to perform the health economic analysis data will be gathered on health care resource utilisation (including adverse events, additional or reinterventions to the knee, pain medication, visits to a range of medical specialists and general practitioner visits) and productivity loss resulting from work absence and/or reduced labour input due to sickness assessed by the Work Productivity and Activity Impairment (WPAI) questionnaire at baseline and at 3-month , 6-month , 9-month , 12-month and 24-month postintervention. (46,47)

The analysis of these endpoints will be performed by means of the cross-sectional difference of the endpoints at 6, 12 and 24 months following the three comparisons similar to the primary endpoint (cooled RF versus sham, conventional RF versus sham and cooled versus conventional RF) and by means of an analysis of longitudinal changes for the whole follow-up of the study.

We chose to assess the proportion of patients with a pain reduction of at least 50% assessed by the NRS compared to baseline despite the fact that the IMMPACT guidelines recommend only a threshold of 30%. (37) This decision was made since a 50% threshold is the most used threshold in the clinical setting as well as in previous studies on RF on chronic knee pain. This choice will facilitate the comparison with the current literature.

Exploratory endpoints

This trial aims additionally to define the phenotype of patients suffering from PPSP in Belgium and the Netherlands as no large regional studies have been performed in this population and to assess the proportion of patients requiring additional interventions after RF treatment. The latter includes minimally invasive interventions (IA steroid injections, IA hyaluronic acid, platelet rich plasma infiltrations, repeat RF of the genicular nerves) and surgery (primary/revision TKA and other knee related surgery) and will be measured using the variable 'time to additional interventions' recorded at each time point.

Data collection and management

Follow-up is organised with online questionnaires (used at baseline, 1-month, 3-month, 6-month, 9-month, 12-monht and 24-month postintervention), telephonic consultations (at the end of the run-in phase) and in-hospital visits at baseline, 1-month, 3-month, 6-month, 12-month and 24-month postintervention as shown in Table 2 (and online supplemental Table 1). Baseline data include demographic data (e.g., age, sex, body mass index), medical history, information on the knee (e.g., symptom duration, OA grade, presence of neuropathic pain assessed by the DN4), medication use, questionnaires (e.g., WOMAC, HADS, PCS) and functionality tests (e.g., Timed up and go test, 6 min walk test). The data will be collected in an electronic case report form in CASTOR EDC in a pseudoanonymised manner and will be stored according to the current legal requirements.

Statistical plan

Sample size

The sample size was calculated to have 80% statistical power to detect a 10-point difference in the total WOMAC score between the compared groups with an estimated standard deviation of 15 at 6 months after intervention. Ten points is reported to be the minimally clinically relevant difference in the total WOMAC score. As we plan three comparisons (cooled RF versus sham, conventional RF versus sham, and cooled RF versus conventional RF), the Bonferroni correction for multiple testing was used to adjust the alpha used for testing (0.05/3 = 0.017) the superiority hypotheses. (48) For

each knee pain aetiology (OA and PPSP separately), given the 2:2:1 randomisation ratio and after adjustment for a drop-out rate of up to 10%, we plan to include 80 patients in the conventional RF group, 80 in the cooled RF group and 40 in the sham group adding up to 400 patients in total. To compute the sample size we used the formula for computing sample sizes to detect a between-group difference on a continuous outcome. (49) To do the computation, we used R version 4.0.2 with the package Trial Size V.1.3.

Statistical analysis

All analyses will be performed according to the intention-to-treat principle (ITT) for each group apart (OA and PPSP). Baseline characteristics will be reported stratified by group. Continuous variables will be reported as mean and SD or median and first and third quartile, depending on the nature of the distribution. Categorical variables will be reported as count and percentage.

Missing data will be imputed using multiple imputation with fully conditional specification, using predictive mean matching to draw imputations for continuous variables. However, for longitudinal analyses, the original data before imputation will be used, taking the likely mechanism of missing data into account in the linear mixed-effects regression.

For the primary endpoint, analysis of variance (ANOVA) with post hoc tests adjusted for multiple testing using the Bonferroni correction will be used. The comparison will be considered statistically significant if the p-value < 0.017 (0.05/3).

The WOMAC score at 12 months and 24 months follow-up will be also analysed longitudinally as a secondary outcome using linear mixed-effects regression. Other continuous secondary outcome parameters (NRS, functional tests, EQ-5D-5L, HADS, PCS, MQS III, WPAI and Health care resource use) will be reported using descriptive statistics and compared between groups at 6 months using ANOVA with post hoc tests, and longitudinal data using linear mixed-effects regression, similar to the primary outcome. PGIC will be dichotomised into intervention success (i.e., scoring "Much improved" or "Very much improved") and compared between groups using Pearson's chi-square test. Time to TKA in the OA group and time to additional intervention in both groups will be assessed within groups using Kaplan-Meier tables. For all secondary hypothesis testing, a conventional alpha of 0.05 will be used.

Table 2 Table of trial procedures of the COGENIUS trial (also see supplemental material file).

Procedures		**Intervention Phase**
	Baseline 3 days prior to To and the latest on To	**To**
Eligibility assessment	x	
Randomisation	x	
Anthropometric measurements	x	
Concomitant medication (e.g. MQS III, opioid dependence)	x	
Medical history	x	
NRS	x	
Previous or additional treatment of the knee	x	
DN4	x	
WOMAC, HADS, and PCS	x	
EQ-5D-5L	x	
Patient's satisfaction and PGIC		
Functional tests (Goniometry, Timed up and go test, and 6min walk test)	x	
Healthcare resource use questions		
WPAI	x	
Intervention		x
Assessment of the success of the blinding procedure		
Adverse events		x
Monitoring of conservative therapy	x	

NRS values after screening will be calculated as the mean value of the 4 previous days. Radiologic imaging for assessment of Kellgren-Lawrence is necessary only for patients who will be included in the OA group. *DN4, douleur neuropathique 4 questionnaire; EQ-5D-L, EuroQoL-5D-5L; FU, Follow-up; HADS, Hospital Anxiety and Depression Scale; MFU, month follow-up;*

To assess the success of the double-blind procedure and thus the internal validity of this trial, we will report the BI values for all treatment arms. All analyses will be performed in the latest version of R after collection of all the study data by a blinded statistical team assigned by the sponsor.

Health economic analysis

A health economic evaluation will be performed from a health care payer perspective following the Belgian guidelines, if appropriate. (50) Individual level health care costs will be calculated using health care resource utilisation data collected during the

	Follow-up Phase					
	T1 (1MFU) 30 days post To ± 3d	**T2 (3MFU)** 90 days post To ± 7d	**T3 (6MFU)** 180 days post To ± 7d	**T4 (9MFU)** 9 months post To ± 14d	**T5 (12MFU)** 12 months post To ± 14d	**T6 (24MFU)** 24 months post To ± 14d
	x	x	x	x	x	x
	x	x	x		x	x
	x	x	x	x	x	x
	x	x	x		x	x
	x	x	x	x	x	x
	x	x	x		x	x
	x	x	x		x	x
		x	x	x	x	x
	x	x	x	x	x	x
	x					
	x	x	x	x	x	x
	x	x	x		x	x

MQS III, Medication Quantification Scale III; NRS, Numerical Rating Scale; OA, osteoarthritis; PCS, Pain Catastrophizing Scale; PGIC, Patients' Global Impression of Change; T, timepoint; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index score; WPAI, Work Productivity and Activity Impairment questionnaire.

trial. The most relevant health care elements include the initial intervention received, subsequent hospital visits, related adverse events, additional or re-interventions to the index knee, pain medication, medical specialists and general practitioner visits. Belgian market prices or reimbursement fees will be used to value resource use. The measure of effectiveness is the Quality-Adjusted Life Year (QALY). QALYs will be calculated using the area under the curve approach using the EQ-5D-5Lscores. A cost-utility analysis will be conducted using an ITT approach and cost-effectiveness will be expressed using an incremental cost-effectiveness ratio (ICER): the difference in costs divided by the difference in QALYs. (51) Non-parametric bootstrapping techniques

are used to address the uncertainty surrounding the differences in costs and effects, and to estimate the probability of (cooled) RF intervention being cost-effective for various willingness to pay thresholds for the ICER, presented in a cost-effectiveness acceptability curve (CEAC). Several one-way sensitivity analyses will be performed to assess the robustness of results. Due to the expected benefit of (cooled) RF intervention on the ability to participate in society, an additional scenario analysis will include the cost-effectiveness estimate from a societal perspective, including productivity costs.

Assessment and management of risk of trial

The risk associated with the trial interventions is estimated to be comparable to the risk of standard medical care based on the following: (1) the RF equipment device has a CE Marketing Authorisation in Europe and it is used in this trial in accordance with its indication and (2) as COGENIUS is designed as a pragmatic trial, the other study procedures do not deviate from routine clinical practice in Belgium and The Netherlands, apart from the use of more standardised functional tests and questionnaires. These however do not add additional safety risks to the study subjects.

Patient and public involvement

Individual patients and patient representatives from 3 patient organisations (Vlaamse Reumaliga, VMCP and ReumaNet vzw) who represent patients with chronic knee pain and knee OA were involved in the formulation of the research question, design of the study and protocol development. The close collaboration resulted in among others: change of the randomisation rate from 1:1:1 to 2:2:1, formulation of comprehensible informed consent forms and trial information brochures and active participation of two patient experts in the trial steering committee of the COGENIUS as patient researchers.

Status of study

The first patient was enrolled in the study on June 2 2022. The last patient his last visit is expected in 2026.

Ethics and dissemination

Ethics approval was obtained from the central Ethics Committee of the University of Antwerp (Number Project ID 3069 - Edge 002190 - BUN B3002022000025) and the Ethics committee of Maastricht University (Number NL80503.068.22 - METC22-023) following national requirements and the separate ethics committees of each participating hospital. As such approval was consented from the following local Ethics Committees of the hospitals (reference number if provided): AZ Klina (N/A), UZ Leuven (S66382), AZ Maria Middelares (MMS.2023.002), UCL Saint-LUC (N/A), AZ Delta (N/A), AZ Groeninge (AZGS2022002), Hôpital Erasme- ULB (CTC-2022-055 P2022/108), Rijnstate (N/A), AZ Turnhout (N/A), Ziekenhuis Oost-Limburg (Z-2021109), Jessa Ziekenhuis (2022/002), CHR de la Citadelle (N/A), and CHU de Liège (N/A). The protocol has been reviewed by the funder (KCE) and by high-quality independent peer review experts contacted by the funder. Upon completion, the results of the study will be published in high-quality open access peer-reviewed journals and will be submitted for presentation at national and international congresses of pain and orthopaedic scientific societies. The full study report will be accessible on ClinicalTrials.gov and results will be additionally disseminated in the COGENIUS website and websites of patient organisations. Substantial amendments that require review by EC will not be implemented until the EC grants a favourable opinion for the study.

Discussion

The COGENIUS trial is designed to compare the effectiveness of conventional and cooled RF interventions versus a sham procedure in patients suffering from therapy-resistant chronic knee pain. To our knowledge no previous powered randomised controlled trial reported this comparison in mentioned population. The design further allows the comparison of both RF treatments to each other and the evaluation of the cost effectiveness of the RF treatments in two large populations: knee OA and PPSP after a total knee prothesis.

Beside our aim to provide novel clinical information by this pragmatic trial, we addressed several topics relevant to chronic knee pain research during the design of the protocol. Firstly, to include a representatively large population, recruitment of patients will happen in two countries and 15 hospitals in total assuring a wide geographical distribution. Small sample size is often reported to be a limitation of systematic reviews on RF. Secondly, we stringently incorporated a multimodal approach to treat knee pain in the protocol during run-in and patient follow-up. This was done conform to guidelines on the treatment of knee pain and also clinical practice increasing the external validity of the trial. (9,11–13) The results of the trial will thus reflect the additional effect of RF treatment on top of optimal conservative care. Thirdly, the primary outcome of the COGENIUS is planned at 6 months and the total follow-up extends to 24 months. This contrasts with previously reported trials on RF of the genicular nerves where the primary endpoint is often at 3-6 months and follow-up averages around 6 months. There is a resulting controversy on the expected duration of the effect of RF due to a potential nerve regeneration. (52) We aim to provide mid-term to long-term information on the effect of RF. Lastly, there is only a single study of Desai et al. that reports a cost-effectiveness analysis. Lack of information on the cost-effectiveness of different RF treatments compared to each other and to usual care prevents incorporation of RF in clinical decision-making algorithms and healthcare reimbursement strategies. We try to address these topics in the COGENIUS trial.

There are a few inherent limitations to the protocol of this trial. We opted to use no diagnostic block prior to the study intervention. This decision was based on the study of McCormick et al. in which the standard prognostic block (1 mL of local anesthetic and a 50% threshold of success) did not lead to improved outcomes. Furthermore, there are no prospective studies showing a better outcome with the use of prognostic genicular nerves blocks, multiple studies do not perform a prognostic block, and a prognostic block leads to additional patient discomfort and a potential risk of infection especially in PPSP patients post-TKA. (53–56) The use of a 80% threshold for success could lead to better patient selection in the future, however presently no prospective studies use this criterion. (57)

Inherent to a relative new technique, there is still evolution in which the RF procedure is performed. Kim et al. wonder whether it would be better to treat more nerves without answering the question. (22) Despite this, a comparison of Fonkoue et al. of a RF treatment between 3 and 5 genicular nerves showed no differences. (58) The anatomical targets for the genicular nerves during the RF procedure are also regularly updated to increase the chance of treatment success. We incorporated the revised anatomic landmarks of the SMGN and SLGN in this protocol. We concluded however, that treating three genicular nerves most accurately reflects present clinical practice.

Contributors

TV conceived the study, designed the study protocol, provided domain knowledge expertise and clinical input, revised the manuscript and is co-chief investigator. AB conceived the study, designed the study protocol, provided domain knowledge expertise and clinical input and revised the manuscript. SvK designed the study protocol, provided statistical and epidemiological support and revised the manuscript. MK designed the study protocol, provided statistical and epidemiological support, aided with health economics analysis and revised the manuscript. JB provided domain knowledge expertise and clinical input and revised the manuscript. VB provided domain knowledge expertise and clinical input, revised the manuscript and is co-chief investigator. MS designed the study protocol, provided domain knowledge expertise and clinical input, revised the manuscript and is co-chief investigator. PE provided domain knowledge expertise and clinical input and revised the manuscript. PV provided domain knowledge expertise and clinical input and revised the manuscript. KT designed the study protocol, provided support with grant application and clinical trial management and revised the manuscript. JVZ conceived the study, designed the study protocol, provided domain knowledge expertise and clinical input, revised the manuscript and is chief investigator. All authors have contributed substantially to the manuscript and agree with the content.

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Competing interests

None declared.

Patient and public involvement

Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication

Not applicable.

Provenance and peer review

Not commissioned; externally peer reviewed.

Supplemental material

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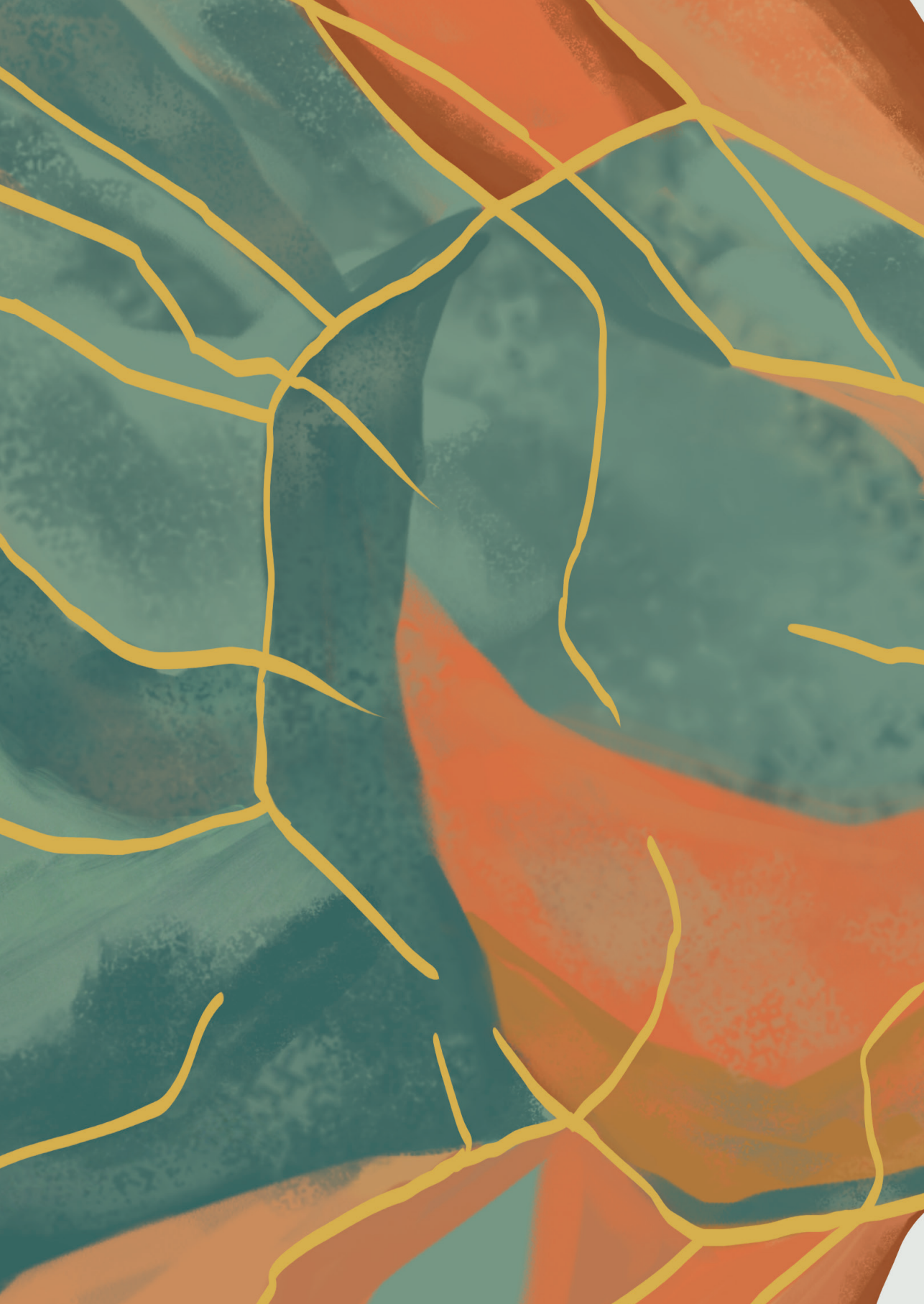
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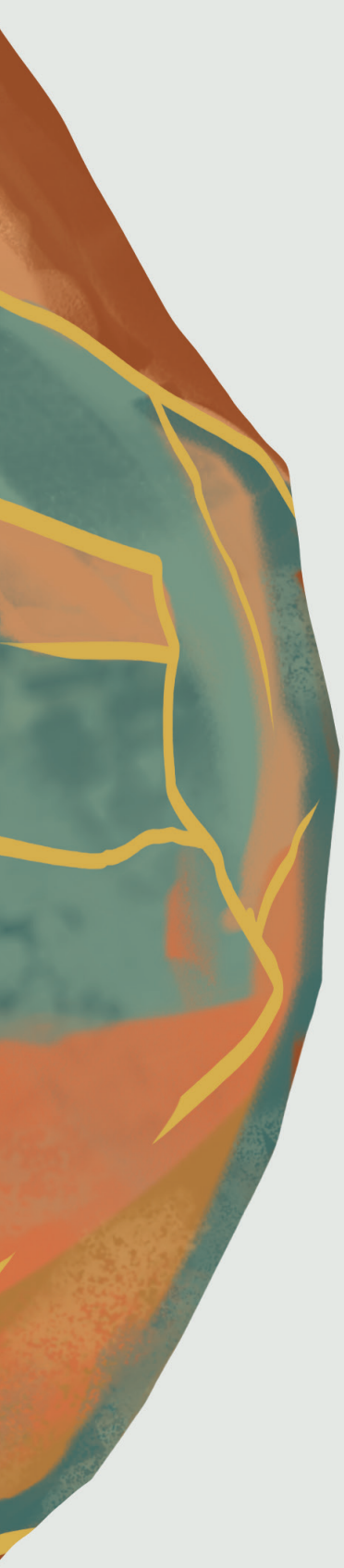
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CHAPTER 8

General discussion and conclusion

General discussion and conclusion

This thesis investigates the clinical outcomes of different radiofrequency (RF) treatments of the genicular nerves in patients with chronic knee pain due to osteoarthritis (OA) and in those with persistent post-surgical pain (PPSP) after a total knee arthroplasty (TKA). This thesis is structured around three research questions (RQ).

RQ 1 - Is a radiofrequency treatment of the genicular nerves effective in reducing pain and improving other patient outcomes?

The first publication of **Choi et al.** in 2011 demonstrated that RF of the genicular nerves was successful in giving pain relief for chronic knee pain due to OA Kellgren-Lawrence (KL) grade two to four, up to three months after the treatment.[1] They compared an RF of three genicular nerves (superolateral, superomedial and inferomedial) with a sham procedure in 19 patients per group, after they got more than 24 hours pain relief after a diagnostic block with local anesthetic. The sham procedure included an identical procedure without activating the RF generator. At three months they analyzed 17 and 18 patients respectively in the RF and sham group. They found at that timepoint that 59% of the RF patients got more than 50% pain relief versus none of the sham group.

Following this landmark study, numerous subsequent studies were initiated, primarily comparing an RF of the genicular nerves with another active treatment. Overall, these studies reported mainly positive results witch successful outcomes ranging from 27 to 74% at 6 months of follow-up.[2-8] As with all new techniques, initial knowledge is inherently incomplete. Through ongoing discussion and scientific debate, refinement and optimization of the technique is needed based on the findings of recent studies. Despite the early success, the study by Choi et al. was criticized for several reasons.[9-12]

First, the study had a relatively small sample size of only 38 patients. Although the study was adequately powered (80%) with a two-tailed alpha of 0.05 based on a pilot study of 20 patients, the limited sample size may restrict the generalizability of the findings and introduce potential bias.

Secondly, there was a potential selection bias due to the inclusion of patients who experienced more than 24 hours of pain relief after a diagnostic genicular nerve block using a local anesthetic with a shorter duration of action. Hereby, possibly selecting patients more prone to a placebo response. Furthermore, there is also controversy on the use of diagnostic and prognostic blocks.[12] Diagnostic blocks help

in identifying the anatomical structure which possibly could be the cause of pain, whereas prognostic blocks help in predicting the possible outcome of a treatment. The diagnosis of knee OA is a clinical diagnosis and combined with imaging, there is a high sensitivity and specificity, therefore there is little added value of diagnostic genicular blocks.[13] On the use of prognostic blocks, the evidence is mixed.[12] Critics argue that they are unnecessary given their associated risks and costs, the relatively well-defined pain generator in knee OA, high response rates to blocks and the lack of added value demonstrated in a RCT by McCormick.[14] Proponents, however, contend that prognostic blocks improve patient selection, clinical outcomes and cost-effectiveness as studies demonstrated better outcomes with higher response cut-offs.[15, 16] Furthermore, the study of McCormick, which discouraged the use of prognostic blocks, had methodological limitations. Because of the mixed evidence the decision to use prognostic block should be made based on a case-by-case basis, taking into account patient characteristics, clinician experience and clinic resources.[12]

A final criticism is that in the study of Choi et al. only three of ten nerves that innervate the anterior knee are targeted. The decision to target only three of ten nerves was driven by concerns regarding potential motor nerve injury.[1] Off course, creating bigger or more lesions to improve the treatment success is inherently limited by the concern of unintentionally damaging the surrounding tissues leading to permanent complications.

In an attempt to further address this research question, **Malaithong et al.** conducted a double blinded RCT in which they treated patients with chronic knee pain due to knee OA KL grade 3 and 4 who experienced more than 50% pain relief following a prognostic block.[17] They compared a bipolar RF treatment, which creates a larger lesion, with a sham procedure in 64 patients. Thirty-two patient received a bipolar RF treatment of 90°C during 180 seconds, preceded by an injection of 2 ml lidocaine 2% with 2.5 mg dexamethasone at each of the three genicular nerves. The sham procedure consisted of the same injection but the RF generator was not activated. Patients were followed for up to 12 months with 26 and 27 patients analyzed in the control and RF group, respectively. They found no statistically significant differences ($p=0.40$) in average VAS pain score between groups (in RFA group 3.2 ± 2.6 vs 2.6 ± 2.4 in control group) at 12 months or at any other time point. The authors concluded that the absence of demonstrated efficacy, together with anatomical evidence indicating that the knee joint is innervated by numerous nerves and preliminary studies suggesting superiority of lesioning strategies targeting more than three nerves, supports the need for controlled trials using more aggressive lesioning approaches.

Table 1 Characteristics of different studies.

Study	Intervention	Comparator	Results	Limitations
Choi et al[1]	Conventional RF 3 genicular nerves	Genicular nerve block with 2 ml lidocaine 2% per nerve	Significant difference in pain relief	• Small sample size (n=38) • Selection bias • Targeting 3 out 10 nerves
Malaithong et al[17]	Bipolar RF 3 genicular nerves	Genicular nerve block with 2 ml lidocaine 2% and 2.5 mg dexamethasone per nerve	No significant differences in pain relief	• Genicular nerve block with steroids isn't a sham procedure.
Kwon et al[18]	Cooled RF 3 genicular nerves	Genicular nerve block with 2 mL lidocaine 1% and 5 mg triamcinolone per nerve	Significant difference in pain relief	• Small sample size (n=40)
Makkar et al[19]	2 conventional RF lesions 3 genicular nerves	Subcutaneous injection of 1 ml lidocaine 1% per site	Significant difference in pain relief	• Small sample size (n=60)

However, the negative findings of the Malaithong study may be confounded by the absence of a true sham procedure, as the control intervention consisted of a genicular nerve block (GNB) using local anesthetic and corticosteroid. Several studies have reported that such blocks may produce sustained analgesic effects.[20, 21] Elsaman et al. compared GNB with intra-articular (IA) injection and found significantly greater improvement in the GNB group at 12 weeks.[20] Similarly, Fonkoue et al. compared GNB targeting three versus five genicular nerves and observed significant pain reduction lasting up to 12 weeks in both groups. The same was observed by Malaithong et al. There was a persistent and statistically significant reduction in pain from baseline in both treatment arms at 12 months, and furthermore, 36.7% of the patients experienced prolonged pain relief after the prognostic block alone, obviating the need for RFA. These findings suggest that a GNB with steroids has a therapeutic effect and isn't a true sham procedure.

After the study by Malaithong et al., two additional studies reported positive results of RF of the genicular nerves compared with sham procedures.[17-19] The first was the study by **Kwon et al.**, who compared cooled RF targeting the three classical genicular nerves with a sham procedure consisting of a GNB using local anesthetic and steroids in patients with knee OA KL grade 2–4. They found that the responder rate was

significantly higher in the cooled RF group for up to six months after the intervention. Although this was also not a true sham procedure as with the study by Malaithong, the study demonstrated a positive effect of RF, potentially related to the larger lesion size produced by cooled RF. The second study, by **Makkar et al.**, was a randomized controlled trial comparing also a larger lesion approach (two conventional RF lesions) at the three classical targets with a true sham procedure involving a subcutaneous local anesthetic injection. This study included patients with knee OA KL grade 2 or higher. At three months, the RF group demonstrated significantly lower pain scores compared with the sham group.

In conclusion, the effectiveness of RF treatment targeting the three classical genicular nerves remains controversial, with studies on knee OA showing mixed results. Nevertheless, most investigations report positive outcomes in patients with knee OA. These findings have been extrapolated to patients with PPSP after TKA, although only a limited number of studies specifically address this population.[12, 22] The majority of published reports are retrospective or small randomized controlled trials, resulting in low-quality evidence**.** Moreover, the mechanisms underlying PPSP differ from those in OA.[23] They are multifactorial, involving inflammatory, vascular, and neuropathic components. A recent cadaver study demonstrated that prosthetic knees maintain genicular nerve anatomical locations comparable to native knees but exhibit smaller nerve diameters and fibrosis of the infrapatellar branch of the saphenous nerve**.** In addition, the absence of a nearby arterial branch for the superolateral genicular nerve may reduce the accuracy of ultrasound-guided targeting. However, these anatomical differences alone do not fully explain the reduced pain relief observed after RF in this patient group.

Since the first RCT in 2011 investigating RF treatment of the genicular nerves, interest and research in this area have grown considerably. As with any emerging technique, evolution in response to new findings is expected, and while significant progress has been made, much remains to be learned. The **COGENIUS study**, a large RCT comparing conventional and cooled RF with a sham procedure in patients with OA and PPSP, is expected to provide valuable insights into optimizing treatment strategies for these patients and will finally answer this research question.[24]

RQ 2 - Is there a difference in effect between different radiofrequency modalities such as conventional, pulsed or cooled radiofrequency?

Different RF modalities have distinct mechanisms of action and, consequently, different rationales for their clinical use. Compared with conventional RF, **PRF** is considered a neuromodulative technique designed to minimize tissue destruction. This theoretical advantage makes PRF potentially safer, with fewer side effects and a reduced risk of deafferentation pain. However, there are only a limited number of RCTs directly comparing pulsed and conventional RF of the genicular nerves. Interpretation of the available evidence is further complicated by the use of different anatomical target, from intra-articular to nerves, across studies. One large RCT included in this thesis, conducted by **Santana-Pineda et al.**, demonstrated pain relief in both groups. [25] However, the effect was significantly stronger in the conventional RF group. Based on the currently available evidence, conventional RF is therefore recommended over PRF.

One of the main controversies remains if creating a larger lesion, leads to better clinical outcomes.[12] **Cooled RF**, which produces a larger lesion compared with conventional RF, may theoretically improve results by increasing the likelihood of capturing the intended nerve. However, a larger lesion also carries a greater risk of unintended damage to adjacent tissues and cooled RF is also associated with a greater cost. As genicular nerve RF is a relatively new technique, with the first report in 2011, it is not a surprise that the optimal approach is still evolving and the search for the ideal **anatomical target** continues. The original three targets described by **Choi et al.** (the superolateral (SLGN), superomedial (SMGN), and inferomedial (IMGN) genicular nerves) were later questioned based on anatomical cadaveric and imaging studies.[1, 12, 26, 27] Traditionally, the SLGN and the SMGN were targeted at the midpoint of the anterior–posterior (AP) femoral shaft. However, **Fonkoue et al.** argued that the superolateral and superomedial targets should be positioned more posteriorly and distally. The IMGN position was identical. Using these revised targets, they reported monopolar RF accuracy rates of 100% for the SMGN and 90% for the SLGN.[27] More recent MRI studies by **Hillery et al.** have supported these findings, demonstrating that the classical targets are often located too anteriorly, with the nerves situated more posteriorly on imaging.[28]

Table 2 Depth percentage measurements for each genicular nerve branch, expressed as percentages of the total depth through the cortex (the anterior border to posterior border distance).

Study	SMGN % depth AP	SLGN % depth AP	IMGN % depth AP
Choi et al[1]	50	50	50
Fonkoue et al[27]	100	100	50
Hillery et al[28]	71	66	77

Beyond the initial indication of OA, PPSP after TKA has also emerged as an indication for genicular nerve RF. This raised the question of whether anatomical targets remain the same after major surgery such as TKA. A recent cadaveric study found that prosthetic knees share comparable genicular nerve anatomical locations with native knees, although nerve diameters were smaller and fibrosis of the infrapatellar branch of the saphenous nerve was observed. Additionally, the absence of a nearby arterial branch to the SLGN may reduce the accuracy of ultrasound-guided targeting.[23]

In a critical review **Ferreira-Silva et al.** have emphasized that the course of the SMGN and the SLGN along the periosteal surface between the diaphysis and epiphysis is highly variable.[12] Therefore, it may be overly simplistic to assume that a single anatomical landmark can reliably capture all branches. Given this variability, placing the RF cannula anywhere along the posterior half of the femur at the diaphysis–epiphysis junction will likely capture at least some genicular nerve branches. This raises the question of whether intentionally creating larger lesion sites—aimed at encompassing as many branches as possible in this region—could improve clinical outcomes. Techniques such as cooled RF enable the creation of such larger lesions.

From a theoretical standpoint, enlarging the lesion to increase the probability of nerve capture appears reasonable. However, this strategy must be balanced against the increased risk of collateral tissue damage and the higher material cost of cooled RF. Several studies have investigated cooled RF in this context and have reported promising results.[29] Nevertheless, many of the trials are no direct head to head comparison between the two different RF modalities. Furthermore, the larger studies are industry-sponsored, which also introduces the potential for bias.[2, 8]

The pilot COCOGEN study suggested that cooled RF may offer superior outcomes at 6 months post treatment but the non-inferiority limit was inconclusive.[7] The 12-month results indicated that this potential benefit was particularly evident in patients with PPSP after TKA, but not for OA-related pain.[30] The ongoing COGENIUS study is expected to provide more definitive evidence as this a large direct head-to-head comparison of conventional and cooled RF with the use of updated anatomical targets.[24]

In addition to creating a bigger lesion size, an equally important research question is whether targeting more than three genicular nerves results in improved clinical outcomes. Critical appraisal of anatomical studies has demonstrated that up to ten genicular nerves may innervate the anterior knee.[31] Furthermore, retrospective clinical data suggest a trend toward improved outcomes when more than three nerves are targeted. In a study by **Chen et al.**, a positive outcome was associated with targeting more than three nerves.[15] Similarly, **Forero et al.** compared a three-nerve approach with a six-nerve approach and reported significantly lower mean resting pain scores at 6 months in the six-nerve group.[32] **Caragea et al.** also found that targeting more than three nerves was associated with a greater likelihood of treatment success.[33]

However, prospective randomized evidence is less convincing. **Fonkoue et al.** conducted a prospective randomized controlled trial in 55 patients with KL grade 2–4 OA.[21] Patients were randomized to receive a GNB targeting either the three classical nerves (SMGN, SLGN, IMGN) or five nerves (SMGN, SLGN, IMGN, recurrent fibular nerve, and infrapatellar branch of the saphenous nerve). Although significantly lower pain scores were observed in the five-nerve group at 1 hour post-procedure, no differences were found at any other timepoints up to three months. Importantly, the study used large injection volumes and different cumulative steroid doses (60 mg vs 100 mg triamcinolone), which may have influenced outcomes. Similarly, **Bhargava et al.** conducted an RCT in 180 patients with grade 2–4 knee OA, comparing three-nerve versus five-nerve GNB.[34] Both groups showed significant pain reduction. However, no significant differences between groups were observed in pain relief up to 3 months. Differences in cumulative steroid dosing between groups were again present. **Köse et al.** evaluated an expanded targeting strategy that included pulsed RF of the RFN and IPBSN in addition to standard genicular RF.[35] They reported greater pain relief in the five-nerve group compared with the standard approach. However, there was no significant difference in patient satisfaction between the groups and several methodological concerns limit interpretation:

- Possible reporting bias, as patients may have been aware of receiving three versus five injections.
- Addition of pulsed RF to the IPBSN and RFN, despite evidence suggesting pulsed RF may be less effective than conventional RF.
- Overlapping 95% confidence intervals between groups

Taken together, although retrospective studies suggest improved outcomes when more than three nerves are targeted, high-quality randomized evidence does not consistently confirm this benefit. Moreover, methodological limitations in existing

trials hinder definitive conclusions. Therefore, large, well-designed comparative effectiveness trials directly comparing the standard three-nerve technique with expanded nerve-targeting strategies are required to determine the optimal lesioning approach and treatment parameters.

In this context, the results of the Sequenced Strategy for Knee Osteoarthritis Pain (SKOAP) trial will be particularly informative.[36, 37] The SKOAP trial is a multi-site, randomized pragmatic study evaluating treatments for individuals with knee OA pain using a two-phase sequential design. In Phase 1, all participants receive guideline-based best practices care and are randomized to best practices alone, best practices plus duloxetine, or best practices plus duloxetine and a web-based CBT pain coping program (painTRAINER). Phase 2 evaluates three procedural treatment strategies: (a) intra-articular injections (hyaluronic acid, steroid plus bupivacaine), (b) GNB with liposomal bupivacaine with steroid and sham RF, and (c) genicular nerve RF combined with steroid injection of more than 3 nerves. Beyond comparing the effectiveness of these interventions, SKOAP will also examine clinical characteristics and patient-level factors that are associated with treatment response.

Table 3. Characteristics of different studies.

Study	Design	Comparator	Results	Limitations
Chen et al.[15]	Retrospective	4 to 10 nerves	Targeting >3 nerves associated with positive outcome	Retrospective nature
Forero et al.[32]	Retrospective	6 nerves	6 nerves group superior pain relief	Retrospective nature
Caragea et al.[33]	Retrospective	> 3 nerves	Targeting >3 nerves associated with positive outcome	Retrospective nature Unclear which nerves targeted
Fonkoue et al.[21]	RCT	5 nerves	No significant differences except at 1 hour post intervention	Large injection volumes Different cumulative steroid doses
Bhargave et al.[34]	RCT	5 nerves	No significant differences	Different cumulative steroid doses
Köse et al.[35]	RCT	5 nerves	5 nerves group superior pain relief	No significant difference in patient satisfaction Several methodological concerns

In conclusion, RF treatment of the genicular nerves is a relatively new and evolving technique. Newer anatomical targets have been identified in the posterior half of the femur. Conventional RF is currently recommended over PRF. Cooled RF appears to result in improved clinical outcomes compared with conventional RF, particularly in patients with PPSP following TKA. However, the results of the COGENIUS study are expected to clarify whether cooled RF is truly superior to conventional RF. Future research should also investigate whether targeting a greater number of nerves leads to better outcomes. The SKOAP study is anticipated to provide further insights into this question.

RQ 3 - What is the place of a radiofrequency treatment of the genicular nerves in the treatment algorithm of chronic knee pain?

An RF treatment of the genicular nerves is a relatively novel technique with it first description first published in 2011 by Choi et al.[1] Before it can be fully integrated into the treatment algorithm for chronic knee pain, its effectiveness and safety profile must be demonstrated and compared with existing treatment options. Currently, less invasive approaches remain the first-line management strategy for chronic knee pain. These include **conservative therapies** such as physiotherapy, gait aids, and weight management, as well as pharmacological treatments. Commonly used medications include paracetamol, topical or oral non-steroidal anti-inflammatory drugs, and duloxetine. Opioids are generally not recommended for the management of chronic non-malignant knee pain. However, mixed-action opioids such as tramadol may be considered in selected patients with severe or high-impact pain.[29, 38] Despite these options, pharmacological therapy does not always provide sufficient pain relief. Furthermore, particular caution is required in patients with comorbidities due to the potential risk of adverse effects and drug interactions.

When conservative treatment fails to provide adequate symptom control, several **minimally invasive treatment** options can be considered for **knee OA**. The first is an **intra-articular corticosteroid injection**. These injections have been shown to provide short-term pain relief, therefore they are recommended in many clinical guidelines.[39, 40] However, controversy has emerged in recent years, as some studies suggest that intra-articular corticosteroid injections may accelerate the structural progression of OA.[41-44] A second intra-articular injection option is **hyaluronic acid**. It is hypothesized that viscosupplementation improves joint lubrication and thereby reduces pain. However, the available evidence does not consistently demonstrate a clinically meaningful benefit, and due to the heterogeneity of the studies, most clinical guidelines do not recommend its routine use.[39]

Regenerative medicine has been proposed as a potential alternative that may go beyond symptom control. Therefore, considerable interest has been directed toward intra-articular injections of **platelet-rich plasma** (PRP). Some studies suggest favorable outcomes for intra-articular PRP in patients with knee OA. However, it should be noted that the quality of evidence remains low and that the available studies show substantial heterogeneity. Consequently, PRP is not currently recommended by most clinical guidelines for knee OA and, if used, it should preferably be applied within a research setting.[39]

Another minimally invasive therapy is the subcutaneous or intravenous injection of **nerve growth factor monoclonal antibodies** such as tanezumab. Tanezumab has been shown to be effective in reducing pain associated with knee OA. However, clinical trials have demonstrated that patients treated with tanezumab have a higher risk of rapidly progressive OA and an increased likelihood of requiring total joint replacement compared with patients treated with comparator medications or placebo. Therefore, its use should be approached with caution.[45]

Following the initial publication in 2011, multiple comparative randomized controlled trials have evaluated **RF treatment of the genicular nerves** and demonstrated promising effectiveness with a favorable safety profile.[46-49] Compared with intra-articular infiltrations such as corticosteroids, hyaluronic acid, or PRP, RF treatment has been studied more extensively and has shown longer durations of pain relief without evidence of rapidly progressive OA or other serious adverse effects.[4, 8, 50, 51] This growing body of evidence led to its first inclusion in a clinical guideline in 2019, when the American College of Rheumatology issued a conditional recommendation for radiofrequency ablation as a treatment option for knee OA pain. Conventional and cooled radiofrequency treatment of the genicular nerves may be considered in patients with therapy-resistant knee pain due to OA, particularly when pain is moderate to severe and the Kellgren–Lawrence grade is II–IV.

An alternative approach to nerve ablation is **chemical neurolysis of the genicular nerves** using alcohol or phenol. Although only a limited number of studies are available, these have also reported favorable outcomes.[52-56] The main advantage of chemical ablation is that it is less expensive. However, the resulting lesion is less controlled compared with RF treatment. Given the larger body of evidence supporting RF, radiofrequency ablation remains the preferred technique.[29]

Another emerging technique is **embolization of the genicular arteries** for the treatment of knee OA pain. This procedure works by reducing blood flow to the inflamed synovial tissue within the knee joint. Early studies have shown promising results, although the procedure carries a small risk of complications such as avascular necrosis therefore it use should be in study setting. [57-61]

For chronic knee pain caused by **PPSP after TKA**, treatment options are limited. **RF treatment of the genicular nerves** may be particularly valuable in this context, as intra-articular injections are more difficult to perform and carry a risk of infection in the presence of a prosthetic joint.[62] Additionally, RF treatment avoids the use of corticosteroids. Other potential treatment options for PPSP include **spinal cord stimulation or dorsal root ganglion stimulation**.[63] However, the available evidence for these techniques remains limited, and large randomized controlled trials are lacking. Therefore, these therapies are preferably offered within a research setting.

Identifying **prognostic factors** for invasive treatments, such as interventional procedures and TKA, is essential.[64, 65] Within a biopsychosocial model of chronic pain, pain is understood as the result of an interplay between nociceptive, neuropathic, and nociplastic mechanisms.[66] Importantly, nociplastic pain tends to respond poorly to conventional medical and surgical treatments. Therefore, future research should focus on identifying patients in whom nociplastic pain predominates, both in OA and in persistent PPSP following TKA. Current literature suggests that multiple pain locations, higher levels of fear and depression, lower radiographic severity of OA, and elevated scores on central sensitization questionnaires are important risk factors associated with nociplastic pain profiles.[67, 68]

In conclusion, no disease-modifying pharmacological agents for knee OA have yet been identified. Approximately 50% of patients initially diagnosed with symptomatic knee OA are estimated to eventually undergo surgical treatment in the form of total knee arthroplasty, which represents one of the largest contributors to direct medical costs.[29] However, between 10% and 35% of patients undergoing TKA experience persistent pain, with approximately 15% reporting pain with a high impact on daily functioning.[69, 70] Consequently, there remains a clear need for effective therapies with a low risk of adverse effects within a multimodal and multidisciplinary treatment algorithm embedded in a biopsychosocial model. Radiofrequency treatment of the genicular nerves represents a promising minimally invasive treatment option for chronic knee pain due to OA or persistent postsurgical pain.

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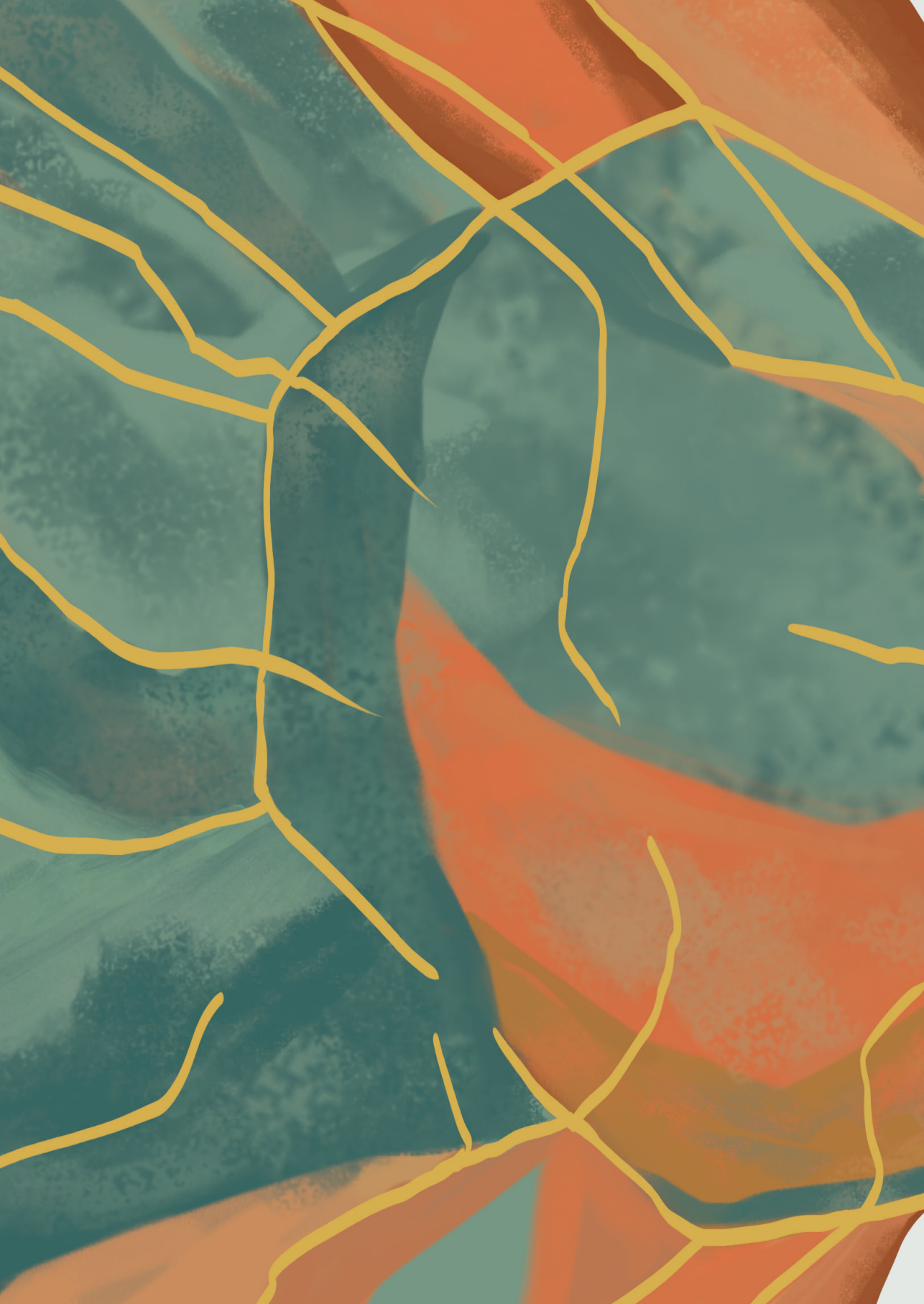
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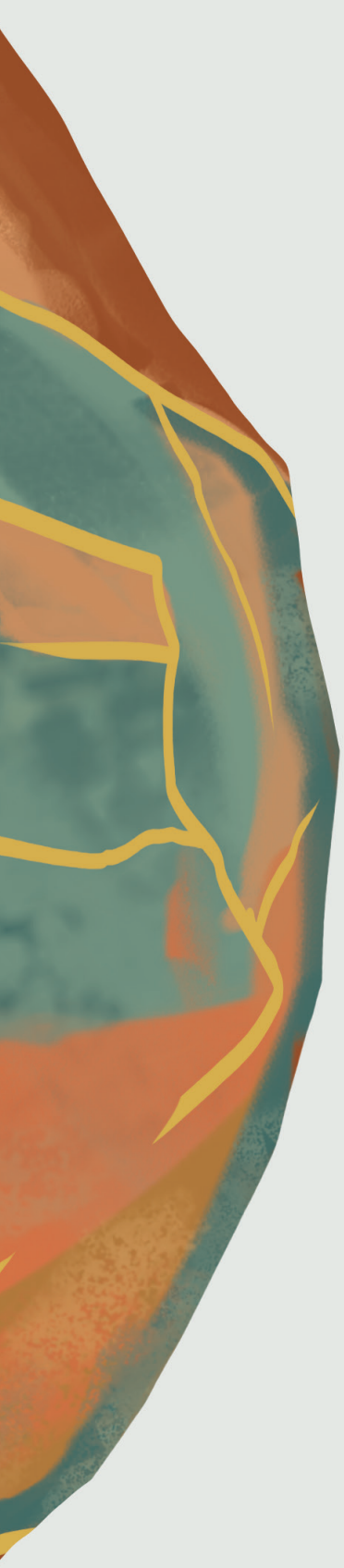
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CHAPTER 9

Summary /
Nederlandse samenvatting

Summary

The aim of this thesis was to investigate the clinical outcomes of different radiofrequency (RF) treatments of the genicular nerves in patients with chronic knee pain due to osteoarthritis (OA) and in those with persistent post-surgical pain (PPSP) after a total knee arthroplasty (TKA). RF treatment of the genicular nerves has emerged as a promising interventional pain management technique for chronic knee pain. Several RF modalities are currently in clinical use, including conventional RF, pulsed radiofrequency (PRF), and cooled RF. These techniques differ in their mechanisms of action, lesion characteristics, and theoretical risk–benefit profiles, yet their relative effectiveness and optimal clinical application remain subjects of ongoing debate. Together, the studies presented in this thesis aim to clarify the role, effectiveness, and comparative value of different RF modalities targeting the genicular nerves, thereby contributing to a more evidence-based and optimized interventional treatment strategy for patients with chronic knee pain.

The review presented in **Chapter 2** provides an comprehensive overview of the pathophysiology, diagnosis, and current treatment strategies for chronic knee pain due to OA. The existing literature was systematically reviewed and recommendations on interventional treatments were formulated by the use of a modified Delphi approach. The findings indicated that when conservative measures fail to provide satisfactory pain relief, a multidisciplinary and integrative approach is recommended. These include pharmacological treatment, psychological therapy, physiotherapy, and procedural options such as intra-articular injections, RF ablation, and surgery. A conventional and cooled RF treatment of the genicular nerves were recommended for moderate to severe chronic knee pain due to OA when conservative and an intra-articular steroid injection failed to provide pain relief.

In **Chapter 3**, the existing literature on the use of PRF for various indications, including knee pain, was reviewed. PRF was developed as an alternative to conventional RF with the aim of modulating nociceptive signaling without causing tissue destruction. This minimal invasive technique has gained interest as treatment for different chronic pain conditions due it long-lasting effects and low risk of complications. However, robust evidence remains limited, highlighting the need for future research to determine optimal parameters, such as which nerves best should be targeted and the ideal duration of PRF treatment.

To further elucidate the role of PRF of the genicular nerves in the management of chronic knee pain due to OA, **Chapter 4** describes a randomized controlled trial comparing the analgesic and functional outcomes of PRF with those of conventional

RF. The study included patients with chronic knee pain secondary to Kellgren–Lawrence (KL) grade 3 and 4 OA. A total of 188 patients were randomized to receive either PRF or conventional RF of the superolateral, superomedial, and inferomedial genicular nerves and were followed for up to 12 months. The results showed that both treatment modalities led to significant reductions in pain, functional disability, and analgesic medication use. However, conventional RF consistently resulted in superior pain relief and better outcomes on most secondary measures throughout the 12-month follow-up period. Complications were minimal in both groups. In addition, this study identified several predictors of treatment success at 6 months following a RF intervention. Reduced treatment efficacy was associated with more advanced OA, higher baseline pain intensity, and the presence of comorbid depression, anxiety disorders, or diabetes mellitus.

Chapter 5 presents the results of the COCOGEN study which is a double-blind, non-inferiority randomized controlled trial comparing cooled RF with conventional RF of the genicular nerves. Cooled RF is another RF modality that creates a larger lesion which potentially could lead to improved clinical outcomes by overcoming anatomical variability. This study included patients with chronic knee pain due to KL grade 2–4 OA as well as patients with PPSP following TKA, with a follow-up extending up to 6 months. The primary outcome was the proportion of patients achieving at least a 50% reduction in pain at 3 months post-intervention. Secondary outcomes included knee pain intensity, functional status, quality of life, emotional health, and adverse events up to 6 months post-intervention. Conventional RF was evaluated for non-inferiority to cooled RF with respect to pain reduction at the 3-month follow-up. There was no statistically significant difference in the primary outcome. The non-inferiority analysis yielded inconclusive results with respect to the predefined non-inferiority margin. No statistically significant differences were observed between groups for any of the secondary outcomes, and no serious adverse events were reported. Both conventional and cooled RF resulted in pain reduction in patients with OA and PPSP. Although cooled RF appeared to be associated with a higher proportion of patients achieving clinically meaningful pain relief, this difference did not reach statistical significance. Consequently, this pilot study was unable to demonstrate non-inferiority of conventional RF or superiority of cooled RF. Larger, adequately powered randomized controlled trials are therefore required to confirm these findings and determine whether cooled RF provides a clinically meaningful advantage over conventional RF.

Both the long-term clinical outcomes and the cost-effectiveness results of the COCOGEN study are further described in **Chapter 6**. Of the 49 patients initially included, 40 completed the full 12-month follow-up. At that timepoint, the proportion

of patients achieving at least a 50% reduction in pain was 22.2% (4/18) in the conventional RF group and 22.7% (5/22) in the cooled RF group (p>0.05). The only statistically significant difference observed was in mean absolute numerical rating scale scores at 12 months between cooled RF and conventional RF in patients with PPSP (p=0.02). Both RF modalities resulted in sustained pain reduction at 12 months. Differences between other outcomes were not statistically significant. No serious adverse events were reported. The health economic evaluation demonstrated that cooled RF was associated with lower costs and improved quality-adjusted life years compared with conventional RF in patients with PPSP, but not in those with OA.

To address the remaining questions arising from the pilot COCOGEN study, **Chapter 7** presents the study protocol of a large randomized controlled trial, the COGENIUS study. This trial evaluates the effectiveness and cost-effectiveness of conventional and cooled RF of the genicular nerves compared with a sham procedure in patients with chronic knee pain due to OA or PPSP following a TKA. For each indication 200 patients will be included with a follow-up of two years. The study is currently ongoing. All participants will undergo a run-in period of one to three months during which conservative treatment will be optimized. Following this period, patients will be randomized in a 2:2:1 ratio to receive conventional RF, cooled RF, or a sham procedure. The primary analyses will compare the effectiveness of each RF modality with the sham procedure, with secondary analyses comparing conventional RF with cooled RF. All analyses will be conducted separately for each indication. The primary outcome measure is the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score at 6 months. Secondary outcomes include knee pain intensity, physical function, health-related quality of life, emotional health, medication use, healthcare and societal costs, and adverse events assessed up to 24 months post-intervention.

In conclusion, based on the studies presented in this thesis, conventional RF of the genicular nerves demonstrates superior clinical effectiveness compared with PRF in patients with chronic knee pain due to OA. Furthermore, cooled radiofrequency appears to offer additional clinical and economic benefits over conventional RF, particularly in patients with persistent post-surgical pain following TKA. Consequently, RF treatment of the genicular nerves has earned a position within the treatment algorithm prior to surgery in OA and as a therapeutic option for persistent post-surgical pain after total knee arthroplasty.

Nederlandse samenvatting

Het doel van dit proefschrift was het onderzoeken van de klinische uitkomsten van verschillende radiofrequente (RF) behandelingen van de geniculaire zenuwen bij patiënten met chronische kniepijn door artrose (osteoartritis, OA) of door persisterende post-chirurgische pijn (persistent post-surgical pain, PPSP) na een totale knie prothese (TKP). Een RF behandeling van de geniculaire zenuwen heeft zich recent ontwikkeld tot een veelbelovende interventionele behandeling voor chronische kniepijn. Momenteel worden verschillende RF modaliteiten in de klinische praktijk gebruikt, zowel conventionele RF, gepulseerde radiofrequentie (PRF) als gekoelde RF. Deze modaliteiten verschillen van elkaar in werkingsmechanisme, laesie kenmerken en theoretisch risico-batenprofiel. Hun relatieve effectiviteit en optimale klinische toepassing blijft echter het onderwerp van discussie. De studies in dit proefschrift proberen samen de rol, de effectiviteit en de waarde van de verschillende RF modaliteiten te verduidelijken. Hiermee hopen we bij te dragen aan een evidence-based en optimale behandelstrategie voor patiënten met chronische kniepijn.

Het artikel in **hoofdstuk 2** biedt een uitgebreid overzicht van de pathofysiologie, diagnostiek en huidige behandelstrategieën voor chronische kniepijn ten gevolge van OA. De beschikbare literatuur werd systematisch beoordeeld en aanbevelingen voor interventionele behandelingen werden geformuleerd met behulp van een gemodificeerde Delphi-methode. De bevindingen tonen aan dat, wanneer conservatieve maatregelen onvoldoende pijnverlichting bieden, een multidisciplinaire en integratieve benadering aangewezen is. Deze omvat een farmacologische behandeling, psychologische interventies, kinesitherapie en procedures zoals intra-articulaire injecties, RF behandelingen en chirurgie. Conventionele en gekoelde RF behandelingen van de geniculaire zenuwen worden aanbevolen bij matige tot ernstige chronische kniepijn door OA wanneer conservatieve behandelingen en intra-articulaire corticosteroïdinjecties onvoldoende effect bekomen.

In **hoofdstuk 3** wordt de bestaande literatuur over het gebruik van PRF voor diverse indicaties, waaronder kniepijn, besproken. PRF werd ontwikkeld als alternatief voor conventionele RF met als doel de nociceptieve signaaloverdracht te moduleren zonder weefseldestructie te veroorzaken. Deze minimaal invasieve techniek heeft een toenemende belangstelling gekregen als behandeling voor verschillende indicaties vanwege de potentiële langdurige effecten en het lage risico op complicaties. De ondersteunende literatuur is echter beperkt, hetgeen de noodzaak aan verder onderzoek naar optimale behandelparameters onderstreept, zoals welke zenuwen het meest geschikt zijn als doelwit en de ideale behandelduur.

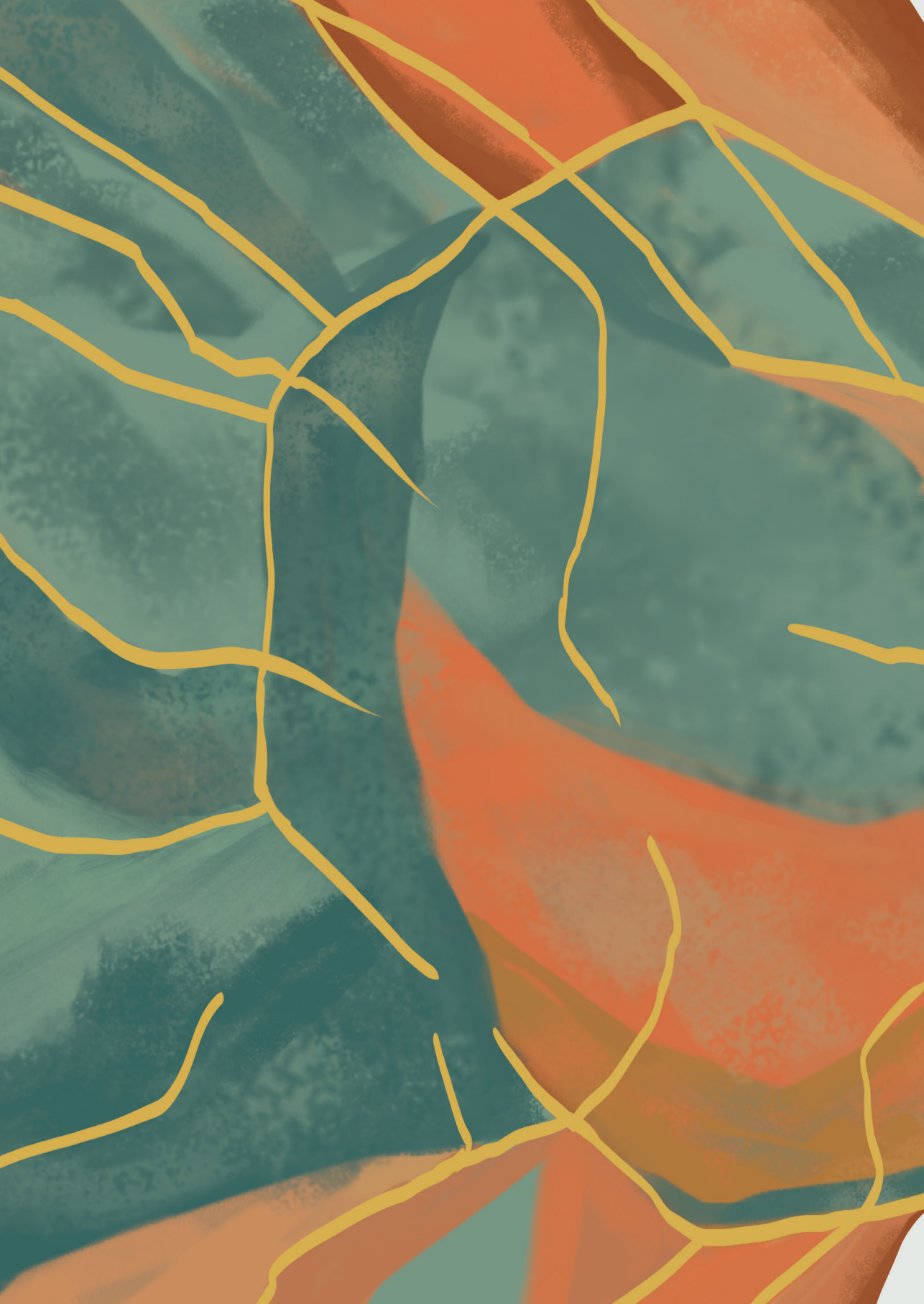
Om de rol van PRF bij de behandeling van chronische kniepijn door OA verder te verduidelijken, beschrijft **hoofdstuk 4** een gerandomiseerde gecontroleerde studie waarin de pijnstillende en functionele uitkomsten van PRF van de geniculaire zenuwen worden vergeleken met die van conventionele RF. In deze studie werden patiënten geïncludeerd met chronische kniepijn als gevolg van OA Kellgren–Lawrence (KL) graad 3 en 4. In totaal werden 188 patiënten gerandomiseerd om PRF of conventionele RF van de superolaterale, superomediale en inferomediale geniculaire zenuwen te ondergaan met 12 maanden opvolging. Beide modaliteiten resulteerden in significante reducties van pijn, functionele beperkingen en het gebruik van pijnmedicatie. Conventionele RF leidde echter consistent tot een grotere pijnreductie en gunstigere uitkomsten op de meeste secundaire eindpunten gedurende de volledige follow-up. Complicaties waren in beide groepen minimaal. Daarnaast werden verschillende voorspellers van behandelsucces op zes maanden na de interventie geïdentificeerd. Een slechter resultaat van de behandeling was geassocieerd met gevorderde OA, een hogere initiële pijnintensiteit en de aanwezigheid van depressie, angststoornissen of diabetes mellitus.

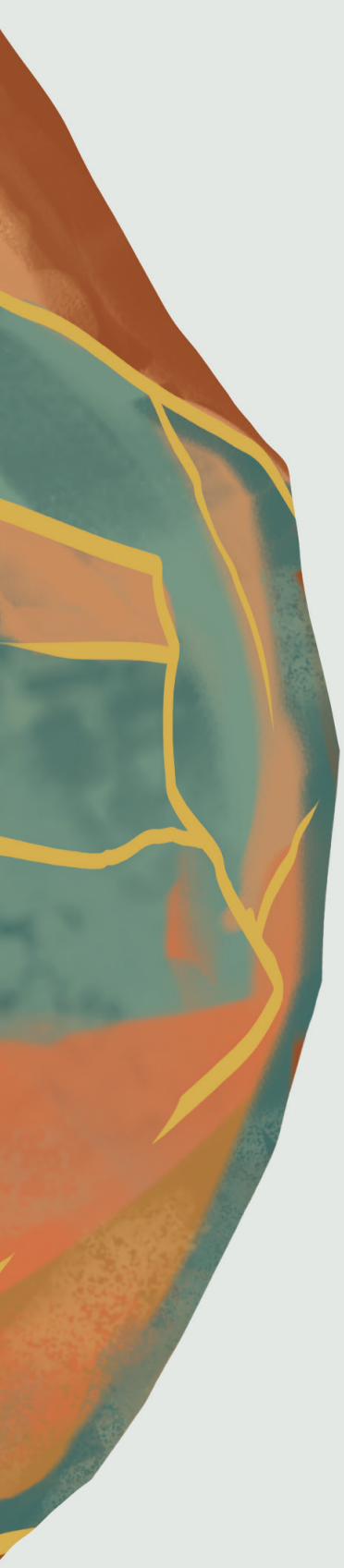
Hoofdstuk 5 presenteert de resultaten van de COCOGEN-studie, een dubbelblinde, gerandomiseerde gecontroleerde non-inferioriteitsstudie waarin gekoelde RF wordt vergeleken met conventionele RF van de geniculaire zenuwen. Gekoelde RF is een RF modaliteit die grotere laesies creëert, hetgeen theoretisch kan leiden tot verbeterde klinische uitkomsten door de invloed van anatomische variabiliteit te verminderen. In deze studie werden patiënten geïncludeerd met chronische kniepijn door OA KL graad 2 tot 4, evenals patiënten met PPSP na TKP, met een follow-up tot zes maanden. De primaire uitkomst was het percentage patiënten dat drie maanden na de interventie ten minste 50% pijnreductie bereikte. Secundaire uitkomsten omvatten kniepijn intensiteit, functionele status, kwaliteit van leven, emotioneel welzijn en bijwerkingen tot zes maanden na de interventie. Conventionele RF werd getoetst op non-inferioriteit in vergelijking met gekoelde RF wat betreft pijnreductie na drie maanden. Er was geen statistisch significant verschil in de primaire uitkomst. De resultaten van de non-inferioriteitsanalyse lieten geen definitieve conclusie toe op basis van de vooraf gedefinieerde non-inferioriteitsmarge. Er werden geen statistisch significante verschillen tussen de groepen gevonden voor de secundaire uitkomsten. Er werden geen ernstige bijwerkingen gerapporteerd. Zowel conventionele als gekoelde RF resulteerden in pijnvermindering bij patiënten met OA en PPSP. Hoewel er bij gekoelde RF een hogere proportie van patiënten was die een klinisch relevante pijnreductie bereikten, werd er geen statistisch significant verschil aangetoond. Dit piloot onderzoek kon dan ook geen non-inferioriteit van conventionele RF noch superioriteit van gekoelde RF aantonen. Grotere, adequaat gepowerde, gerandomiseerde gecontroleerde studies zijn noodzakelijk om deze bevindingen te bevestigen en na te gaan of gekoelde RF een klinisch relevant voordeel biedt ten opzichte van conventionele RF.

De lange termijn klinische uitkomsten en de kosteneffectiviteit van de COCOGEN-studie worden verder beschreven in **hoofdstuk 6**. Van de 49 geïncludeerde patiënten voltooiden 40 de volledige follow-up van 12 maanden. Na 12 maanden bedroeg het percentage patiënten met ten minste 50% pijnreductie 22,2% (4/18) in de conventionele RF-groep en 22,7% (5/22) in de gekoelde RF-groep (p>0,05). De gemiddelde absolute pijn intensiteit na 12 maanden bij patiënten met PPSP was het enige statistisch significante verschil tussen gekoelde en conventionele RF (p=0,02). Beide RF modaliteiten resulteerden in aanhoudende pijnreductie na 12 maanden. Voor de overige uitkomsten werden geen statistisch significante verschillen waargenomen. Er werden geen ernstige bijwerkingen gemeld. De economische evaluatie toonde aan dat gekoelde RF bij patiënten met PPSP gepaard ging met lagere kosten en een hogere kwaliteit van leven in vergelijking met conventionele RF, maar niet bij patiënten met OA.

Om de resterende vragen, die voortvloeien uit de piloot COCOGEN studie, te beantwoorden, beschrijft **hoofdstuk 7** het protocol van een grootschalige, gerandomiseerde gecontroleerde studie: de COGENIUS-studie. Deze studie evalueert de effectiviteit en kosteneffectiviteit van conventionele en gekoelde RF van de geniculaire zenuwen in vergelijking met een sham procedure bij patiënten met chronische kniepijn door OA of PPSP na TKP. Voor elke indicatie worden 200 patiënten geïncludeerd met een follow-up van twee jaar. De studie is momenteel lopende. Alle deelnemers doorlopen eerst een inloopperiode van één tot drie maanden waarin de conservatieve behandeling wordt geoptimaliseerd. Vervolgens worden patiënten in een 2:2:1-verhouding gerandomiseerd naar conventionele of gekoelde RF, of een sham procedure. De primaire analyse vergelijkt de effectiviteit van elke RF modaliteit met de sham procedure, en indien effectief, zal een secundaire analyse conventionele met gekoelde RF vergelijken. Alle analyses worden afzonderlijk uitgevoerd per indicatie. De primaire uitkomst is de Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) na zes maanden. Secundaire uitkomsten omvatten kniepijn intensiteit, fysiek functioneren, gezondheid gerelateerde kwaliteit van leven, emotioneel welzijn, medicatiegebruik, zorg- en maatschappelijke kosten en bijwerkingen tot 24 maanden na de interventie.

Tot slot, op basis van dit proefschrift kan worden geconcludeerd dat conventionele RF van de geniculaire zenuwen effectiever is dan PRF bij patiënten met chronische kniepijn door OA. Daarnaast lijkt gekoelde RF bijkomende klinische en economische voordelen te bieden ten opzichte van conventionele RF, vooral bij patiënten met PPSP na TKP. Een RF behandeling van de geniculaire zenuwen heeft daardoor een plaats verworven binnen het behandelalgoritme, namelijk voorafgaand aan chirurgie bij OA en als therapeutische optie bij PPSP na TKP.





CHAPTER 10

Impact paragraph

Impact paragraph

Chronic knee pain represents a major global health burden.[1] It negatively affects patients' functional capacity and quality of life, while also generating substantial societal costs due to increased healthcare utilization, work absenteeism, and reliance on informal caregivers.[2-4] Despite the wide range of available treatment options, important gaps remain in the current management of chronic knee pain due to osteoarthritis (OA). In particular, there remains a notable lack of adequate intermediate treatment options between conservative management and a total knee arthroplasty (TKA). Therefore the transition from conservative management to a final TKA, is often made too rapidly.[2] Moreover, TKA is not fail-proof, as approximately one in five patients develops persistent post-surgical pain (PPSP).[5, 6] In addition, TKA represents the most costly intervention within the treatment algorithm.[7-9] This highlights the need for an effective intermediate treatment which a radiofrequency (RF) treatment of the genicular nerves has the potential to fulfill.

However, several challenges must be addressed before this treatment can be fully implemented in clinical practice. This thesis contributes to overcoming these barriers for implementation by providing clinically, scientifically, and societally relevant evidence supporting the use of RF in patients with chronic knee pain due to OA and PPSP following TKA. By systematically evaluating and comparing different RF modalities (conventional RF, pulsed RF (PRF), and cooled RF) this thesis offers important insights that help refine interventional pain management strategies for this growing patient population.

From a clinical perspective, the findings demonstrate that conventional RF provides superior and more consistent pain relief compared with PRF in patients with advanced OA, while maintaining a favorable safety profile.[10] At the same time, cooled RF emerges as a promising alternative, particularly for patients with PPSP after TKA, where both clinical outcomes and cost-effectiveness analyses suggest potential added value.[4, 11] These results contribute to a more nuanced understanding of the benefits and limitations of each RF modality and support clinicians in selecting the most appropriate treatment based on individual patient characteristics and clinical context.

From a scientific standpoint, this thesis addresses important gaps in the existing literature by providing high-quality randomized controlled trial data and long-term follow-up outcomes. It also emphasizes the need for further large-scale, adequately powered studies to confirm the comparative effectiveness of RF modalities and to better define optimal treatment parameters.[2] The ongoing COGENIUS trial, as described in

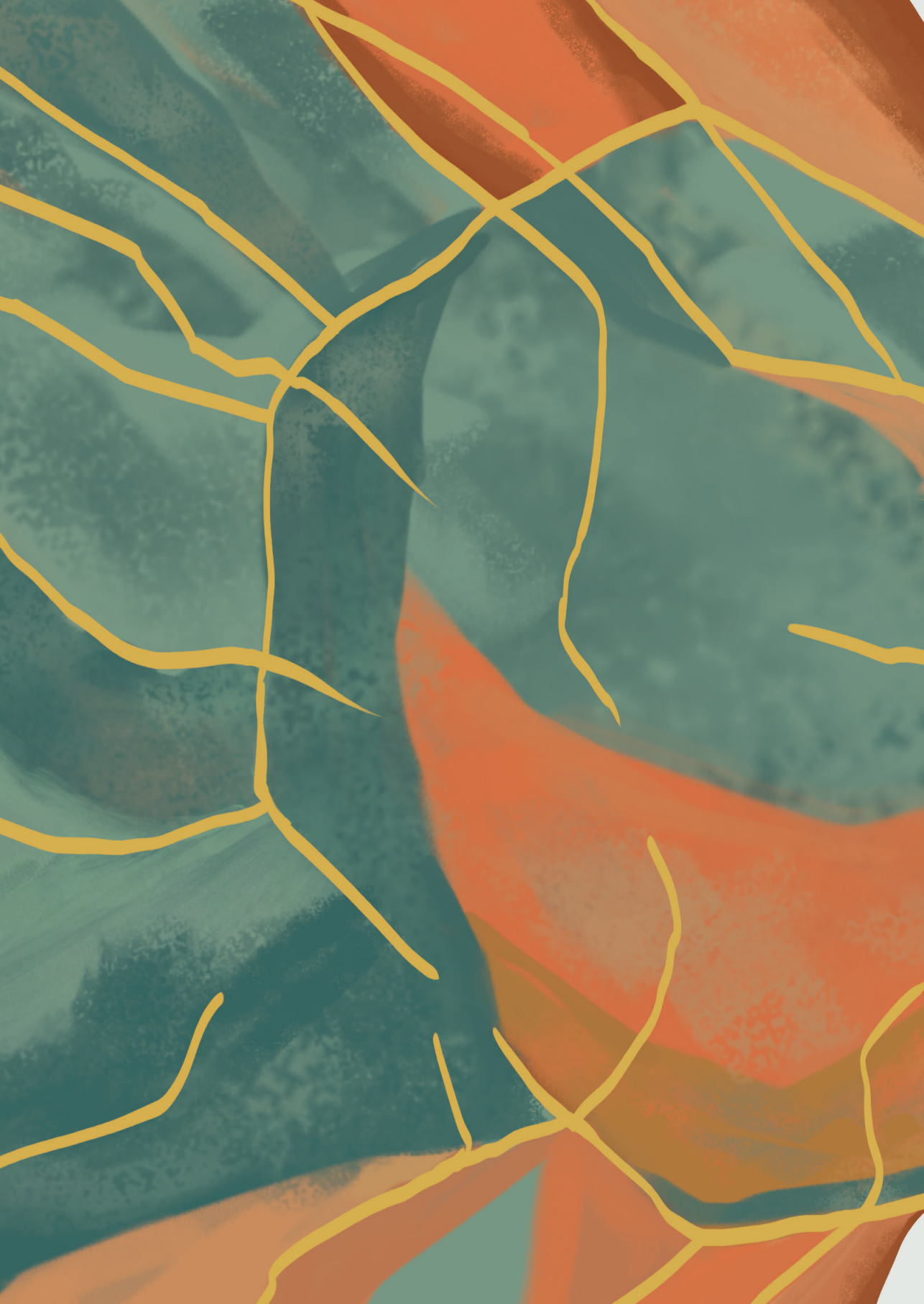
this thesis, represents an important next step and has the potential to further inform clinical guidelines and standard practice.[12] Identification of prognostic factors may further help determine the ideal candidates for interventional treatments, as chronic pain in OA or PPSP often involves a combination of nociceptive, neuropathic, and nociplastic mechanisms.[13]

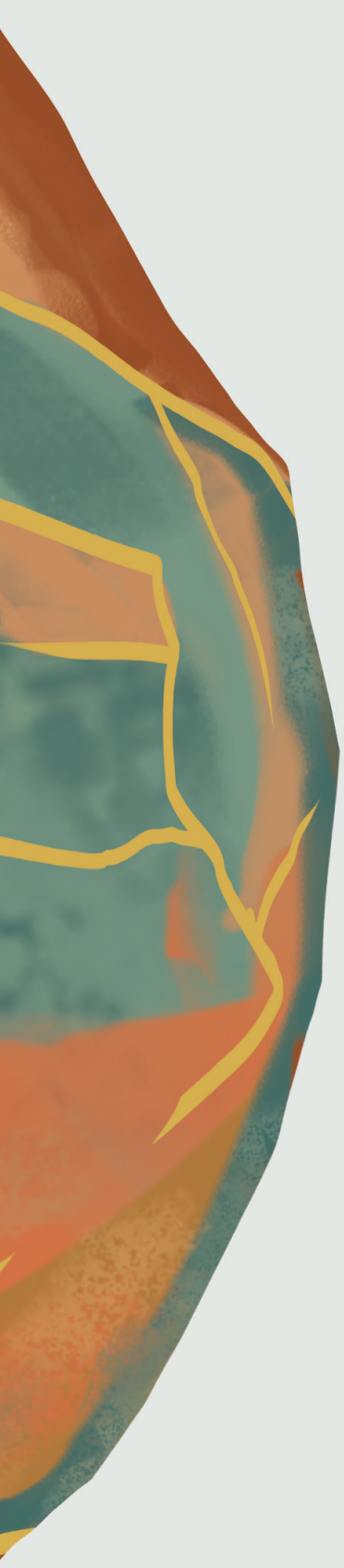
In terms of healthcare systems and policy, this work highlights the potential of RF interventions to reduce reliance on more invasive and costly procedures.[14] By positioning RF treatment within the therapeutic algorithm, after failure of conservative management but before surgical intervention, there is a possible opportunity to decrease healthcare expenditures while simultaneously improving patient outcomes.[2, 14] The inclusion of health economic evaluations further strengthens the relevance of these findings for policymakers and healthcare payers, particularly in the context of increasing demand for cost-effective and sustainable care.

Finally, this thesis contributes to a broader shift in the care pathway of chronic knee pain toward a multidisciplinary and patient-centered approach. In such a care pathway, collaboration between healthcare professionals enhances outcomes beyond what individual professionals can achieve alone. At the same time, patients can play an active role, recognizing the importance of lifestyle modifications and the value of prevention. By integrating interventional techniques such as RF into a comprehensive framework that includes pharmacological, physical, and psychological strategies, this approach supports a more holistic management of pain and function. Ultimately, the findings of this thesis have the potential to improve quality of life for patients, optimize the use of healthcare resources, and guide future innovation in interventional pain medicine.

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APPENDIX

Curriculum Vitae

Curriculum Vitae

Thibaut Vanneste was born in Kortrijk on April 19, 1985, and grew up in Tongeren. He completed his higher secondary education in 2003 at Onze-Lieve-Vrouw Humaniora in Tongeren. He obtained his Bachelor of Medicine at the University of Hasselt in 2006, graduating cum laude. He then continued his medical studies at the Catholic University of Leuven, where he earned his Master of Medicine degree in 2010, also cum laude. During his studies, he developed a strong interest in anesthesiology, which would later become his main field of specialization. He was also active as a student researcher under the supervision of Professor Hellings, an experience that further stimulated his interest in scientific research.

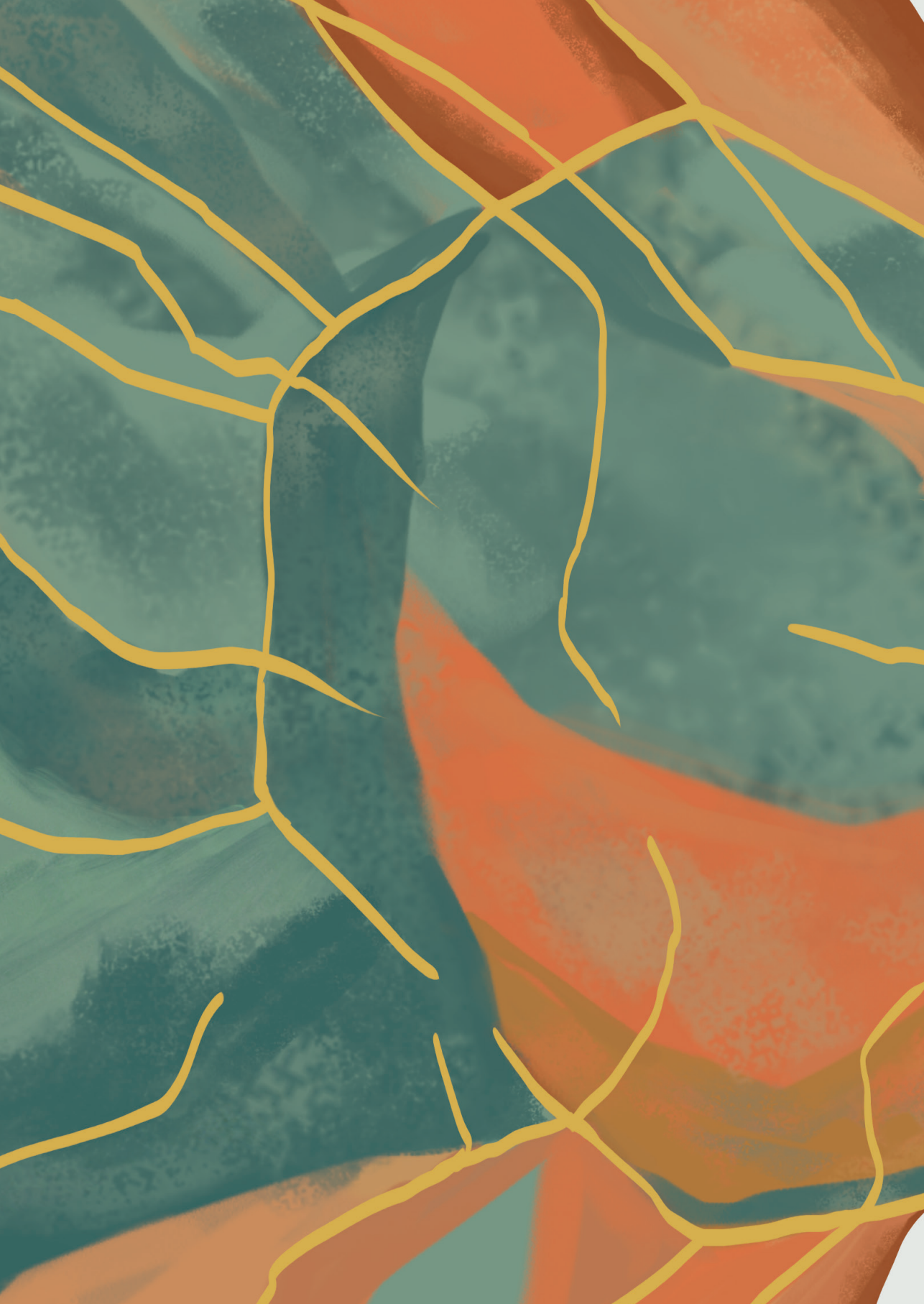
He began his professional career in 2010 as a resident in anesthesiology at UZ Leuven. During his training, he gained broad experience across multiple disciplines, including anesthesiology, intensive care, emergency medicine, and chronic pain management. He worked at ZOL Genk and later returned to UZ Leuven to further expand his expertise. In 2015, he completed his specialist training in anesthesiology.

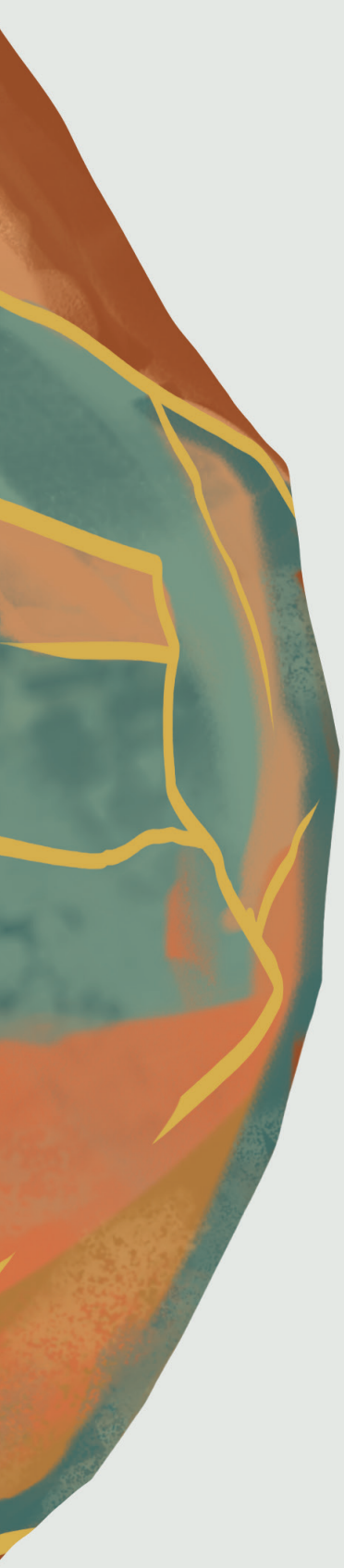
Between 2015 and 2016, he pursued a fellowship in intensive care at ZOL Genk, and obtained his postgraduate degree in intensive care. In 2016, he further broadened his clinical skills with organizational and strategic insight by completing a Master's degree in Management and Policy in Healthcare. Following this, he focused more specifically on chronic pain management, completing a pain fellowship between 2016 and 2017 at the multidisciplinary pain center at ZOL Genk under supervision of Prof. Dr. Van Zundert. His growing interest in this field led him to undertake the 'Fellow of Interventional Pain Practice' (FIPP) examination in 2017, organized by the World Institute of Pain. For his outstanding performance, he was awarded the prestigious Hassenbusch Prize, given annually to the candidate achieving the highest overall score worldwide. In December 2017, he further refined his expertise through an observership with Dr. Narouze in Ohio, USA, specializing in ultrasound-guided interventional pain techniques. In 2023, he also obtained the Certified Interventional Pain Sonologist (CIPS) certification. In 2021, he broadened his education further by obtaining a postgraduate degree in emergency care.

Since 2017, he has been working as a staff member at ZOL Genk, where he is active in the departments of chronic pain, anesthesiology, intensive care, and emergency medicine. Additionally, from 2020 to 2024, he served as a staff member in pain medicine at Maastricht UMC+. In 2021, he initiated a PhD project under the supervision of Prof. Dr. Van Zundert at Maastricht UMC+, focusing on a radiofrequency treatment for chronic knee pain. His scientific interests have resulted in multiple publications in the field of chronic pain.

He is actively involved in education as a speaker and teacher in various national and international organizations and contributes to the organization of congresses and workshops. In addition, he serves as a board member of the 'Vlaamse Anesthesiologische Vereniging voor Pijnbestrijding' (VAVP).

On a personal note, Thibaut is married to Sabrina Munters and is the proud father of Charlotte and Arnaud.





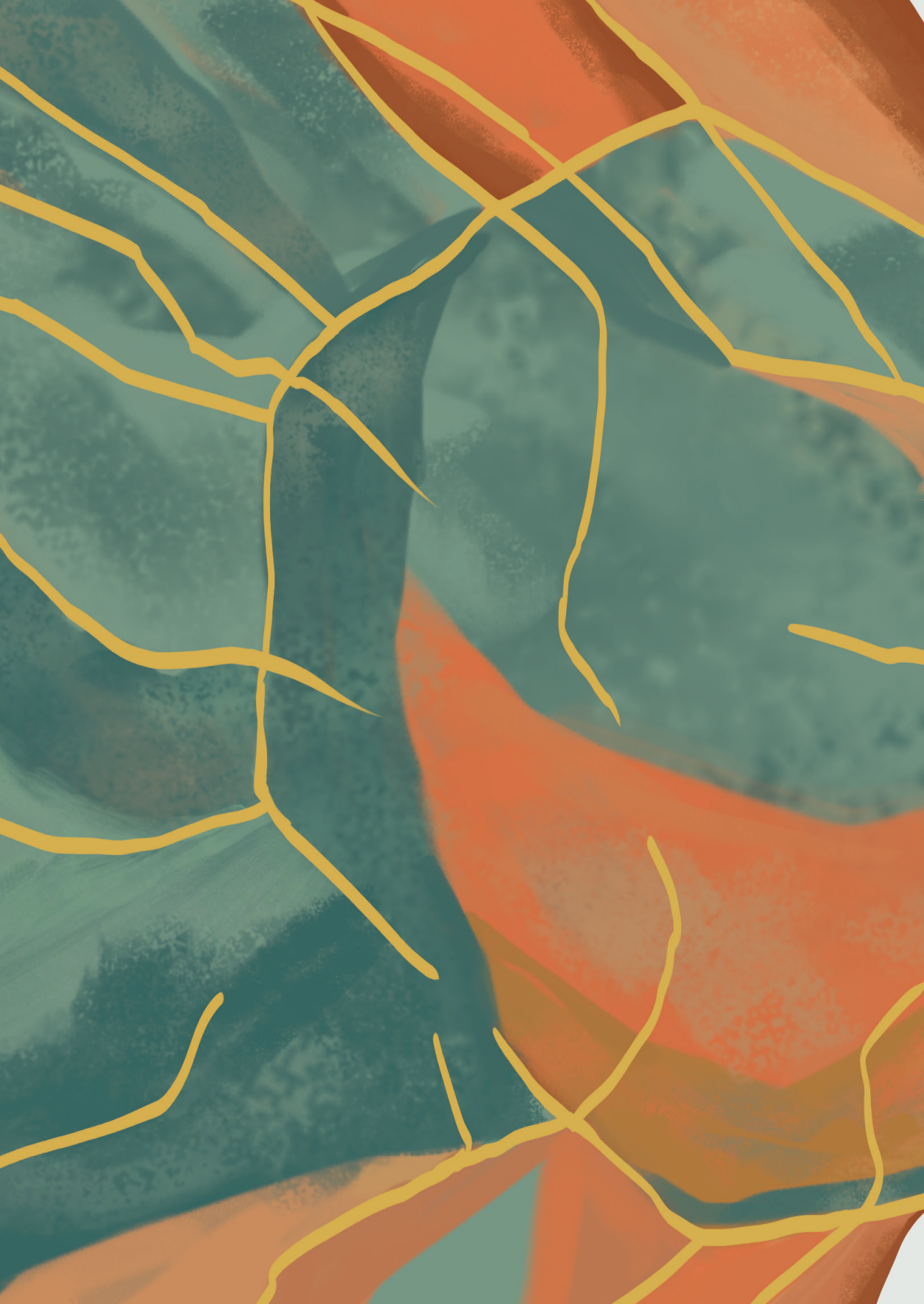
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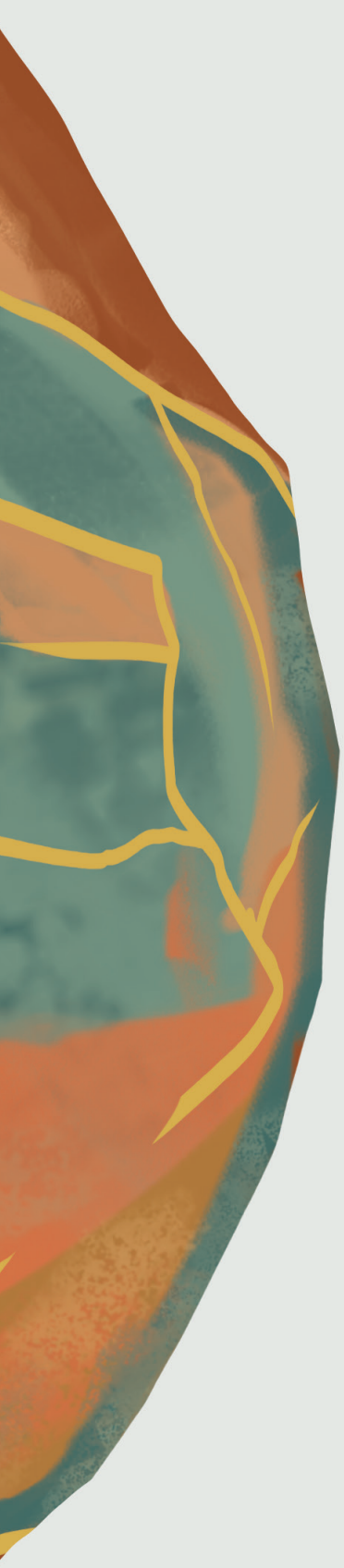
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APPENDIX

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