Targeting the genicular nerves for chronic knee pain:

a multidimensional analysis



Amy Belba

Statements belonging to the PhD thesis:

Targeting the genicular nerves for chronic knee pain:

a multidimensional analysis

By

Amy Belba
Maastricht, September 30th 2026

1. Genicular nerve radiofrequency is a valuable long-term treatment option for chronic knee pain caused by osteoarthritis and persistent post-surgical pain. ~ Chapter 2
2. Cooled radiofrequency is likely cost-effective for persistent post-surgical pain, but less so for osteoarthritis compared with conventional radiofrequency. ~ Chapter 3
3. Chronic knee pain is a highly burdensome condition for which existing treatments are often insufficient, highlighting the need for effective, safe, and evidence-based alternatives. ~ Chapter 4
4. Radiofrequency treatment has a safe profile in both osteoarthritis and persistent post-surgical pain, with rare cases of serious complications. ~ Chapter 5
5. The implementation of the genicular nerve block in the acute perioperative setting is feasible and safe; its analgesic value may be moderate, positioning the genicular nerve block as an additive block in a multimodal protocol. ~ Chapter 6
6. Patients accept and value radiofrequency ablation in the treatment of chronic knee pain and are open to repeat treatment and to treatment protocols targeting more than three genicular nerves. ~ Chapter 7
7. *"You never test the depth of a river with both feet."* ~ African proverb from the Ashanti people in Ghana
8. *"In the Garden of Eden, sin permeated every fibre of society, bringing pain, illness, and death to humankind. In the struggle against it, I could not remain passive; on the contrary, I would do everything within my power to heal and alleviate the suffering of my patients."* ~ Gjergji Belba
9. *"Opinions cannot survive if one has no chance to fight for them."* ~ Thomas Mann
10. *"[ask not] 'What works?' or, 'Does this program work?' but ask instead, 'What works for whom in what circumstances and in what respects, and how?'"* ~ Pawson, R., & Tilley, N. (1997). Realistic Evaluation.

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DISSERTATION

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List of abbreviations

Adverse Event(s)	AE(s)
Belgian Association for Regional Anaesthesia	BARA
Belgian Anaesthesia Trainees	BAT
Body Mass Index	BMI
Cost-Effectiveness	CE
Central Register of Controlled Trials	CENTRAL
Confidence Interval	CI
Continuous Neuroablative Radiofrequency	CNARF
Consolidated criteria for Reporting Qualitative research	COREQ
Complex Regional Pain Syndrome	CRPS
Degenerative knee Pain group	DP
Dorsal Root Ganglion	DRG
Euroqol 5-Dimension 3-Level	EQ-5D-3L
Euroqol 5-Dimension 5-Level	EQ-5D-5L
Food and Drug Administration	FDA
Feasibility, Appropriateness, Meaningfulness, and Effectiveness	FAME
Femoral Triangle Block	FTB
Global Burden of Disease	GBD
Genicular Nerve	GN
Genicular Nerve Block	GNB
Global Perceived Effect	GPE
Hospital Anxiety and Depression Scale	HADS
Health Economic Evaluation	HEE
Health-Related Quality of Life	HRQoL
Health Technology Assessment	HTA
Intra-Articular Corticosteroid Injections	IACS
Intra-Articular Hyaluronic Acid Injections	IAHA
International Association for the Study of Pain	IASP
Intracluster (or Intraclass) Correlation Coefficient	ICC
International Classification of Diseases	ICD
Incremental Cost-Effectiveness Ratio	ICER
International Clinical Trials Registry Platform	ICTRP
Fellow of Interventional Pain Practice	FIPP
Inferolateral Genicular Nerve	ILGN

Inferomedial Genicular Nerve	IMGN
Infiltration between the Popliteal Artery and Capsule of the Knee	iPACK
Implantable Pulse Generator	IPG
Intention-To-Treat	ITT
Intravenous	IV
Joanna Briggs Institute	JBI
Kellgren-Lawrence grade	KL grade
Local Infiltration Analgesia	LIA
Medical Consumption Questionnaire	MCQ
Mean Difference	MD
Medicines and Healthcare products Regulatory Agency	MHRA
Medication Quantification Scale III (3)	MQS III (3)
Magnetic Resonance Imaging	MRI
Maximum Voluntary Isometric Contraction	MVIC
North-East	NE
Number Needed to Treat	NNT
Numeric Rating Scale	NRS
Nonsteroidal anti-inflammatory drugs	NSAIDs
North-West	NW
Osteoarthritis	OA
Oxford Knee Score	OKS
Outcome Measures in Rheumatoid Arthritis Clinical Trials-Osteoarthritis Research Society International	OMERACT-OARSI
Productivity Cost Questionnaire	PCQ
Pain Catastrophizing Scale	PCS
Positron Emission Tomography-Computed Tomography	PET-CT
Patient's Global Impression of Change	PGIC
Pulsed Neuromodulative Radiofrequency	PNMRF
Per Os	PO
Persistent Post-Surgical Pain	PPSP
Pulsed Radiofrequency Ablation	PRF
Platelet-Rich Plasma	PRP
Quality-Adjusted Life Year	QALY
Randomised Controlled Trial	RCT
Radiofrequency	RF
Risk of Bias 2	ROB 2

Risk Ratios	RR
Spinal Cord Stimulation	SCS
Standard Deviation	SD
South-East	SE
12-Item Short-Form Health Survey	SF-12
36-Item Short Form Health Survey	SF-36
Superolateral Genicular Nerve	SLGN
Standardised Mean Difference	SMD
Superomedial Genicular Nerve	SMGN
Single-Photon Emission Computed Tomography combined with Computed Tomography	SPECT-CT
South-West	SW
Transcutaneous Electrical Nerve Stimulation	TENS
Total Knee Arthroplasty	TKA
Timed-Up-and-Go	TUG
Antwerp University Hospital	UZA
Visual Analogue Scale	VAS
Western Ontario and McMaster Universities Osteoarthritis Index	WOMAC
Ziekenhuis Oost-Limburg	ZOL
Difference in Costs	ΔC
6-Minute Walking Test	6MWT



Chapter 1

Introduction



Prelude

It was in 1951 that Dr Simon Lajos published a report on a novel surgical technique in the weekly scientific journal 'Orvosi Hetilap' in Hungary.[1] Dr Lajos cut distal nerve branches from the tibial, femoral, and obturator nerves using two surgical incisions: one in the superior medial knee and another in the posterior knee groove in patients suffering from osteoarthritis of the knee. Results were impressive: pain ceased to exist in twenty of the thirty-five operated cases, multiple patients had partial improvement, and only four experienced no effect. Dr Lajos concluded that this surgery should be recommended in all cases of knee osteoarthritis where physical therapy does not work. This was probably the first report of knee denervation for chronic knee pain.

Since 1951, the medical reality has changed dramatically, and the surgical denervation of the knee has not proven to pass the test of time. The surgical technique is invasive and targets nerve branches with possible motor nerve fibres, leading to undesirable motor weakness of the lower limb. However, the concept behind it proved to be intriguing. Targeted lesions of the most peripheral sensory nerves of a joint can reduce pain and improve functionality, and following this, more than half a century later in 2011, Dr Woo-Jong Choi performed the first recorded modern percutaneous ablation of the knee joint.[2] He targeted three of the most distal sensory nerves of the knee, named the genicular nerves, with radiofrequency current under local anaesthesia. From that point on, multiple attempts have been made to optimise this technique in light of improved anatomical and technological knowledge. The genicular block and radiofrequency treatment of the genicular nerves lie at the heart of this dissertation.

In the following paragraphs, I am going to first offer an overview of the condition of chronic knee pain, focusing on osteoarthritis and persistent post-surgical pain. Secondly, I will describe the radiofrequency treatment. Thirdly, the use of the genicular nerve block for the treatment of acute knee pain will be described together with its potential advantages and disadvantages. This introduction will continue with a rationale for engaging in this thesis, presenting the need for more research in chronic knee pain, and the knowledge gaps on the use of the genicular block in acute and chronic knee pain. Finally, the research questions will be elaborated.

1 From knee osteoarthritis to persistent post-surgical pain

Chronic knee pain is an umbrella term that encompasses all conditions that cause pain in the knee joint. According to the International Classification of Diseases, ICD-11, chronic knee pain is defined as pain that persists or recurs for more than 3 months.[3] The knee, as a major weight-bearing joint, is particularly prone to degeneration.[4] The knee joint has complex biomechanics and an intrinsic low stability, which increases its susceptibility to injury. Its rich and complex innervation further heightens vulnerability to chronic pain conditions.[5]

While mostly the culprit of chronic knee pain is osteoarthritis (OA), other conditions that lead to knee pain are persistent post-surgical pain (PPSP), inflammatory arthropathies, infections, Complex Regional Pain syndrome (CRPS), and post-traumatic pain.

1.1 Knee osteoarthritis

Individuals with knee OA represent the largest group affected by osteoarthritis. Globally, an estimated 86.7 million people were living with knee OA in 2020, with a significantly higher prevalence among women.[6] The global lifetime risk of developing knee OA is 9.31%, and the likelihood of symptomatic disease increases steadily with age.[4,6] For those affected, knee OA results in an important personal burden, including pain, reduced physical function, disability, and considerable socio-economic consequences.[7]

The burden of knee OA is steadily increasing due to the ageing of the population, increasing obesity, and lifestyle changes.[4,8] Projections based on Global Burden of Disease (GBD) 2021 estimate a 74·9% increase in the prevalence of knee OA from 2020 to 2050.[4] Similar trends are observed in Belgium and the Netherlands. In Western Europe, the lifetime prevalence of knee OA is estimated at 10.01%, slightly exceeding the global average. In the Netherlands, data from the Nationaal Kompas Volksgezondheid indicate a continued increase in knee OA prevalence between 2021 and 2023.[9]

From a **pathophysiological perspective**, OA remodels the whole knee joint, of which the articular cartilage is the structure typically affected in early disease.[10,11] Biomechanical, inflammatory, and metabolic alterations contribute to articular cartilage damage and impairment of physiological processes at the level of the subchondral bone, synovium, meniscus, ligaments, bursa, nerves, and muscles. Magnetic Resonance Imaging of the knee can identify these early cartilage changes.[12] The two instrumental factors leading to disease degeneration, mechanical factors (repeated loading) and chronic low-grade inflammation, result in time in subchondral bone and extra-articular joint involvement.

Multiple **risk factors** for developing knee OA have been identified, including genetic predisposition, increasing age, sex (predominantly female), overweight, mechanical factors, and low-grade inflammation. Increased age, the strongest risk factor for OA, manifests in a frequent diagnosis from the age of 40 years old.[4] Women are disproportionately affected, with a female-to-male prevalence ratio of 1.69.[6] Mechanical risk factors include malalignment, abnormal joint shape, heavy physical work, and repetitive execution of high-impact sports. Of these factors, mechanical factors and excess weight constitute the two most modifiable risks.[13]

Patients with knee OA frequently initially **present clinically** with pain, which is typically of mechanical origin. The anteromedial knee is the quadrant most frequently affected by OA.[14] **The mechanisms driving OA pain** are complex and not fully understood.[15] The predominant type of pain is nociceptive, reflecting the inflammatory and non-inflammatory response to repetitive mechanical forces, and manifesting as movement-evoked pain.[15,16] Chronic low-grade inflammation may lead to neovascularisation, neurovascular invasion of joint tissues, and degeneration of C-fibre nerve endings, contributing to neuropathic pain.[17] In more advanced disease, peripheral and central sensitisation become increasingly important.[18] Peripheral sensitisation may lead to dysregulation of noradrenergic and serotonergic descending pathways at the level of spinal wide dynamic range neurons and abnormal activation of the periaqueductal grey in the brainstem.[18] Around 35% of patients with knee OA experience characteristics of neuropathic or nociplastic pain.[19] Aside from pain, patients report reduced knee function, joint effusions, muscle weakness, instability of the joint, morning stiffness, and psychological distress.

The **diagnosis** of knee OA is clinical, based on patients' symptomatology and examination.[20] The addition of imaging of the knee increases the specificity of the diagnosis.[20,21] The Kellgren-Lawrence grading (grade I to IV) is universally used to classify disease progression.[22]

Management of chronic knee pain should be approached using the biopsychosocial framework.[23,24] This acknowledges pain as a complex phenomenon that can be managed from multiple angles: *biological contributors* such as patient genetics and demographics, knee joint mechanics, metabolic and inflammatory mechanisms; *psychological contributors* such as pain catastrophizing, depression, and kinesiophobia; and finally, *social factors* such as decrease of mental health, social isolation, and impact on relationships.

Recommendations from international bodies on conservative care of knee OA group them into non- pharmacological and pharmacological care.[25-28] A synthesis of these recommendations is presented in **Figure 1**.

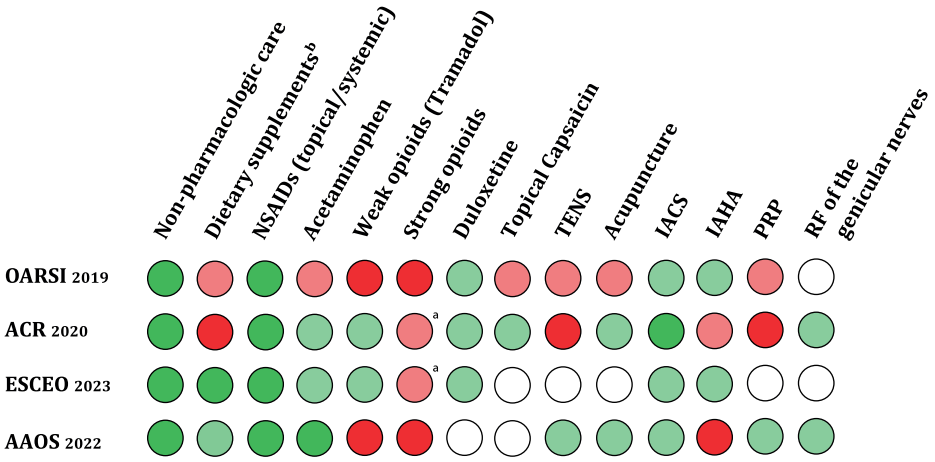

Figure 1. Summary of the recommended non-surgical treatments for knee OA.[25-28]

Light green: Weak positive recommendation; Dark green: Strong positive recommendation; Light red: Weak negative recommendation; Dark red: Strong negative recommendation; White: No recommendation.

[a]: only indicated for end-stage knee OA.

[b]: Glucosamine, Chondroitin.

NSAIDs: Nonsteroidal anti-inflammatory drug; TENS: Transcutaneous Electrical Nerve Stimulation; IACS: intra-articular corticosteroid injections; IAHA: intra-articular hyaluronic acid injections; PRP: Platelet-Rich Plasma; RF: radiofrequency.

Non-pharmacological care targets biopsychological factors. Cornerstone treatments are physiotherapy, where land-based and aquatic exercise improve functioning without accelerating disease, and weight management. Other important treatments include education, self-management, and the use of walking aids. A meta-analysis suggests that the effect size of weight loss is small and comparable to that of Nonsteroidal anti-inflammatory drugs (NSAIDs), however, without adverse events.[29]

Pharmacological care aims primarily at symptom control. Starting from the multifactorial mechanisms that lead to OA one can classify the pharmacological care based on its mechanism of work: *Acetaminophen and NSAIDs* decrease noxious pain perception and decrease low-grade inflammation in the joint (Acetaminophen: Number needed to treat (NNT) 16 and 4.5-9.8 respectively); *Duloxetine* alters the descending spinal pathways in patients with neuropathic/nociplastic pain (NNT 6); *Intraarticular Corticosteroid Injections* decrease low-grade inflammation in the joint (NNT 8-10); and *Intraarticular Hyaluronic Acid Injections* by means of anti-inflammatory, anabolic, analgesic, and chondroprotective mechanisms.[30] The literature remains

discordant on the long-term effects of intra-articular knee injections, where several studies report accelerated OA progression, while others report no increased incidence of total knee arthroplasty (TKA) at five years after injection.[31]

There are currently **no disease-modifying drugs** recommended for knee OA.[11,32] Several medications or supplements have been investigated with negative results, including Glucosamine, chondroitin, statins, and biologicals (e.g., anti-Nerve Growth Factor/ Tumour necrosis factor antibody therapy/Interleukin-1 receptor antagonist).[11] Platelet-Rich Plasma and Mesenchymal stem cell injections are the only pharmaceuticals with a promising disease-modifying effect.[33] Studies on Platelet-Rich Plasma and Mesenchymal stem cells are, however, cursed with a lack of standardisation, resulting in mixed evidence.

Patients with moderate to advanced knee OA that is refractory to conservative treatments often undergo **surgical interventions**. It is estimated that 30-50% of individuals first diagnosed with symptomatic knee OA will undergo knee arthroplasty in the span of their lifetime.[34,35] Knee arthroplasty is a widely used, cost-effective procedure in patients with knee OA, with up to 75% of patients reporting satisfaction with the outcomes and improved quality of life.[36] By removing diseased joint surfaces and restoring joint biomechanics, TKA can alleviate subchondral knee pain. However, although this procedure relieves knee pain and improves function, up to 25% of patients express dissatisfaction, and some experience therapy-resistant PPSP.[8,37,38]

1.2 Persistent post-surgical pain

Persistent post-surgical pain (PPSP) is a relatively underreported condition.[39] It was formally recognised as a distinct entity with the introduction of ICD-11 in 2022, and epidemiological and demographic data remain limited. Historically, PPSP has been described using various terms, including postoperative pain, dissatisfaction following TKA, and persistent pain. Although PPSP can occur after different knee operations, it is most commonly reported after TKA.

Despite the lack of national prevalence data on PSPS after TKA in Belgium and the Netherlands, both countries rank among the top ten in Europe in terms of annual knee surgical procedures.[40] Surgical interventions constitute the greatest economic burden in patients with chronic knee pain. According to the Dutch Arthroplasty Register (LROI), 41,165 knee arthroplasties were performed in 2024 (three-year average: 39,296), while RIZIV/INAMI data report 28,757 procedures in Belgium in 2024, both showing upward trends and highlighting the growing clinical and economic burden of knee OA and PPSP.[41]

Diagnosis of PPSP requires pain persisting for more than 3-months in the absence of an identifiable orthopaedic cause.[42] PPSP is a diagnosis of exclusion: imaging (radiography, computed tomography, bone scintigraphy) and laboratory tests can aid in the work-up to identify fitting problems of the implants, abnormalities in the bone-prothesis interface, inflammatory or allergic response to implanted material, periprosthetic fractures, joint infection, and CRPS.[43] The nature of pain in PPSP is a combination of nociceptive, neuropathic, and nociplastic pain, with neuropathic pain features being particularly frequent.[44] In a meta-analysis, Ghoshal et al. identified that higher preoperative anxiety and depression were important **risk factors for developing PPSP.**[45]

Management strategies for PPSP largely parallel those for knee OA. Treatment of PPSP is primarily symptomatic and focused on rehabilitation, pharmacological treatment, and psychological interventions.[39,46] There is growing evidence on the use of interventional treatments for PPSP, including RF of the genicular nerves, pulsed RF of peripheral nerves, peripheral nerve stimulation, genicular artery embolisation, spinal cord stimulation, and dorsal root ganglion.[47]

Despite advancements in conservative and interventional care, many chronic OA and PPSP patients experience refractory pain and limitations in function.[48] The aforementioned epidemiological and procedural data underscore an urgent need for cost-effective strategies and optimisation of care for patients with knee OA and PPSP. In response to this need, a national campaign was initiated in Belgium in 2022 by RIZIV/INAMI to increase healthcare professionals' awareness of non-operative treatment options for knee OA before knee arthroplasty.

The treatment gap is particularly evident in three patient groups. In young OA patients, an early TKA is undesirable due to resulting changes in proprioception and knee function, an importantly shorter median time to revision surgery (4.4 years in operated individuals younger than age 60), and a limited lifespan of a knee prosthesis (approximately 82% survival of an arthroplasty implant at 25 years follow-up).[49] The resulting higher chance of revision surgery leads to high personal and social costs. In the elderly patient with OA, the placement of a TKA is associated with a high perioperative risk due to age-related comorbidities. Finally, PPSP patients have limited treatment options as medical conservative treatments are often insufficient, intra-articular injections are not indicated, and no surgical treatment is possible. In these populations, and more broadly, a minimally invasive treatment such as the radiofrequency ablation of the genicular nerves could offer symptom reduction, delay of a TKA, and, on an individual level, lead to improvement of quality of life.

2 Radiofrequency ablation of the genicular nerves

2.1 General introduction

RF treatment of the genicular nerves is a relatively recent, minimally invasive technique aimed at reducing chronic knee pain.[50] This treatment is symptomatic and aims to disrupt pain transmission by means of partial thermal denervation of the most distal articular sensory branches of the anterior knee, named the genicular nerves.

Over the past decades, researchers have broadened the application of the RF technology to peripheral joints such as the knee, hip, and shoulder. Of these, the RF of the knee joint is mostly studied. The first three clinical reports on RF for chronic knee pain were published in 2011. While Karaman et al. applied intra-articular pulsed RF and Ikeuchi et al. targeted two distal sensory branches—the medial retinacular nerve and a distal branch of the saphenous nerve—Choi et al. were the first to describe RF ablation of the three genicular nerves that would later become the standard targets in clinical practice.[2,51,52] Subsequent studies, including the introduction of cooled RF and expansion of the indications to PPSP in 2015, have positioned the RF of the genicular nerve as a safe and effective treatment for patients with therapy-resistant knee pain.[53]

During RF, an alternating current at 500 kHz, produced by a generator and delivered through an electrode, results in ionic oscillations in the targeted tissue.[54] The oscillations cause friction and heat generation around the electrode tip, resulting in a predictable area of thermal lesion of the nerve that attenuates pain conduction. Heat transfer from tissue to the probe tip is continuously monitored by a thermocouple, creating a feedback mechanism that maintains the desired temperature at the tissue–probe interface. RF ablation causes partial nerve injury and triggers Wallerian degeneration distal to the lesion. As a result, the nerve injury is reversible, which could explain why RF ablation provides long-lasting but not always permanent pain relief. In addition, tissue desiccation and charring limit further RF current propagation beyond the lesion, thereby constraining lesion size.

Four main **radiofrequency modalities** are used for treatment of chronic knee pain*:* conventional RF, cooled RF, bipolar RF, and pulsed RF.[50] Of these, continuous or conventional RF, cooled RF, and bipolar RF have ablative properties, while pulsed RF is non-ablative. Cooled RF probes use the circulation of water through the probe tip to dissipate the rise in temperature at the tissue-probe interface, limiting desiccation and charring. This results in the delivery of more current to the targeted tissue, creating a larger lesion. In bipolar RF, RF current is delivered to the area between two electrodes

positioned approximately 1cm apart. While conventional, cooled, and bipolar RF create a disruption in nerve tissue, pulsed RF is hypothesised to act through neuromodulatory mechanisms.[55] Frequently used settings for each RF modality are displayed in **Figure 2.**[50,56]

	Probe thickness	Active tip	Tissue-tip interface temperature	Tissue temperature	Duration of treatment	Shape of lesion
Conventional RF	18-20G	5-10 mm	70-80°C	70-80°C	90 sec	Eliptical
Bipolar RF	18-20G	5-10 mm	70-80°C	70-80°C	90 sec	Eliptical
Pulsed RF	18-20G	5-10 mm	42°C	42°C	4-10 min	
Cooled RF	17G	4 mm	60°C	80°C	90-150 sec	Spherical

Figure 2. Frequently used parameters of RF material and settings used during RF for the knee joint.

The lesion shape created by the RF probe varies based on the modality used and influences needle placement. Conventional RF produces an elliptical lesion, requiring parallel alignment with the nerve, whereas cooled RF generates a more spherical, angle-independent lesion. RF of the genicular nerves is typically performed under fluoroscopic and/or ultrasound guidance.

Anatomical studies on the anterior **knee joint innervation** indicate that up to 10 distal purely sensory genicular nerves innervate the anterior knee joint.[5] Three classical RF targets are the superomedial (SMGN), the superolateral (SLGN), and the inferomedial genicular nerve (IMGN). The location of the genicular nerves shows considerable interindividual variability in native knees (**Figure 3**), likely with even greater variation following knee surgery.

Several systematic reviews suggest that RF is a **safe and effective treatment** for chronic OA knee pain, with an effect size of 32 to 74% of OA patients at 6 months.[53,58,59] Data on the effectiveness of RF in PPSP and post-traumatic knee pain are scarce.[53] Mid-length data show the effect of the RF of the genicular nerves remains present at 6 to 12 months.[60] Adverse events are mild and transient, including neuritis, hypoesthesia, and bruising. Rare but more severe adverse events have been reported in case reports and include periarticular hematoma, hemarthrosis, septic arthritis, pes anserine injury, third-degree skin burn, and complex regional pain syndrome.[59] Although septic arthritis may be a particular concern in PPSP patients, no cases have been reported in this population. Due to heterogeneity in techniques, variability in control interventions, and limited long-term safety data, international guidelines currently provide only a weak recommendation for RF in knee OA (see **Figure 1**).

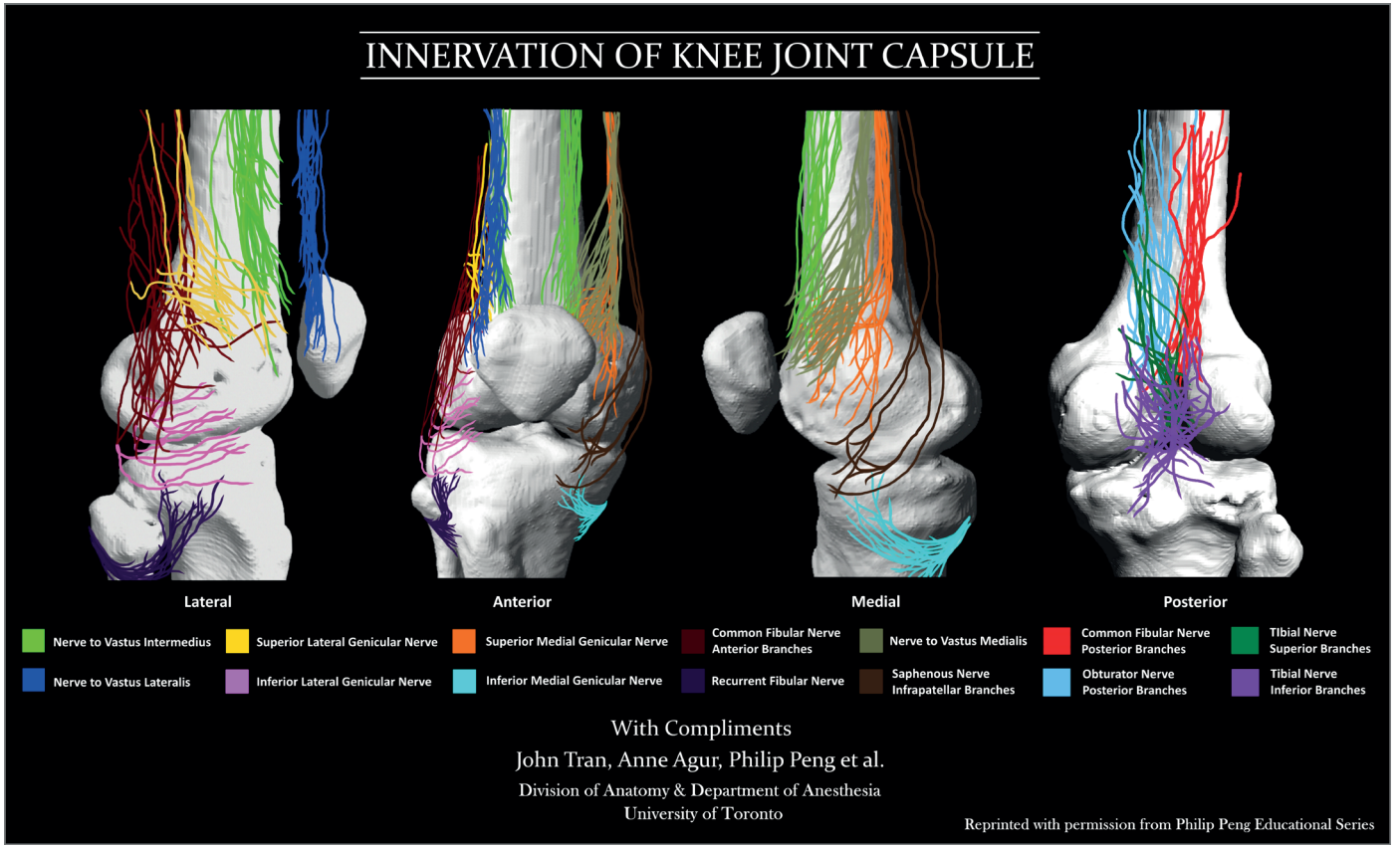

Figure 3. Innervation of the anterior knee joint capsule.

Reproduced with permission from the Philip Peng Educational Series. Tran J, Agur A, Peng P, et al., Division of Anatomy and Department of Anaesthesia, University of Toronto.[57]

In the following sections, I will address the RF treatment of the genicular nerves from clinical, implementation, societal, and individual patient perspectives.

2.2 Technical considerations and clinical challenges

Technical considerations that aim to improve the effectiveness of RF treatment are increasing accuracy in nerve capture, treating multiple genicular branches, and utilising RF techniques that create larger thermal lesions (such as cooled RF, bipolar RF of multi-tined needles).[61,62]

2.2.1 Number of nerves to target and evolution of anatomical landmarks

Anatomical studies by Tran et al. and Fonkue et al. indicate that the traditional targets for the SMGN and SLGN described by Choi et al. require revision and a more posterior needle placement to improve nerve capture.[63,64] The three classical nerve targets can be supplemented by RF of the inferior lateral genicular nerve, nerve to vastus medialis, nerve to vastus lateralis, nerve to vastus intermedius, recurrent fibular nerve, and the infrapatellar branch of the saphenous nerve. While in the large retrospective cohort of Chen et al. targeting more than three nerves clearly increased treatment success, protocols for lesioning these novel targets are not yet validated in large trials or compared to the effectiveness of the commonly used protocols.[65]

2.2.2 The choice of ablative technique

Variation in the RF technique consists mainly of the type of image guidance (fluoroscopy, ultrasound, combined fluoroscopy and ultrasound) and the choice between conventional monopolar RF single-tined needle, multitoned needle, bipolar RF, and cooled RF.

There are currently no published direct comparisons of the RF modalities outside of trials in this thesis. When ultrasound- and fluoroscopy-guided RF treatments were compared in the randomised controlled trials (RCTs) of Kim et al. and Sari et al., similar clinical effects were achieved.[66,67] These studies validate the ultrasound-guided protocols, whose advantages include real-life visualisation of the neurovascular bundle and reduction in radiation exposure.

2.2.3 Adequate patient selection and use of prognostic blocks

RF of the genicular nerves is typically considered for patients with moderate to severe, therapy-resistant chronic knee pain—often those diagnosed with knee OA, Kellgren-Lawrence grade II-IV or PPSP, having tried conservative treatments for at least 6 months, and showing a positive prognostic genicular nerve block (GNB).[68] Among these criteria, the use of a prognostic block before RF remains the most debated due to questions about its predictive value, and what constitutes a successful block (single

vs. double, injectate volume, or pain relief threshold). In McCormick et al.'s RCT, a prognostic block using 1 ml of local anaesthetic, which by itself leads to substantial local spread, and a 50% pain relief threshold did not improve RF outcomes.[69,70]

2.2.4 Long-term safety

Long-term safety data of the RF treatment remain limited. Follow-up in existing studies is a maximum of two years, and although no cases of persistent deafferentation pain with OA disease progression have been reported, such complications remain a theoretical concern, especially as more nerves are targeted.

2.3 Implementation challenges and the societal perspective

Beyond clinical efficacy, decisions about implementing the RF technique and expanding its use require translation of trial evidence into real-world health systems and assessment of its value at the health-system level.

Thus, the translation of RF treatment into routine clinical practice faces several challenges. First, diversity in protocols and technical controversies leads to variability in clinical practice and potentially variable treatment effectiveness. In addition, while RCTs apply stringent patient selection criteria, real-world patients are often older, multimorbid, and experience chronic knee pain due to a broader range of aetiologies than OA and PPSP, including post-traumatic knee pain and knee pain of unknown aetiology. Despite these differences, effectiveness outcomes reported in RCTs are, on average, comparable to those observed in two large-scale real-world cohorts [56,71]

Second, practical considerations such as physician preference, availability of RF equipment, and procedural costs substantially influence clinical decision-making. In this context, ultrasound-guided RF may facilitate implementation of the technique in settings where fluoroscopy is unavailable.

Third, current research has focused predominantly on clinical effectiveness, with limited evidence on cost-effectiveness. Beyond this thesis, only two studies by Desai et al. have evaluated the cost-effectiveness of RF, reporting it to be cost-effective when assessed against the commonly used US willingness-to-pay threshold of US$100,000 per quality-adjusted life year.[72,73] Evidence on cost-effectiveness is essential to inform reimbursement decisions.

Fourth and finally, RF needs to be integrated into national care pathways by clearly defining its role relative to knee injections and surgical interventions, and by establishing explicit referral guidelines from both primary and secondary care for RF treatment.

2.4 Individual perspective

The individual, patient-level perspective is a critical yet currently underexplored dimension of the RF treatment for chronic knee pain. While existing research primarily focuses on clinical outcomes, patients should be central not only to clinical care but also to the development of research. Chronic knee pain affects patients' psychological well-being, sleep, social participation, and quality of life, and these aspects are insufficiently captured by quantitative evaluation alone.[24] Understanding how patients experience the RF procedure, perceive its benefits and burdens, and define meaningful improvement is essential for ensuring that the intervention is acceptable, patient-centred, and aligned with real-world needs. At present, there are no qualitative data exploring patients' experiences and preferences regarding RF of the genicular nerve, as such representing an important gap that limits both the refinement of the intervention and the design of future clinical and economic studies.

3 The genicular nerve block for treatment of acute knee pain

Adequate multimodal analgesia, including the use of peripheral nerve blocks, has been shown to facilitate early mobilisation and reduce opioid consumption in patients undergoing a TKA.[74] While the search for an ideal nerve block or combination of nerve blocks is ongoing, an optimal technique for TKA should provide effective analgesia to both the anterior and posterior aspects of the knee while minimising motor blockade and thereby preserving early ambulation.[75] In this context, the GNB combined with either a popliteal artery and capsule of the knee block or posterior local infiltration analgesia may offer an optimal balance between analgesic efficacy and motor preservation.[76,77]

To date, only a limited number of randomised controlled trials have evaluated the effectiveness of the GNB. These studies emphasise the value of GNB as an adjunct to the adductor canal block, demonstrating a significant analgesic benefit compared with both popliteal artery and capsule of the knee and sham procedures in this setting.[78-82] Furthermore, a recent trial by Cuñat et al. demonstrated the non-inferiority of GNB compared with local infiltration analgesia for postoperative pain control following TKA.[83] However, these trials primarily position GNB as an add-on technique, and it remains unclear whether GNB alone provides sufficient analgesic coverage of the anterior compartment of the knee. To determine its full clinical value, GNB should also be evaluated for practical and logistical factors, including the time required to perform the block and the ease of ultrasound-guided execution when compared with alternatives such as local infiltration analgesia.

Research questions and the specific projects

The overall aim of this doctorate is to improve symptoms and quality of life in patients with chronic knee pain by targeting the genicular nerves, using a rigorous and patient-centred research approach in which patients, clinicians, and researchers work collaboratively. To ensure that the findings are relevant beyond efficacy alone, the elaboration of this thesis follows the Joanna Briggs Institute **FAME framework** (Feasibility, Appropriateness, Meaningfulness, and Effectiveness). Feasibility will examine whether RF of the genicular nerves can be integrated into current clinical practice, encompassing practical considerations such as cost-effectiveness and patient willingness to undergo the intervention. Appropriateness will assess how well RF aligns with the needs of individuals with knee OA. Meaningfulness will explore how patients experience and value the intervention. Finally, effectiveness will be evaluated by whether the genicular nerve block and RF achieve their intended clinical outcomes. These domains overlap with key elements of health technology assessment, which are important for interpreting the findings in terms of clinical, societal, and policy impact.

This thesis seeks to answer the following research questions:

1. What is the clinical effectiveness and cost-effectiveness of radiofrequency treatment for chronic knee pain, and how do different radiofrequency modalities compare in terms of effectiveness and cost-effectiveness?

The therapeutic effectiveness and cost-effectiveness of the RF treatment of the genicular nerves in OA and PPSP patients are addressed in Chapters 2, 3, and 4. These chapters include three studies: results from the RECORGEN observational cohort, 12-month effectiveness and cost-effectiveness results of the COCOGEN trial, and the protocol of a Cochrane systematic review designed to test the effectiveness and safety of RF treatment.

2. What is the safety profile of radiofrequency treatment for chronic knee pain?

Chapters 2 and 3 report on adverse events of the RF treatment in chronic knee pain in an observational cohort, the RECORGEN, and a pilot RCT, the COCOGEN trial. The forthcoming case report article in Chapter 5 examines safety concerns associated with the RF treatment, alongside a detailed account and reflection regarding a patient who developed CRPS following cooled RF in the context of PPSP after TKA.

3. Does the genicular nerve block provide adequate perioperative analgesia in patients undergoing a total knee arthroplasty?

In Chapter 6, the effectiveness and the applicability of the genicular block for the treatment of acute pain during a TKA are explored in the GENIFEM trial.

4. How do patients with chronic knee pain experience the current treatment options, with particular attention to radiofrequency treatment?

Chapter 7 covers chronic OA pain patients' experiences with available treatment options, with a special interest in RF of the genicular nerves, their reflections on participating in the COGENIUS trial, and their preference for future RF treatment research.

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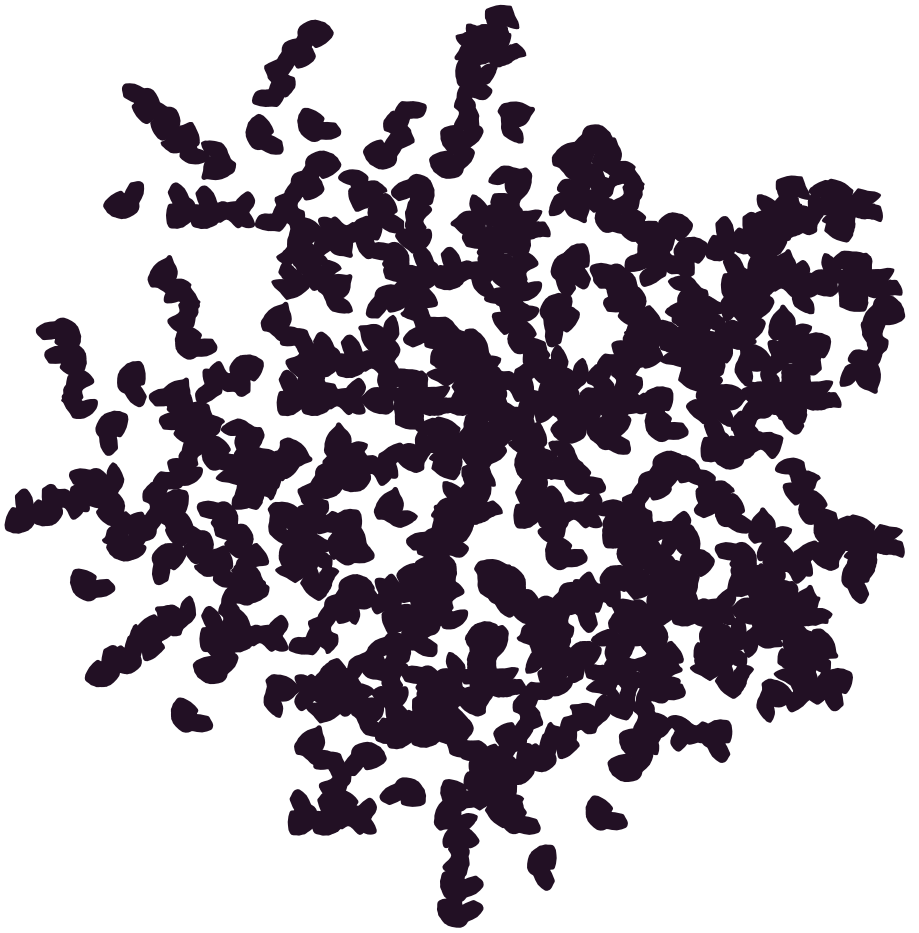

Chapter 2

A retrospective study on patients with chronic knee pain treated with ultrasound-guided radiofrequency of the genicular nerves (RECORGEN trial)

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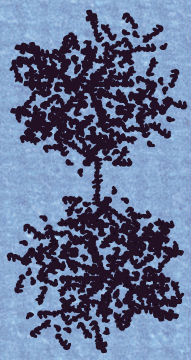

Abstract

Introduction

Radiofrequency (RF) treatment of the genicular nerves is a promising treatment for chronic osteoarthritic and persistent postsurgical knee pain (PPSP), refractory to conventional medical management.

Methods

The RECORGEN study is a retrospective single-centre cohort study of patients treated with ultrasound-guided conventional RF of the genicular nerves for chronic knee pain in Hospital Oost-Limburg, Genk, from September 2017 to June 2020. Subgroup analysis based on the aetiology of pain (PPSP and degenerative knee pain) was performed in addition to the total study population analysis. Outcome parameters were global perceived effect (GPE), Numeric Rating Scale for pain, consumption of strong opioids, and safety of the treatment at 6 weeks and cross-sectionally at a variable time point. Treatment success was defined as GPE ≥50%.

Results

Sixty-eight cases were screened, of which 59 (46 diagnosed with PPSP and 13 with degenerative knee pain) were included in the study. Treatment success at 6 weeks was achieved in 19 of 59 interventions (32.2%) and was similar in both groups. Seventeen responders were evaluated at follow-up. 45.1% (8/17) continued to have a positive effect at the second time point. The mean duration of effect of the RF treatment was 8.3 months. Safety analysis at 6 weeks and at the second time point showed a good safety profile of the treatment.

Conclusion

Conventional RF of the genicular nerves was clinically successful in more than 30% of the study population refractory to conventional medical management. Overall, the treatment was well tolerated. The mean duration of effect was 8.3 months.

Introduction

Osteoarthritis (OA) is a major health burden, which is largely attributable to knee osteoarthritis.[1] Usual treatment modalities for knee OA are physiotherapy, self-management programs, lifestyle changes, knee braces, acupuncture, walking aids, and limited pharmacological treatment (oral analgesics like paracetamol, oral or topical nonsteroidal anti-inflammatory drugs, and intra-articular corticosteroids).[2] When conservative treatment is insufficient, non-responders rely on surgery and/or prescribed opioids despite their adverse effects. More than 50% of the population once diagnosed with knee OA will undergo a total knee arthroplasty (TKA) in their lifetime.[3] The fragile elderly with knee OA, however, often face a high intraoperative risk and the young OA population is confronted with repeated surgery due to the limited lifetime of a prosthesis. Moreover, a considerable number of patients develop persistent post-surgical knee pain (PPSP), a multifactorial and mostly neuropathic pain disorder.[4] Twenty to fifty-three percent of the patients develop chronic disabling pain after TKA that exists beyond the time for normal healing.[5–9] While recent studies have explored prediction tools to assess the risk of developing this complication, PPSP remains a condition with little treatment options.[4,5,10–14] After a negative intensive orthopaedic diagnostic approach, usual treatment consists of conservative therapy with analgesics and physiotherapy.[4,15] The residual pain after TKA is most commonly located anteriorly.[4,15]

Radiofrequency (RF) treatment of the genicular nerves is a relatively novel and minimally invasive intervention that aims to reduce knee pain and increase knee functionality.[16,17] Firstly described by Choi et al.[18] in 2011, RF is a promising technique that could improve the quality of life of patients with knee OA and PPSP.[4] Conventional RF treatment targets the anterior sensory innervation of the knee, decreasing the transmission of pain signals by means of a thermal lesion. The targeted genicular nerves are the superomedial, inferomedial, and the superolateral genicular nerves, which are branches of the femoral, saphenous, obturator, common peroneal, tibial, and sciatic nerves.[19–22] Until present, only minor localised adverse events (AEs) have been reported [16,17] but concern remains over long-term desensitisation of the knee leading to misuse and progression of OA.[23,24]

The primary goal of this study is to evaluate the effectiveness of the ultrasound-guided conventional RF treatment of the genicular nerves in patients who have chronic anterior knee pain due to PPSP or in patients who have a degenerative disease, and to estimate the duration of this effect. Secondary objectives are to evaluate the safety, the change in use of strong opioids, functional improvement, and the need for rescue therapy.

Methods

Study design

The RECORGEN study is a retrospective single-centre observational cohort of all patients treated with RF at the multidisciplinary chronic pain centre in the Hospital Oost-Limburg, Genk, between 1 September 2017 and 30 June 2020. The follow-up period varied for each patient, with a minimum of 6 weeks and a maximum of 27 months. The study protocol was approved by the ethical committee of the Hospital Oost-Limburg (approval number 20/0005U).

Participants

All consecutive patients with chronic knee pain who received RF treatment of the genicular nerves within the time frame were considered eligible. Patients who suffered from chronic widespread pain were excluded. The flow diagram is presented in **Figure 1**. Patients were divided into two subgroups following the aetiology of pain: the PPSP group and the degenerative knee pain group (DP).

Data collection and procedures

The data were collected from the medical patient record at baseline and at 6 weeks after the procedure. For the follow-up, only patients who had a successful treatment at 6 weeks received a questionnaire by mail in October 2020. A telephone contact was made 2 weeks later with those who did not respond. Informed consent for participation in the study was requested and obtained via mail. These data are further referred to as data of the second time point.

Data collection was standardized by using patient case report forms in the online Castor data management tool. Each procedure per knee was considered a unique observation, and bilateral procedures were assessed specific for each treated knee. Data on the patient level was gathered and analysed per treated knee. We collected the following demographic and clinical data at baseline: age, sex, Numeric Rating Scale for pain (NRS), symptom duration, indication for the procedure, use of strong opioids and history of previous knee surgery. Strong opioid analgesics were defined as all opioids excluding tramadol and codeine. Data collected at 6 weeks post-intervention included: NRS pain, global perceived effect (GPE), AEs, and concomitant use of strong opioids. GPE was expressed in percentage of improvement, ranging from 0- 100%. Data at the second time point were only collected for patients who reported treatment success at 6 weeks, as the probability of symptom improvement after 6 weeks was considered negligible. Data collected at the second time point included the variables measured at 6 weeks after the procedure, together with subjective functional outcome and data on other invasive treatments performed on the knee of interest in the time interval.

RF procedure

All patients underwent an ultrasound-guided conventional RF treatment of the three genicular nerves (superomedial, inferomedial, and superolateral) after a positive diagnostic block (defined as at least 50% pain reduction) with lidocaine 2% 1 ml at each of the genicular nerves. Both procedures were executed under sterile conditions, and no sedation was used. The used RF technique was like those previously reported in the literature.[25–27] Conventional RF was performed at a temperature of 70 °C for 90 seconds per nerve after reaching a sensory threshold of less than or equal to 0.5 V and after excluding motor stimulation at 1.0 V. The used RF probe was a 10 cm 21 G Cosman cannula with a 5-mm active tip.

Outcomes

The primary endpoint was the proportion of patients with treatment success at week 6, defined as a GPE of ≥50% compared to baseline. Secondary endpoints were the proportion of patients with treatment success at the second time point, NRS reduction ≥50% compared to baseline at week 6 and at the second time point, subjective physical functioning at the second time point, long-term treatment effect defined as the period with pain reduction, use of strong opioids at week 6 and at the second time point and rescue interventions. Outcomes were analysed for the entire sample and according to the aetiology of pain.

Finally, adverse events were evaluated at both time points after RF treatment. Their number, type, and severity are included in the secondary endpoints.

Efforts to address potential sources of bias were the following: One researcher (AB) performed the collection of data diminishing interobserver variability, and data were gathered in standardised patient report forms.

Statistical analysis

All data are presented for the whole cohort and stratified by DP and PPSP groups as mean values and standard deviation (SD), or as median values and interquartile range, depending on the distribution of the data. Groups were not compared to each other statistically as there were no a priori hypotheses on baseline differences.

Treatment effect was described as success rates based on the GPE and NRS differences between baseline and post-treatment scores of at least 50%, and was described as count and percentage with 95% confidence interval (CI). Within-group change in NRS scores was tested using the paired-samples t-test for the whole cohort and stratified by group. As only one patient was treated bilaterally, no adjustment for correlated (multilevel) data was performed. Microsoft Excel version 16.0 and R version 4.0.4 were used for all analyses.

Results

Participant flow

There were 68 procedures of conventional RF treatment of the genicular nerves of the knee after a positive diagnostic block. Sixty-one cases were included in the study. Exclusion from the study was only due to presence of chronic widespread pain (n = 7). Fifty-nine cases, 13 (22%) of the DP group and 46 (78%) of the PPSP group, completed the follow-up period of 6 weeks, and two patients were lost to follow-up. There were no other missing values for the primary endpoint. Nineteen of the 59 patients (32.2%) reported successful treatment at 6 weeks. These patients were contacted in October 2020; the outcome was analysed at the second time point. The response rate to the questionnaire was 89%. The mean (±SD) time to follow-up was 17 months (±10).

Baseline characteristics

Baseline demographic and clinical characteristics of the whole cohort, the DP group and the PPSP group separately are presented in **Table 1**. Seventy-eight percent (46/59) of the cohort belonged to the PPSP group. Forty-three of 46 cases developed PPSP after a TKA, and 15 of them underwent multiple TKA surgeries. The patients in the DP group suffered from OA (8/13), soft tissue (e.g., ligament) disease and posttraumatic pain. 27% of all patients used strong opioids.

Table 1. Baseline data of the included patients expressed in mean values (±SD).

Baseline data	Degenerative knee pain (*n* = 13)	PPSP (*n* = 46)	All patients (*n* = 59)
Mean age (±SD) at baseline consultation	45.5 (±15.9)	66.9 (±13.9)	62.2 (±16.9)
Sex distribution, *n*			
Female	7 (53.8%)	33 (71.7%)	40 (67.8%)
Male	6 (46.2%)	13 (28.3%)	19 (32.2%)
Index knee			
Right	9 (69.2%)	18 (39.1%)	27 (45.8%)
Left	4 (30.8%)	28 (60.9%)	32 (54.2%)
Patients on strong opioids at baseline consultation			
No use of strong opioids	10 (76.9%)	33 (71.7%)	43 (72.9%)
Use of strong opioids	3 (23.1%)	13 (28.3%)	16 (27.1%)
Mean NRS (±SD) prior to RF treatment	7.8 (±1.7)	7.3 (±1.7)	7.4 (±1.8)

The mean age (±SD) at baseline was 62 years (±16.9). Duration of knee pain before intervention followed an asymmetric distribution. The median duration of pain was 42 months (1st and 3rd quartile: 24 and 72 months). Three of 59 subjects underwent a second RF treatment at the index knee, while only one patient underwent the treatment on both knees.

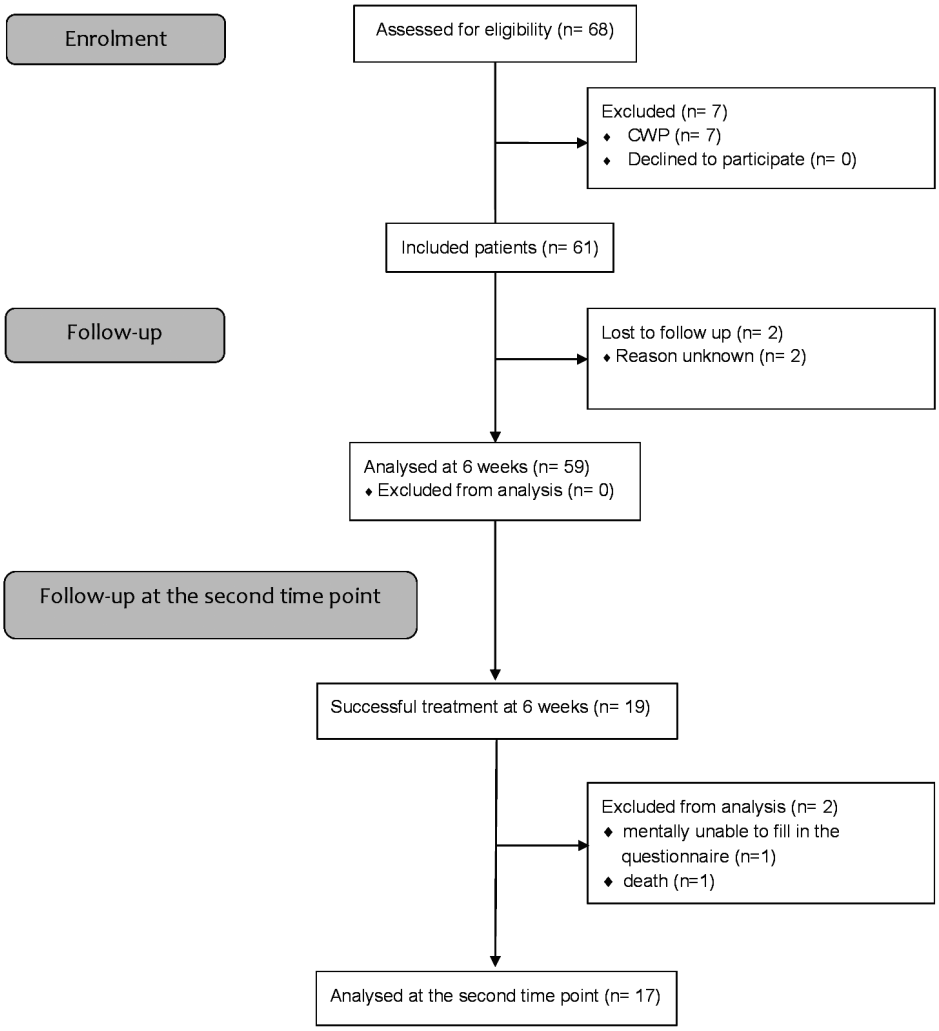

Figure 1. Patient flow during the progression of the study.

Effectiveness and duration of effect

GPE

At 6 weeks after treatment, 42.4% of all patients experienced some improvement in pain as expressed on the GPE. Treatment success (≥50% improvement of GPE) was achieved in 32.2% (95% CI: 20.6%–45.6%) of all 59 patients at week 6, with 30.8% (95% CI: 9.1%–61.4%) and 32.6% (19.5% – 48.0%) success rates in the DP group and PPSP group respectively (**Table 2**). Treatment success at the second time point was obtained in 35.3% (95% CI: 14.2%–61.7%) of the patients who had treatment success at 6 weeks (**Table 3**). Interestingly, none of the three patients who underwent a second RF on the index knee reported treatment success after the second procedure while the patient who underwent RF in both knees did experience repeated treatment success.

Table 2. Clinical outcomes at week 6 illustrated stratified by treatment group and for the complete cohort.

Clinical outcomes at week 6 per treatment group	Degenerative knee pain	PPSP	All patients
GPE			
GPE 0–24%	6/13 (46.2%)	27/46 (58.7%)	33/59 (55.9%)
GPE 25–49%	3/13 (23.1%)	3/46 (6.5%)	6/59 (10.2%)
GPE 50–74%	2/13 (15.4%)	6/46 (13.0%)	8/59 (13.6%)
GPE 75–100%	2/13 (15.4%)	9/46 (19.6%)	11/59 (18.6%)
Missing data	0/13 (0%)	1/46 (2.1%)	1/59 (1.7%)
Treatment success (GPE ≥50%)	4/13 (30.8%)	15/46 (32.6%)	19/59 (32.2%)
NRS			
NRS reduction ≥50%	4/13 (30.8%)	9/46 (19.6%)	13/59 (22.0%)
Mean NRS (±SD) in treatment success (GPE ≥50%)	2.8 (±1.5)	3.4 (±1.7)	3.2 (±1.7)
Mean NRS (±SD) in treatment failure (GPE <50%)	7.1 (±2.4)	7.5 (±1.5)	7.4 (±1.8)
Patients on strong opioids	3/13 (23.1%)	8/46 (17.4%)	11/59 (18.6%)
Patients on strong opioids in treatment success group	1/4 (25%)	3/15 (20%)	4/19 (21.1%)
Patients on strong opioids in treatment failure group	2/9 (22.2%)	5/31 (16.1%)	7/40 (17.5%)
Adverse events	3/13 (23.1%)	6/46 (13%)	9/59 (15.3%)
Severe adverse events	0/13 (0%)	1/46 (2.2%)	1/59 (1.7%)

NRS

Mean NRS (±SD) of the whole cohort at baseline was 7.4 (±1.8) and reduced to 6.0 (±2.7) at 6 weeks, p = 0.001. The mean NRS of the patients included in the second follow-up was 5.5 (±1.9), p = 0.034 compared to baseline. In the DP group, the mean NRS (±SD) at baseline was 7.8 (±1.8) and reduced to 5.6 (±3.1) at 6 weeks (p = 0.029) while the mean NRS (±SD) in the PPSP group was 7.3 (±1.7) at baseline, which reduced to 6.1 (2.6) at 6 weeks (p = 0.008). The mean duration of effect (±SD) in the whole population was 8.3 (±6.8) months. **Figure 2** shows the distribution of pain scores for each of the follow-up moments. **Figure 3** depicts evolution in the NRS score of all the patients that were followed up until the second time point.

NRS reduction of ≥50% at week 6 was achieved in 13 (22%, 95% CI: 12.3%–34.7%) of all participants and this was still present in five of the 13 patients at the second time point (38.5%, 95% CI: 13.9%–68.4%). NRS reduction of ≥50% at week 6 was achieved in 4/13 (30.8%, 95% CI: 9.1–61.4%) of DP participants, whereas NRS reduction of ≥50% at week 6 was achieved in 9/46 (19.6%, 95% CI: 9.4%-33.9%) of PPSP patients.

Mean NRS (±SD) in the treatment success group at 6 weeks was 3.2 (±1.7) and 3.8 (±1.8) at the second time point. The mean difference from baseline to 6 weeks in NRS in the treatment success group was 4.1 (95% CI: 3.1–5.1, p < 0.001), and the mean difference from baseline to the second time point was 1.6 (95% CI: 0.1–3.1, p = 0.034).

Other

Eight of seventeen (47.1%) of the subjects with treatment success at 6 weeks reported an increase in functionality at the second time point. Six of these patients also experienced improvement in pain. Two of the patients who had a temporary effect of RF treatment received rescue Platelet Rich Plasma therapy and intra-articular corticosteroid injections. No patient underwent a TKA procedure during the observation period.

Strong opioids

At baseline, 16 (27.1%) of all patients used strong opioids. Only 11 (18.6%) of all patients needed the use of strong opioids at 6 weeks after treatment despite treatment success or failure. Seven of the 13 (53.8%) PPSP patients who used strong opioids at baseline continued to use them at 6 weeks. A single patient in the PPSP group started using strong opioids at 6 weeks. In the DP group, there were only three patients (23.1%) who used opioids at baseline, and they still relied on them at 6 weeks.

Six (35.3%) of the patients followed up used strong opioids at the second time point. Compared to baseline, only two PPSP opioid naïve patients who did not experience any remaining treatment effect started to use strong opioids, while one PPSP patient stopped despite treatment failure. No changes in opioid use were noticeable in the DP group compared to baseline. Of the six patients who still experienced treatment effect at the second time point only one used strong opioids. Retrospectively, this patient also used strong opioids at baseline while the other five patients did not.

Tolerability and safety

At 6 weeks, four patients (6.8%) experienced hypoesthesia after the treatment. Other adverse events were only reported once: instability while walking, increase in pain, a self-limiting hematoma, and a flare of complex regional pain syndrome (CRPS). Therapy-related AE were thus registered in 15.3% of the patients at 6 weeks. CRPS in a PPSP patient was the only serious AE that was reported.

Patients contacted at the second time point did not report new AEs. One person reported persistent paraesthesia in the lateral knee.

Table 3. Clinical outcomes at the second time point stratified by treatment group and for the complete cohort.

Clinical outcomes at the second time point	Degenerative knee pain (*n* = 4)	PPSP (*n* = 13)	All patients (*n* = 17)
GPE ≥50%	2/4 (50%)	4/13 (30.8%)	6/17 (35.3%)
Mean NRS (±SD)	5.3 (±2.0)	5.5 (±1.9)	5.5 (±1.9)
Mean NRS (±SD) in patients with GPE ≥50%	4.0 (±0.0)	3.8 (±2.2)	3.8 (±1.8)
Mean NRS (±SD) in patients with GPE <50%	6.0 (±2.0)	6.6 (±0.8)	6.5 (±1.2)
Adverse events	0/4 (0%)	1/13 (7.7%)	1 /17 (5.9%)
Patients on strong opioids	1/4 (25%)	5/13 (38.5%)	6/17 (35.3%)
Subjective increase in functionality	1/4 (25%)	6/13 (46.2%)	7/17 (41.2%)
Other interventional treatments of the knee	0/4 (0%)	2/13 (15.4%)	2/17 (11.8%)

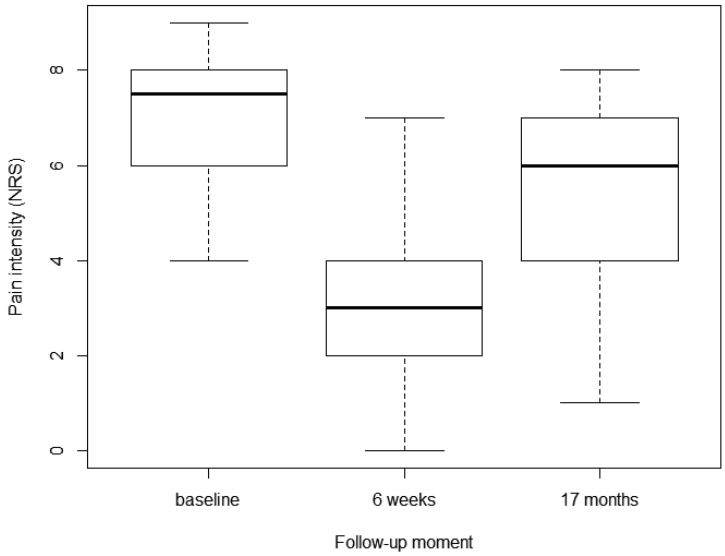

Figure 2. The average post-treatment pain scores (NRS) using time since treatment as independent variable.

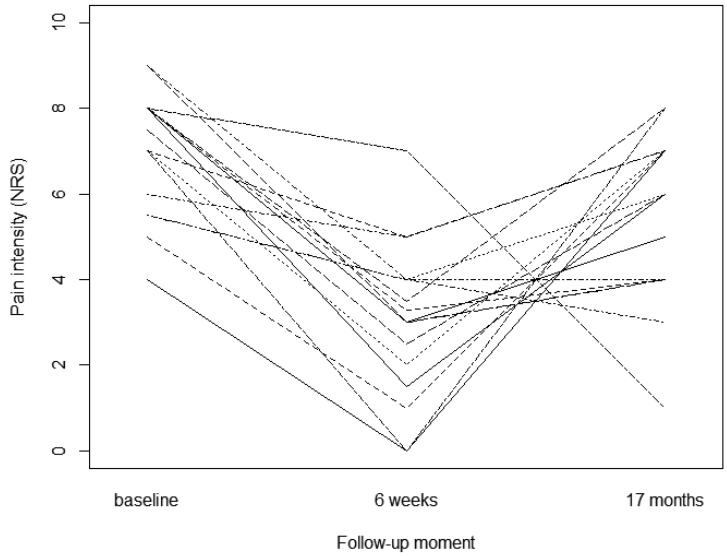

Figure 3. Evolution in pain intensity scores (NRS) during the follow-up of all patients that were followed up until the second time point.

Discussion

In this retrospective single-centre cohort study, we analysed the effectiveness and safety of a conventional RF treatment of the genicular nerves in 13 patients with chronic anterior knee pain due to degenerative disease or other non-surgical conditions in 13 patients and 46 PPSP patients during a maximum follow-up of 27 months. This is to our knowledge the first study in a large population of PPSP patients. We report an overall clinical success of the RF treatment of 32%. This result was similar in each group. The mean duration (±SD) of the treatment effect was 8.3 (±6.8) months.

Only 22% of the cases included in this study received RF treatment for degenerative knee pain. The success rates of RF of the genicular nerves in this group are considerably lower compared to previous studies of RF on knee OA.[16,18] Studies investigating RF in OA patients suggest that the conventional radiofrequency ablation has an average effectiveness of 65% three to 12 months after treatment.[16,18] This discordance may result from a learning curve after the introduction of a new technique, which evolved during the three years of the study. Another evident rationale is the heterogeneity of the patients in the DP group, including chronic knee pain of various origin such as soft tissue (e.g., ligament) disease and posttraumatic pain, refractory to conservative treatment, while in other studies, RF is mainly performed in patients with OA grade 2–4.[7,16] Additionally, the mean age of the analysed group is remarkably younger than the mean age of the population presenting with knee OA pain. The average effectiveness data presented earlier is derived by studies performing predominantly fluoroscopy-guided RF techniques.[16] Therefore, the execution of the RF technique using ultrasound imaging could have impacted the results; however, Sarı et al. showed similar clinical results when using ultrasound imaging compared with fluoroscopy.[28,29] All the previously mentioned parameters could influence the outcome of RF and further research should identify the best indications for RF of the knee.

The majority (78%) of the analysed population included were PPSP patients. To our knowledge, this is the largest study evaluating effectivity of RF in this sub-group. Baseline characteristics of PPSP patients indicate a marked dominance of females which is reported to be less in the literature.[30] The predominant surgery that preceded PPSP was a TKA. We report a 32.6% success rate of the conventional RF treatment in the PPSP group at 6 weeks. Ogalla et al.[31] reported a reduction in visual analogue scale scores of >50% in 75% of the 16 analysed PPSP patients at 1 month and 65% at 6 months in a prospective observational study. Qudsi-Sinclair et al.[32] published the only RCT on RF for PPSP comparing conventional RF to intra-articular injections with local anaesthetics and corticosteroids. Efficacy in pain scores, disability, and quality of life was similar in all 28 patients at 3–6

months with a mean NRS reduction (±SD) of 2.6 (±2.7) at 6 months after RF treatment. Additionally, two isolated case reports by Protzman et al. and by Metnzies et al. show positive results of conventional and cooled RF at 3 and at 9 months.[6,33] The result of our study on PPSP is less encouraging than the previous publications on PPSP.[31–33] This study shows possible important differences in effectiveness of RF treatment of the genicular nerves in a real-world setting compared to prospective studies. One probable noteworthy factor is that physician performance is influenced by increasing experience, especially in such innovative interventions. Another important consideration is the possible abnormal nerve growth and altered location of the genicular nerves after surgery which could make them difficult to target in PPSP patients. Furthermore, the different pathophysiological mechanisms of PPSP compared to OA, outlining PPSP of a predominantly neuropathic nature, might be accountable for this variation in effectiveness.[4,34]

Traditionally, the superomedial, superolateral, and inferomedial genicular nerves are targeted during the RF procedure. Recent anatomical studies of the knee innervation indicate that there are 10 genicular nerves that innervate the anterior knee and that anatomical variations exist.[21,35,36] The cadaver study of Fonkoue et al. proposes revised anatomical landmarks for the original genicular nerves.[36] Chen et al. and McCormick et al. advocate that ablation of up to ten genicular nerves could improve outcomes of this treatment.[35,37] Future clinical trials incorporating this improved knowledge of the innervation of the knee are necessary for optimisation of the RF technique for chronic knee pain.

While we defined success in this study as GPE ≥50%, frequently used definitions in the literature are a decrease of ≥50% in a pain intensity scores like NRS and values of knee composite scores.[7,16] The choice of the GPE in this study was dictated from the clinical practice of the hospital where this score is used to assess a favourable outcome. Concerns on RF safety are addressed in this study by means of a mean (±SD) follow-up of 17 months (±10). At 6 weeks after treatment, the most frequent AE was hypoesthesia in four cases. One patient belonging to the PPSP group experienced a flare of CRPS which was considered a serious AE. Patients contacted at the second time point did not report new AEs. Paraesthesia was persistent in one PPSP patient and temporary in two of the patients who were followed up until the second time point after reporting it at week 6. Reassuringly, the number of complications was lower in the PPSP group compared to the DP group.

Regarding medication use, patients used less strong opioids at 6 weeks after treatment in both groups despite treatment success or failure. Arguably, this is due to the information patients received on adequate treatment of non-oncologic pain by the

pain clinician. Strong opioid use increased at the second time point. However, data should be regarded with caution as this study included a broad range of ages, where elderly had multiple comorbidities or pain problems.

One of the limitations of this study is inherent to its retrospective nature. The data gathered on pain, functionality scores and medication were limited to the annotations in a non-standardised medical record. We could not gather objective evaluation of knee function and recall bias might influence the results of duration of the effect of the treatment. A second limitation is that comparison with previous studies is difficult due to the use of ultrasound as guidance for the procedure as most of the studies use fluoroscopy-guided RF. Another limitation concerns the subgroup analysis of degenerative knee pain. These results need to be interpreted with caution due to the small number of patients included in this group.

The major strength of this study is that it represents real-world data with a large population of primarily PPSP patients. The findings of this study suggest that anatomic changes and different pathophysiological mechanisms of pain in this group could result in a lower success rate of conventional RF. Future studies should address this concern.

In conclusion, the observational data presented in this study position conventional RF treatment of the genicular nerves of the knee as a relatively effective and safe therapy in more than 30% of patients suffering from refractory degenerative pain and PPSP.

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Chapter 3

Cooled versus conventional radiofrequency treatment of the genicular nerves for chronic knee pain: 12-month and cost-effectiveness results from the multicentre COCOGEN trial

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Abstract

Background

Radiofrequency (RF) treatment of the genicular nerves reduces chronic knee pain in patients with osteoarthritis (OA) or persistent postsurgical 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-blinded, non-inferiority, pilot, randomised controlled trial that compared the effects up to 12 months of cooled and conventional RF in patients with chronic knee pain 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. Here, the primary outcome was the incremental costs per quality-adjusted life year (QALY).

Results

41 of the 49 included patients completed the 12-month follow-up. One patient in the PPSP cooled RF group had substantial missing data at 12-month 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 in the mean absolute numerical rating scale at 12 months after cooled RF and 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 lower 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, as opposed to OA, greater effectiveness at lower costs compared with conventional RF.

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 perioperative risk, and postoperative re-evaluation can be difficult. Young patients have worse outcomes with a higher risk of revision.[5] Further-more, up to 53% of patients develop persistent postsurgical 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 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, 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 patients with OA and PPSP after TKA up to 6 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 the treatment success of cooled RF and 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 part of the COCOGEN pilot randomised controlled trial, of which the 6-month effectiveness results are published in a separate paper.[11] We hypothesised 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) (online **Supplemental file 2**). 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, randomisation, 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 (online **Supplemental file S1**). After stratification per aetiology of pain (OA and PPSP), participants were randomised into two treatment groups, the conventional and cooled RF groups, with an allocation ratio of 1:1 and variable block size of 2 or 4 in the online Castor electronic data capture 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 the 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 anaesthetised with 1 mL lidocaine 2% at each entry point before the 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 s 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 s.

Study endpoints and data collection

Participants were assessed at baseline, 1, 3, 6, and 12 months after the procedure. Data were 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%) versus 8 of 24 with cooled RF (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 (HRQoL) expressed in Euroqol 5-dimension 3-level (EQ-5D-3L) questionnaire, mental health measured by the Hospital Anxiety and Depression Scale (HADS) and by the Pain Catastrophizing Scale (PCS), medication use assessed by the Medication Quantification Scale III (MQS III), and adverse events and incidence of a TKA.[17–23] The NRS score at each time point was the mean score of the previous 4 days except for the 12-month 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 amounting to a total of 48 patients.[24] The 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 analysed following the per-protocol principle as this is more conservative for testing non-inferiority hypothesis. To test for non-inferiority, the mean NRS difference between groups, including 95% CI, was 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% CI, and Pearson's c^2 test was used for the comparison between the treatment groups. We reported the secondary study parameters as mean or percentage of difference including 95% CI. 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 analysed to conform with the Dutch guidelines for health economic evaluation (HEE).[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 year (QALY) was chosen as the measure of the benefit of the cooled and conventional RF intervention. The QALY is the preferred health outcome in economic evaluations and is a combined measure of 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 into four main categories: RF intervention costs, healthcare resource use, costs to patient and family, and productivity costs. The cost of the RF interventions was calculated as the sum of the cost of a day of hospitalisation, the costs of the used material, and the cost of the medical personnel. Healthcare resource utilisation included healthcare-related visits (e.g., general practitioner, physiotherapist, and 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 and braces) and informal care costs. Costs due to lost productivity included costs due to short-term and long-term absences from paid and unpaid work.

Data on other healthcare utilization, 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 health-care use, for example, consultation with healthcare professionals (medical doctor and general practitioner physiotherapist), interventions, hospitalizations, 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 online **Supplemental file 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 HEE

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 imputations 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 were 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-month costs for each respondent. Each of the imputed datasets was analysed separately, and results were pooled using Rubin's rules.

Mean healthcare and societal costs and QALYs for the OA and PPSP subgroups acquired over the 1-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% CI.[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 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 Healthcare 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 healthcare 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-month 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, 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-month follow-up, including the NRS. Between 6 and 12 months, five additional patients dropped out. All randomised 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 the 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 'Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials' 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 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**).

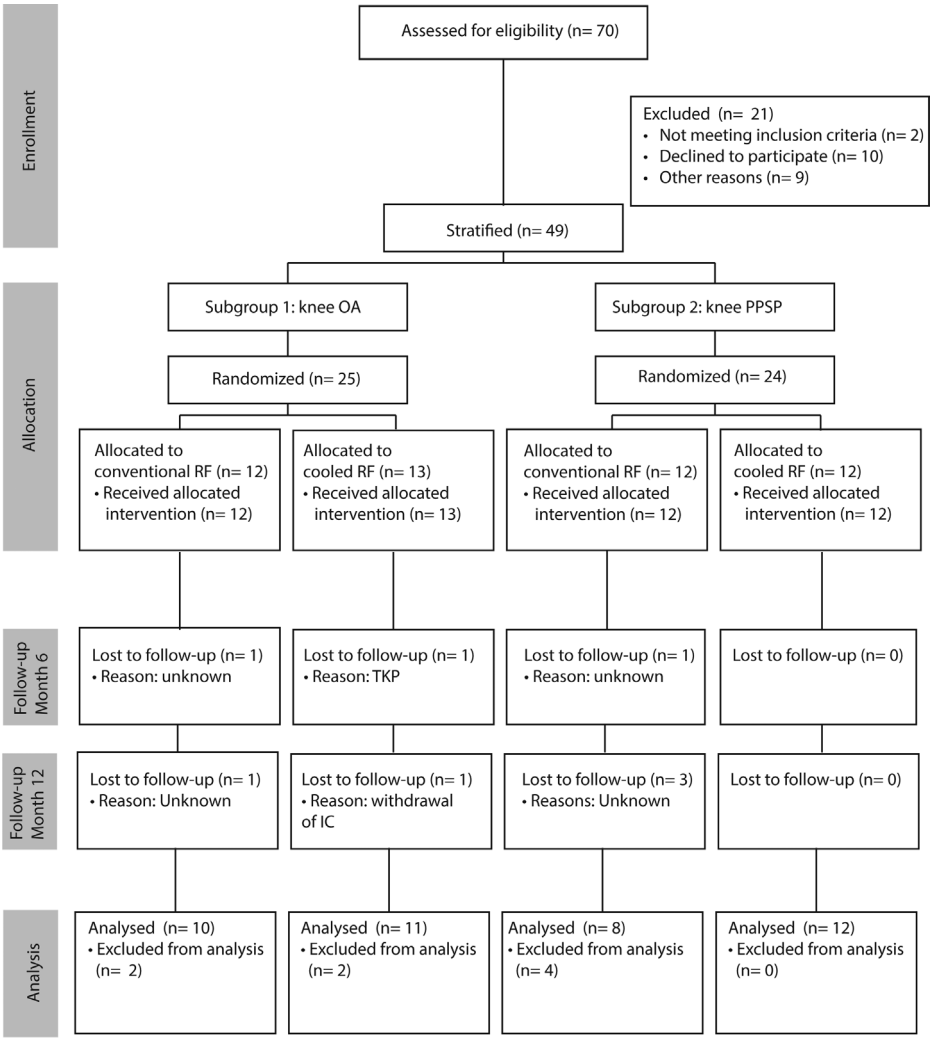

Figure 1. The Consolidated Standards of Reporting Trials flow chart of participants during the trial up to 12 months.

IC, informed consent; OA, osteoarthritis; PPSP, persistent postsurgical pain; RF, radiofrequency; TKP, total knee prosthesis.

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, EQ-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 of follow-up. Mean scores of the other outcomes in the whole population at 12 months are presented per allocated RF treatment in the online **Supplemental file S3**.

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

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

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

[a]P value compares conventional RF with cooled RF procedure.

[b]Pearson's c [2] test used to compare proportions.

Safety analysis

There were no adverse events reported that were possibly or definitively related to the procedure at 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 analysed 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 with PPSP treated with conventional RF were excluded from the analysis, as no data were collected on resource use and costs at any of the follow-up moments. We present in the online **Supplemental file S4** the baseline patient characteristics of the analysed population.

Healthcare use

Costs from a 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 healthcare costs and the costs to patient and family (i.e., out-of-pocket expenses and informal care costs). In the OA group, all three categories (healthcare costs, costs to patient and family, and productivity costs) contributed to the higher total societal costs of the cooled RF group compared with conventional RF.

PPSP			Whole group		
Conv RF, n (%)	Cooled RF, n (%)	P value[a,b]	Conv RF, n (%)	Cooled RF, n (%)	P value[a,b]
1/11 (9.1)	5/12 (41.7)	0.16	4/22 (18.2)	9/24 (37.5)	0.15
0/8 (0)	2/11 (18.2)	0.49	4/18 (22.2)	5/22 (22.7)	1.00
1/11 (9.1)	5/12 (41.7)	0.16	5/22 (22.7)	10/24 (41.7)	0.17
0/8 (0)	5/11 (45)	0.045	4/18 (22.2)	9/22 (40.9)	0.21

OA, osteoarthritis; PPSP, persistent postsurgical pain; RF, radiofrequency.

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 result, 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**).

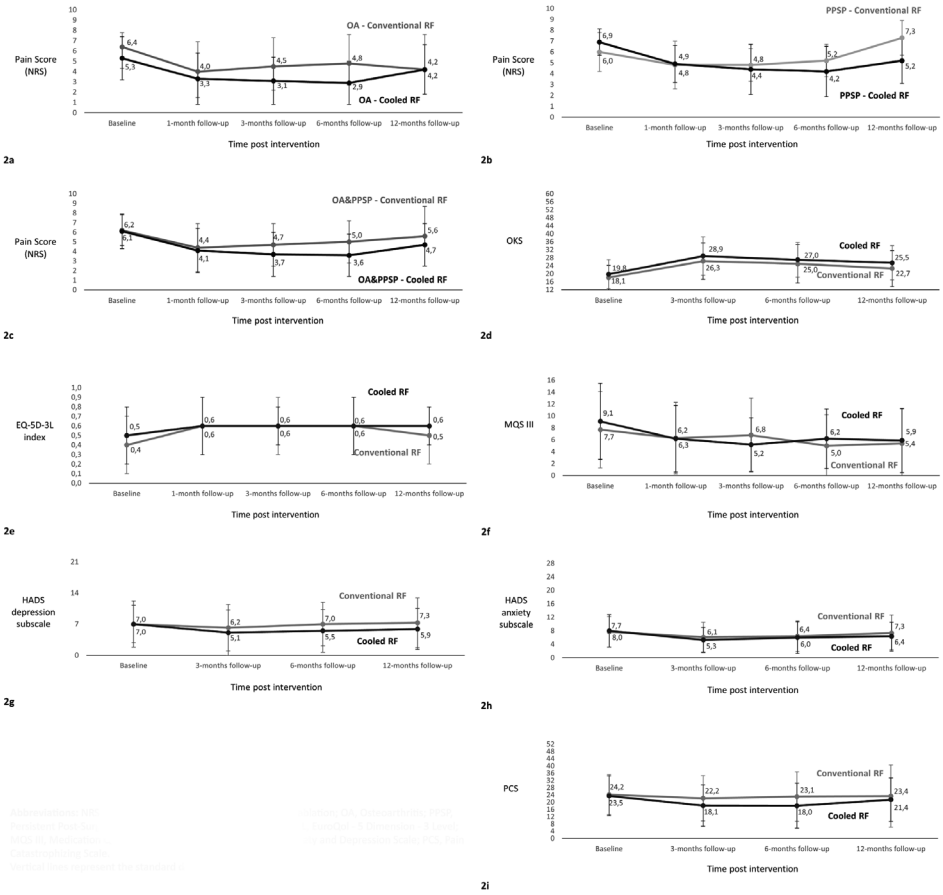

Figure 2. Evolution of the clinical outcomes during the 12-month follow-up of the COCOGEN trial. Vertical lines represent the standard deviation.

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.

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.

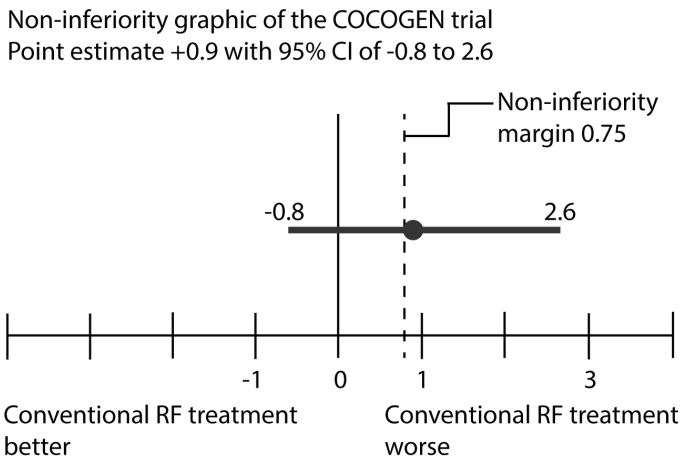

Figure 3. Non-inferiority graphic of the COCOGEN trial.

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

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	Mean (SE)		Unadjusted mean difference (95% CI)[a]	Adjusted mean difference (95% CI)[a]
	Conventional RF	Cooled RF		
Outcomes for the OA group at 12 months after treatment				
QALY	0.604 (0.004)	0.558 (0.002)	−0.046 (−0.227 to 0.134)	−0.040 (−0.187 to 0.106)
Total healthcare-related costs	3405 (64)	4528 (125)	1123 (−2126 to 4372)	371 (−2627 to 3369)
Costs to patient and family	1018 (44)	3391 (85)	2373 (−600 to 5346)	876 (−839 to 2590)
Productivity costs/loss	3881 (0)[b]	6254 (0)[b]	2373 (−5266 to 10012)	2494 (−5544 to 10531)
Total societal costs	8303 (60)	14 173(159)	5860 (−3313 to 15052)	145 (−4485 to 14776)
Outcomes for the PPSP group at 12 months after treatment				
QALY	0.516 (0.002)	0.690 (0)	0.174 (0.014 to 0.334)	0.128 (0.008 to 0.247)
Total healthcare-related costs	4313 (216)	2499 (62)	−1814 (−4711 to 1083)	−1961 (−4848 to 925)
Costs to patient and family	2894 (67)	666 (30)	−2228 (−4518 to 62)	−2002 (−4268 to 258)
Productivity loss	3270 (0)[b]	2286 (0)[b]	−984 (−4258 to 2290)	−366 (−3680 to 2948)
Total societal costs	10 477 (204)	5451 (62)	−5026 (−11022 to 970)	−4376 (−10124 to 1372)

Costs for each category were summed and the mean difference was calculated.
The sample size analysed 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).
[a]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).
[b]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.

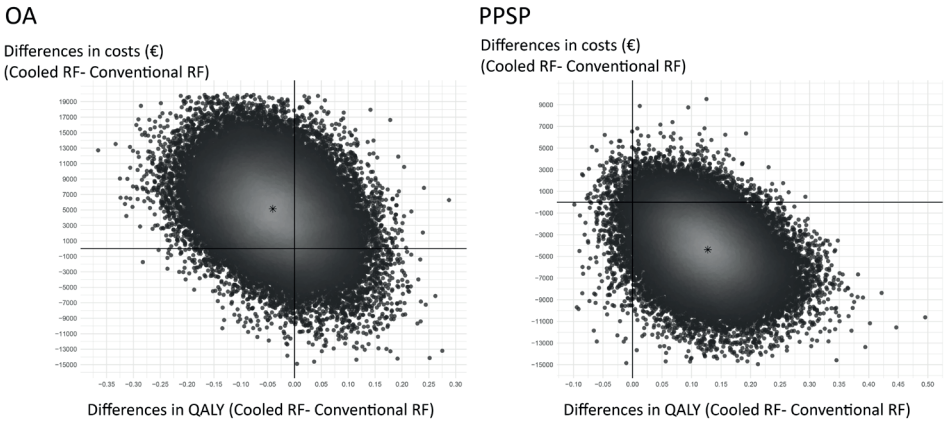

Figure 4. The incremental cost-effectiveness planes for the osteoarthritis and persistent postsurgical pain population representing the cost difference (€) and differences in quality-adjusted life year estimated using EuroQol 5-dimension 3-level between cooled and conventional radiofrequency at the 12-month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

OA, osteoarthritis; PPSP, persistent postsurgical pain; RF, radiofrequency ablation; QALY, quality-adjusted life year.

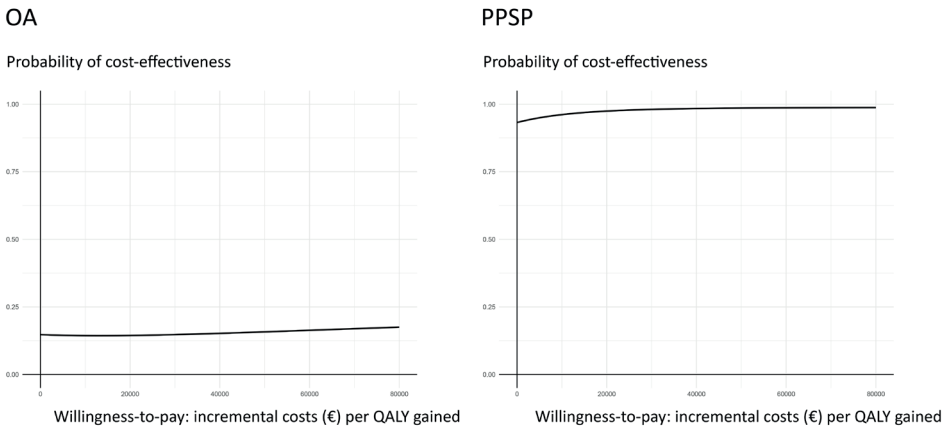

Figure 5. The cost-utility acceptability curve for cooled radiofrequency (RF) compared with conventional RF in the osteoarthritis and persistent postsurgical pain population at 12 months.

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-month results. When treatment success was defined as ≥30% pain reduction, there was also no significant difference between a conventional RF (22.2%) and 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 aetiology 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 patients 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 with intra-articular steroid injections in patients with OA, which strongly favoured 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 healthcare 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 healthcare 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 and a cooled RF at 12 months, supporting the long-term safety of both treatments. Secondary outcomes, including the 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 are 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 with 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 a 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 the 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. Third, 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 healthcare perspectives, in line with Dutch and Belgian guidelines, respectively. Fourth, 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 V.3 score, we do not expect this to have influenced the trial findings. An 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 an inclusion of a sham procedure and a long follow-up to prove the 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 2 years of 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 the inclusion of a sham procedure and long follow-up should be conducted to support these findings.

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Supplementary material

Supplementary material S1
Inclusion and exclusion criteria of the COCOGEN trial.

Inclusion criteria:

- Adult subjects that suffer from moderate to severe (Numeric Rating Scale > 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) grade II to IV on X-ray or MRI was required.
- For PPSP after TKA patients, a negative orthopaedic workout was required.

Exclusion criteria were:

- Body mass index > 40 kg/m2
- Chronic widespread pain
- Untreated psychosocial disease
- Radicular pain in the index leg
- Local or systemic infection (bacteraemia)
- Uncontrolled immune suppression
- Uncontrolled coagulopathy (defined as a supratherapeutic dose of anticoagulation medication)
- Patient 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 (e.g., steroids, hyaluronic acid, platelet-enriched plasma) in the index knee during the 3 months prior to the start of the study
- Previous conventional or cooled radiofrequency 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
- Patients who refused to comply to protocol procedure

Supplementary material S2

Table S2. Unit price in Euro for each cost category (year 2021).

Price for each unit of cost category		**Cost per unit (€)**
Health care resource use [1]		
Health care-related visit	General practitioner (visit)	37
	Occupational physician (visit)	71
	Other health care physician specialist (visit) [b]	101
	Physiotherapist (visit)	37
	Occupational therapist (visit)	37
	Dietician (visit)	37
	Homeopathist (visit)	37
	Psychologist (visit)	71
	Use of home care (home nursing care) (one hour visit)	56
	Use of home care (domestic help in housekeeping) (one-hour visit)	26
	Use of home care (family care) (one-hour visit)	16
	Inpatient day hospitalisation (day)	307
	Inpatient night hospitalisation (day)	529
	Emergency department (visit)	288
	Use of ambulance (trip)	572
Visit to other allied professionals	Social worker (visit)	72
RF intervention costs [a]		
	Cooled RF intervention	1127
	Conventional RF intervention	338
Costs for patients and family		
Out-of-pocket expenses	Warm medical dressing/compress	40
	Medical gel	20
	Analgetic medication (unit)	20
	Brace (unit)	75
Informal care	Informal care (per hour)	16
Productivity costs		
	Productivity loss for paid work (hour)	34.75
	Productivity loss for unpaid work (hour)	14

Table S2. Continued

[a] The cost of the RF interventions (cooled and conventional RF) 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.
[b] The cost price for a health care physician specialist visit was calculated as an average of all specialisations.
Abbreviations: RF, radiofrequency ablation.

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Supplementary material S3

Table S3. The overall effectiveness outcomes at 12-month follow-up timepoints were compared between conventional and cooled RF treatment of the genicular nerves.

	Baseline	
	Conv. RF	Cooled RF
Mean NRS [d] (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 anxiety 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)

Abbreviations: Conv., Conventional; RF, radiofrequency; SD, Standard deviation; PGIC, Patient's Global Impression of Change; OKS, Oxford Knee Score; EQ5-5D-3L, EuroQol-5 Dimension-3 Level; HADS, Hospital Anxiety and Depression Scale; PCS, Pain Catastrophizing Scale; MQS III, Medication Quantification Scale III.

Supplementary material S4

Table S4. Baseline patient characteristics per subgroup (OA and PPSP), including baseline quality of life, pain scores and health care resource use in the intention-to-treat population.

	OA		PPSP	
	Conventional RF	Cooled RF	Conventional RF	Cooled RF
Sample size, n (%)	12 (50)	12 (50)	11 (48)	12 (52)
Female, n (%)	11 (92)	6 (50)	9 (82)	8 (67)
Mean age (SD) in years	62 (14.3)	61 (13.4)	65 (12.1)	65 (8.9)
Mean BMI (SD) in kg/ m2	32.6 (4.9)	28.6 (3.6)	29.2 (5.2)	28.2 (5.6)
Education level, n (%)				
Primary school	3 (25)	4 (33)	2 (18)	3 (25)
Secondary school	6 (50)	5 (42)	8 (73)	9 (75)
Higher education	3 (25)	3 (25)	1 (9)	0 (0)
Mean OKS score (SD)	16.3 (5.6)	21.8 (7.7)	20.1 (6.3)	17.1 (5.4)
Mean NRS score (SD)	6.4 (1.4)	5.3 (2.1)	6.3 (1.6)	6.9 (1.2)
Mean EQ-5D-3L score (SD)	0.444 (0.291)	0.431 (0.344)	0.369 (0.324)	0.494 (0.344)
Mean MQS III score (SD)	9.1 (5.9)	8.1 (6.4)	6.9 (6.8)	10.0 (6.5)

6 months FU			12 months FU		
Conv. RF	Cooled RF	p-value[a,b]	Conv. RF	Cooled RF	p-value[a,b]
5.0 (2.2)	3.6 (2.2)	0.13[c]	5.6 (3.1)	4.7 (2.2)	0.30[c]
5/22 (22.7)	9/24 (37.5)	0.28	3/18 (22.7)	8/22 (36.4)	0.29
25.0 (9.6)	27.0 (8.7)	0.47	22.7 (9.0)	25.5 (8.5)	0.31
0.6 (0.3)	0.6 (0.28)	0.62	0.52 (0.3)	0.6 (0.2)	0.19
7.0 (4.9)	5.46 (4.8)	0.31	7.3 (5.6)	5.9 (4.6)	0.38
6.38 (4.6)	6.0 (4.7)	0.79	7.3 (5.4)	6.4 (4.1)	0.55
23.1 (13.7)	18.0 (12.4)	0.20	23.4 (17.2)	21.4 (12.1)	0.67
5.0 (5.2)	6.2 (5.0)	0.40	5.4 (5.8)	5.9 (5.4)	0.78

a: p-value compares conventional RF versus cooled RF procedure

b: Pearson's Chi-squared test used to compare proportions and Paired T-test used to compare means

c: p-value of mean paired difference between baseline and follow-up NRS

d: mean NRS at 12 months is calculated as the average score of the reported NRS during rest and during movement.

Table S4. Continued

Data is reported in standard deviation (SD) unless otherwise specified.

Abbreviations: BMI, Body Mass Index; OA, Osteoarthritis; PPSP, Persistent Post-Surgical Pain; OKS, Oxford Knee Score; NRS, Numerical Rating Scale; EQ-5D-3L, 3-level, 5-dimensional health-related quality of life; HADS, Hospital Anxiety and Depression Scale; PCS, Pain Catastrophizing Scale; MQS III, Medication Quantification Scale Version III.

Supplementary material S5

Table S5. Results from the cost-utility analysis and sensitivity analysis for the conventional and cooled RF interventions in each population (OA and PPSP) at 6 months.

Outcome	ΔC (95% CI) [a]	ΔE (95% CI) [a]
OA population (n = 24)		
Societal perspective at 6 months	5017 (-2665; 12700)	-0.017 (-0.090; 0.056)
Health care perspective at 6 months	596 (-1853; 3045)	-0.017 (-0.090; 0.056)
PPSP population (n = 23)		
Societal perspective at 6 months	-1409 (-3499; 681)	0.035 (-0.031; 0.100)
Health care perspective at 6 months	-17 (-840; 805)	0.035 (-0.029; 0.102)

[a] The uncertainty expressed in 95% confidence intervals (CI) around the mean difference in costs and effects is calculated using regression analysis, adjusted for baseline differences, and non-parametric bootstrap simulations with 5000 replications.

[b] The probability of cost-effectiveness expresses the percentage of the 5000 bootstrap simulations in which cooled RF was cost-effective.

CE plane				Probability of cost-effective procedure at €20.000 [b]	Is cooled RF cost-effective at €20.000? (Yes/No) [b]
NE (%)	SE (%)	SW (%)	NW (%)		
29	3	6	62	0.09	No
20	12	20	48	0.27	No
7	77	11	5	0.92	Yes
38	47	3	12	0.79	Yes

Abbreviations: OA, Osteoarthritis; PPSP, Persistent Post-Surgical Pain; RF, radiofrequency ablation; ΔC, difference in costs; CE, cost-effectiveness; NE, North-east; SE, South-east; SW, South-west; NW, North-west; CI, Confidence Interval.



Chapter 4

Radiofrequency treatment for chronic knee pain in people with knee osteoarthritis (Protocol)

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Background

Description of the condition

Osteoarthritis is one of the most rapidly increasing health conditions and a leading cause of chronic pain, loss of physical function, and loss of health-related quality of life.[1] It is a progressive degenerative process that affects the joint cartilage and the subchondral bone.[2] Knee osteoarthritis has a high disease burden and is found to be symptomatic in around 12.4% of the adult population.[3,4] Age-standardised prevalence of osteoarthritis could be different across different regions.[1] Differences in the burden of osteoarthritis across regions might be caused by genetic, metabolic, and behavioural factors.[5,6] There is little quantitative evidence to support a particular physiological causal mechanism of the geographical variation. It could be partially explained by differences in occupational distribution, high body mass index (BMI), behaviours such as frequency of kneeling or squatting, joint anatomy, or genetic predisposition.[7] 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 ageing. Complex interactions are thought to be important in disease progression. Age-standardised years lived with disease attributable to osteoarthritis are continuing to rise and will lead to substantial increases in case numbers because of population growth and ageing, and because there is no effective cure for osteoarthritis.[1] As worldwide demographic transitions are expected to continue, the burden of knee osteoarthritis and the socioeconomic costs associated with its management are likely to increase substantially.[3]

Guidelines and recommendations for conservative therapy have been developed by the American College of Rheumatology.[8] Based on the available evidence, strongly recommended therapies are (1) exercise, (2) weight loss in people who are overweight or obese, (3) self-efficacy and self-management programs, (4) tai chi, (5) cane use, (6) tibiofemoral bracing for tibiofemoral knee osteoarthritis, (7) topical nonsteroidal anti-inflammatory drugs (NSAIDs), (8) oral NSAIDs, and (9) intra-articular glucocorticoid injections for knee osteoarthritis. Conditionally recommended therapies are (1) balance exercises, (2) yoga, (3) cognitive behavioural therapy, (4) patellofemoral bracing for patellofemoral knee osteoarthritis, (5) acupuncture, thermal modalities, (6) topical NSAIDs, (7) intra-articular steroid injections and chondroitin sulphate, (8) topical capsaicin, and (9) oral acetaminophen, duloxetine, and tramadol. No effective disease-modifying agents for osteoarthritis have yet been identified, though phase 2 and 3 trials are underway, and, for the time being, preventive strategies focus on weight management and injury prevention.[9] Unfortunately, conservative care for knee osteoarthritis is often insufficient or associated with side effects.[10] Around 50% of

people who are first diagnosed with symptomatic knee osteoarthritis are estimated to eventually undergo a total knee arthroplasty in their lifetime.[11] A radiofrequency treatment of the genicular nerves could be an alternative method to treat knee pain due to osteoarthritis.

Description of the intervention

Radiofrequency treatment of the genicular nerves is a relatively new, minimally invasive, percutaneous technique to treat chronic knee pain.[12,13] When a high-frequency current at 500 kHz, called radiofrequency, is applied in proximity to a sensory nerve by a percutaneous electrode, the heat generated at the electrode tip causes coagulation, which interrupts pain conduction. Radiofrequency treatment of the genicular nerves was first described in 2011 by Choi and colleagues to treat knee pain in people with osteoarthritis.[14] By placing a radiofrequency electrode percutaneously next to three sensory nerves innervating the anterior knee joint, called the genicular nerves, they obtained a reduction in knee pain. This treatment can be performed under fluoroscopic or ultrasound guidance.[15] Currently, the superomedial, superolateral, and inferomedial genicular nerves are the most common nerves targeted by radiofrequency treatment. As the anterior knee is innervated by 10 nerves, further research is needed to determine the optimal number of nerves to target.[16] The current evidence suggests durable improvement in chronic knee pain after genicular nerve radiofrequency treatment when compared with conservative therapy or intra-articular injections with glucocorticoids or hyaluronic acid derivatives.[17,18,19]

Radiofrequency treatment can be divided into four modalities: monopolar (continuous (conventional), pulsed, cooled) and bipolar.[15] These radiofrequency treatments are proposed to work either by creating thermal lesions or by neuromodulative effects, thereby blocking nociceptive transmission. Radiofrequency treatment of the genicular nerves is performed by interventional pain management specialists in hospital settings, including anaesthesiologists or orthopaedic surgeons. Continuous neuroablative radiofrequency (CNARF), pulsed neuromodulative radiofrequency (PNMRF), and cooled radiofrequency treatment of genicular nerves are reported to be successful in alleviating pain and improving physical function in people with knee osteoarthritis who did not respond to conservative treatment or had contraindications to surgery.[20] As this procedure requires specific equipment, trained physicians and a hospital setting, this is a costly procedure. Therefore, it is probably done more often in high-income countries, although, as far as we know, there is no literature on where, globally, radiofrequency is performed the most.

How the intervention might work

Monopolar conventional radiofrequency uses a high-frequency alternating current released from the electrode tip to induce a thermal lesion. The small cross-sectional area of the electrode tip creates an energy flux towards the larger cross-sectional area of the grounding pad. 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.

In monopolar pulsed radiofrequency, thermal tissue injury may be minimised by using 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 pulsed radiofrequency provides clinical benefit is unclear. From a mechanistic point of view, pulsed radiofrequency seems to primarily modulate signalling cascades in the C fibres while leaving nerve conduction in myelinated fibres intact.[21] It is a minimally destructive alternative to conventional radiofrequency treatment and could minimise potential side effects.

When targeting small sensory nerves, there is a risk that landmark-based needle placement may miss the nerves responsible for transmitting pain signals due to anatomic variability. Therefore, modifications were carried out to the conventional radiofrequency technique to create larger lesions. In cooled radiofrequency, by internally cooling the electrode while heating up to 60 °C, scarring of the surrounding tissue is prevented. Therefore, by reducing the impedance, thermal energy can reach further and create a larger lesion.[22]

In monopolar radiofrequency techniques, electrical current flows between the electrode tip and a grounding plate. However, in bipolar radiofrequency, two active electrodes are placed symmetrically, creating a circuit for the electrical current in between, thus also creating a bigger lesion.[15]

Why it is important to do this review

There is a high prevalence and burden of knee osteoarthritis with limited efficacy of current treatments.[10,23,24] The data from the Study of Osteoarthritis Real World Therapies, a clinical prospective observational study conducted in six European countries, suggest that pharmacologic and non-pharmacologic therapies do not meet the needs of a large knee osteoarthritis population and that people with inadequate pain relief resort to opioids.[10] Furthermore, the final treatment of osteoarthritis, a total knee replacement, is not always possible. In frail people, it is not desirable due to the inherent operative risk; in young people, it is not desirable due to the limited

life expectancy of the implants used. This means that some people who need knee replacement at a younger age may eventually need a second operation, with a much higher morbidity. Also, the prevalence of persistent postsurgical pain is as high as 20%.[25,26]

In recent years, several randomised controlled trials have been conducted to evaluate the clinical efficacy of radiofrequency treatment of the genicular nerves for knee osteoarthritis. Most trials suggest that it can be a safe and effective treatment for reduction of pain and improvement of physical function in people with knee osteoarthritis lasting more than three months.[12,13] Despite the general positive reports on patient outcomes, the clinical utility of this therapy remains unclear. This is due to diversity in the types of radiofrequency used, different techniques due to revisions of anatomical landmarks, inconsistent study methodologies and small study sizes.[27,28,20] At the moment, there is no Cochrane review on this topic, despite the growing body of research. Therefore, we aim to conduct a systematic review and meta-analysis to evaluate the safety and efficacy of radiofrequency treatment to relieve pain and improve physical function in people with osteoarthritis of the knee. A high-quality systematic review would help guide policies on the implementation of radiofrequency treatment of the genicular nerves in the treatment algorithm for chronic knee pain due to osteoarthritis.

Objectives

To assess the benefits and harms of radiofrequency treatment of the genicular nerves in people with chronic knee pain due to knee osteoarthritis.

Methods

Criteria for considering studies for this review

Types of studies

We will include all randomised controlled trials (RCTs) and crossover studies regardless of language, date or publication status. While we will describe the characteristics of those published as abstract only, those with unpublished data and ongoing studies, we will not include any results from these in the synthesis of results. Instead, we will classify trials not yet completed as 'ongoing trials', and classify unpublished trials or those published as abstracts only as 'studies awaiting classification' and describe their characteristics in tables in the review. We judge that the carry-over effect has the potential to extend beyond the cross-over phase, and we will therefore only include data from the first period of cross-over RCTs.

Types of participants

We will include male and female adults with chronic knee pain (as defined in the study) and an established diagnosis of knee osteoarthritis according to accepted clinical criteria.[30,31,32] or who self-reported knee osteoarthritis on the basis of chronic joint pain (with or without radiographic confirmation). We will also include trials that included participants with osteoarthritis in other joints, provided that the outcomes for people with osteoarthritis of the knee were presented separately (or could be obtained from the trial authors) or if > 80% of participants in the trial had osteoarthritis of the knee.

Types of interventions

We will include any radiofrequency treatment of the genicular nerves (**Figure 1**). We will pose no limits on the temperature that is used, application time or radiofrequency modality (conventional, cooled, pulsed, or bipolar radiofrequency). See **Figure 1** for nerves that can be targeted.

The radiofrequency technique can be performed using fluoroscopy, ultrasound, any other imaging guidance or a combination. The radiofrequency technique is often preceded by a prognostic block. There is currently controversy about the importance and effect of this block on the outcome of radiofrequency treatment. We will include all studies, regardless of the use of a prognostic block.

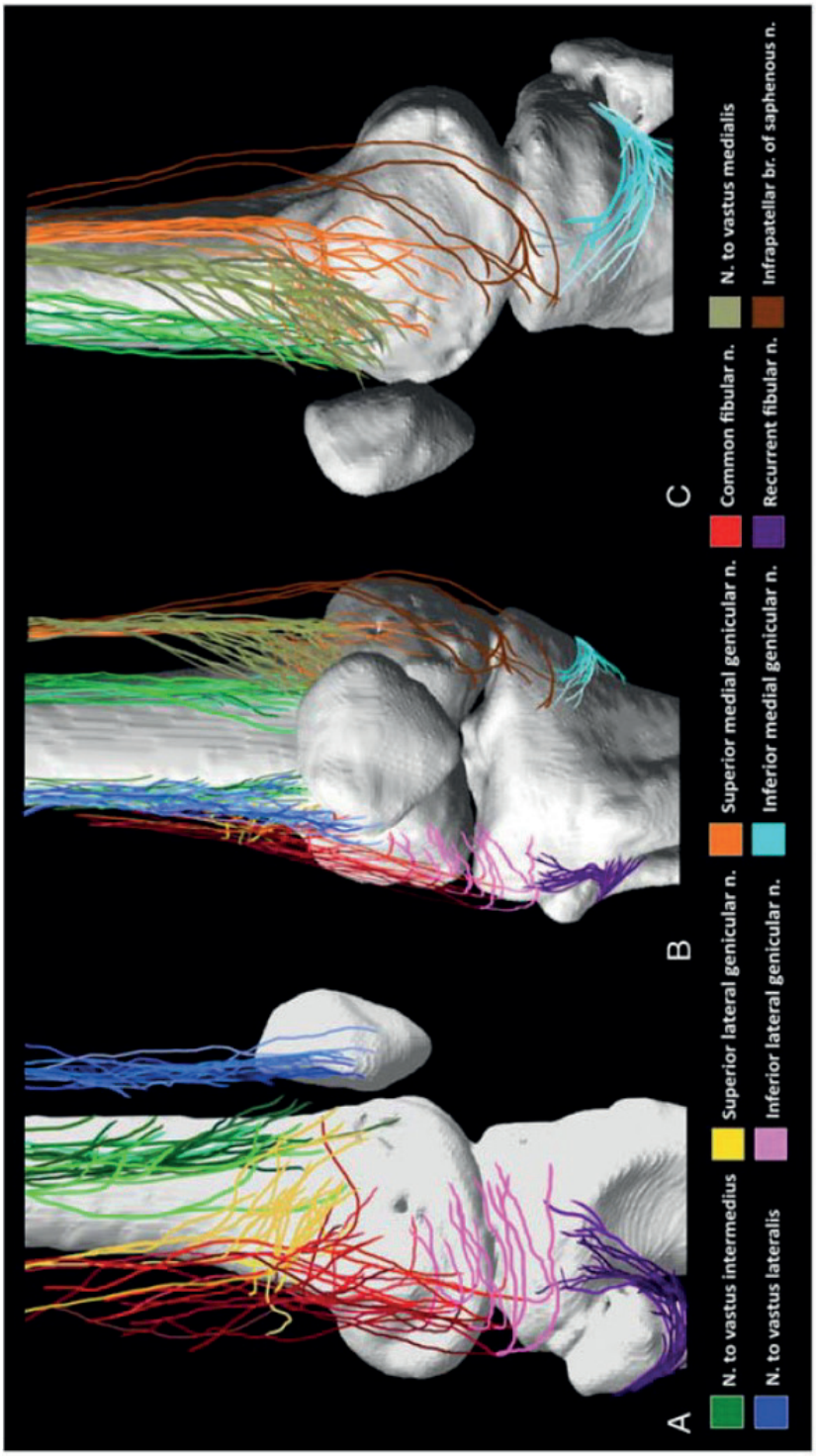

Figure 1. Genicular nerves. (Tran 2018)

The following comparators are eligible for inclusion.

1. Radiofrequency treatment (all modalities combined) versus placebo (inactive control group), defined as any intervention on the genicular nerves where there is no lesion or long-term effect. This includes injections of saline or only needle placement without any injection.
2. Radiofrequency treatment (all modalities combined) versus no intervention (usual care). Usual care includes medication and physiotherapy or exercise.
3. Radiofrequency treatment (all modalities combined) versus intra-articular glucocorticoid injections. Glucocorticoids are available in both crystalline and non-crystalline forms. The crystalline triamcinolone and the non-crystalline prednisolone and methylprednisolone are used most frequently.

Concomitant treatments should be the same in each group, otherwise we will exclude the study. Possible co-interventions are conservative measures such as (a) new analgesic/anti-inflammatory medication prescriptions, (b) psychological support, and (c) physiotherapy. Radiofrequency treatment is not a stand-alone treatment, as conservative management is preferably continued. Conservative management of knee osteoarthritis includes non-pharmacological care (education, lifestyle changes, exercise programs, weight management and psychological support) and pharmacological care (non-steroidal anti-inflammatory drugs, paracetamol).

We will exclude studies that perform radiofrequency treatment on structures other than the genicular nerves, as well as studies that compare one radiofrequency modality with another.

Types of outcome measures

The chosen outcomes are based on the OMERACT-OARSI (Outcome Measures in Rheumatoid Arthritis Clinical Trials-Osteoarthritis Research Society International) core outcome domains for knee osteoarthritis.[29]

Major outcomes

1. Pain (pain overall, pain on walking, WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) pain subscale, WOMAC global scale, Lequesne osteoarthritis index global score, other algofunctional scale, Patient's global assessment, Physician's global assessment, other outcome, no continuous outcome reported (such as a dichotomous response: yes/no))[34]

2. Physical function: self-reported measures (Global disability score, walking disability, WOMAC disability subscore, composite disability scores other than WOMAC, disability other than walking, WOMAC global scale, Lequesne osteoarthritis index global score, other algofunctional scale[34]
3. Participant global assessment of treatment effect
4. Health-related quality of life as assessed by a generic measure (EuroQol 5 dimension 5 level (EQ-5D-5L), EuroQol 5 dimension 3 level (EQ-5D-3L), 12-Item Short-Form Health Survey (SF-12), 36-Item Short Form Health Survey (SF-36) or other scales)[35]
5. Adverse events
6. Serious adverse events
7. Withdrawals due to adverse events

Minor outcomes

1. Radiographic joint structure
2. Medication use (Medication Quantification Scale version 3 (MQS3))

Timing of outcome assessments

We will stratify the primary analysis by follow-up time for pain, function and quality of life: up to three months; three months to one year (primary time point for the primary comparison); more than one year to two years. We will consider the following time points for the extraction of data on pain, function and quality of life: short term (less than three months); intermediate term (three months to one year); long term (one year or longer). For adverse events, withdrawals, serious adverse events, and global assessment, we will extract data at the end of the trial.

Search methods for the identification of studies

Electronic searches

We will search the following databases.

- MEDLINE via Ovid
- EMBASE via Ovid
- Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid

We will conduct a search of ClinicalTrials.gov and the World Health Organisation International Clinical Trials Registry Platform (ICTRP) Search Portal for ongoing or unpublished trials. Information about possibly relevant ongoing studies will be included in the review in the characteristics of ongoing studies table.

For reports of serious adverse effects, we will search the websites of the following regulatory agencies.

- US Food and Drug Administration (FDA) FDA Label Database
- European Medicines Evaluation Agency
- Australian Medicines Safety Update
- UK Medicines and Healthcare products Regulatory Agency (MHRA) pharmacovigilance and drug safety updates

We will search all databases from their inception to the present, and we will impose no restriction on language of publication. Our preliminary search strategy (MEDLINE) will be adapted for use in other electronic bibliographic databases. See **Appendix** for the MEDLINE search strategy.

Searching other resources

We will check reference lists of all primary studies and review articles for additional references. We will search for errata or retractions from included studies published in full text on PubMed and report the date this was done within the review.

Data collection and analysis

Selection of studies

Two review authors (VT and BA) will independently screen titles and abstracts of all the potentially relevant studies we identify as a result of the search, and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will resolve any disagreements through discussion or, if required, we will consult a third person (VL). If review authors are involved in the selected study, a third author (VA) will code the study.

First, we will identify and exclude duplicates and collect multiple reports of the same study under a single reference ID so that each study, rather than each report, is the unit of interest in the review. We will retrieve the full-text study reports/publications. Two review authors (VT and BA) will independently screen the full-text, identify studies for inclusion and identify and record the reasons for exclusion of the ineligible studies. We will resolve any disagreements through discussion or, if required, we will consult a third person (VL). We will record the selection process in sufficient detail to complete a PRISMA flow diagram and characteristics of excluded studies table.[36]

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which we will pilot on at least three studies in the review. One review author (VL) will extract study characteristics from included studies. A second review author (VT) will check

study characteristics for accuracy against the trial report. A third author (VA) will extract data if previous authors are involved in the selected study. We will use EndNote X9 citation management software to store references, remove duplicates, and conduct initial screening[37].

We will extract the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, and date of start of the study.
2. Participants: N; mean age; age range; sex; disease duration; severity of condition expressed as Kellgren-Lawrence grade; diagnostic criteria; BMI; important baseline data on pain, physical function and health-related quality of life; inclusion criteria; and exclusion criteria for participation in the trial.
3. Interventions: intervention (modality, temperature, application time, needle size, which nerves are targeted), comparison, concomitant therapies.
4. Outcomes: major and minor outcomes specified and collected, including measures of precision (e.g. standard error or confidence interval if applicable, or parameters that can be used to compute measures of precision), and time points reported.
5. Information needed to assess bias, as outlined below in the Assessment of risk of bias in included studies section.
6. Notes: funding for trial and notable declarations of interest of trial authors.
7. Information needed to assess GRADE (e.g. baseline risk in the control group for key outcomes).

Two review authors (VT, VL) will independently extract outcome data from the included studies. A third author (VA) will extract data if previous authors are involved in the selected study. We will extract the number of events and number of participants per treatment group for dichotomous outcomes and means, standard deviations and number of participants per treatment group for continuous outcomes.

We will note in the characteristics of included studies table if a study did not report outcome data in a usable way, and if we transformed data or estimated data from a graph. If a study reports both final values and change from baseline values for the same outcome, we will extract the change from baseline values. If both unadjusted and adjusted values are reported for the same outcome, we will extract the adjusted outcomes. If a study reports multiple adjusted estimates of intervention effect, we will choose the one that we judge to minimise the risk of bias due to confounding.

If data for outcomes assessing benefits and harms are analysed based on an intention-to-treat (ITT) sample and another sample (e.g. per-protocol, as-treated), we will extract data based on an intention-to-treat sample, except for safety outcomes for which we will only use an as-treated sample. When studies report outcomes at multiple follow-up times, we will extract data at up to three months (short term), three months to one year (intermediate term) and one year or longer (long term) for all major outcomes. If multiple time points are reported within each of the stratifications, we will extract data at the latest time point in this stratification.

Where multiple measures of pain are reported, we will extract the measure highest on the following hierarchy recommended by Juhl.[38]

1. Global pain (visual analogue scale (VAS) or numeric rating scale (NRS))
2. Pain on walking (VAS/NRS)
3. WOMAC pain subscale
4. Composite pain scores other than WOMAC
5. Pain on activities other than walking (VAS/NRS)
6. Pain at rest or pain during the night (VAS/NRS)

Where multiple measures of function are reported, we will extract the measure highest on the following hierarchy recommended by Juhl.[38]

1. Global disability score
2. Walking disability
3. WOMAC function subscale
4. Composite disability scores other than WOMAC
5. Disability other than walking
6. WOMAC global scale
7. Lequesne Osteoarthritis Index global score
8. Other algofunctional scale

One review author (VL) will transfer data into the RevMan file.[39] We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports.

We will use PlotDigitizer to extract (in duplicate) data from graphs or figures.[40]

Assessment of risk of bias in included studies

Two review authors (VL, BA) will independently assess the risk of bias for each study. We will resolve any disagreements by discussion or by involving another author (VT).

We will assess the risk of bias using the Cochrane risk of bias 2 (ROB 2) tool for RCTs, according to the following domains.[41]

1. Bias arising from the randomisation process
2. Bias due to deviations from intended interventions
3. Bias due to missing outcome data
4. Bias in measurement of the outcome
5. Bias in selection of the reported result

For non-standard RCT designs (such as cross-over studies and cluster-randomised RCTs), we will use a variant of the ROB 2 tool developed for these types of study designs. For cluster-RCTs we will add the domain 'bias arising from the timing and recruitment of participants'. For cross-over RCTs, we will add the domain 'bias arising from period and carryover effects'.

We will grade each potential source of bias as high, some concerns, or low risk, and provide a quote from the study report together with a justification for our judgment in the risk of bias table. Where information on the risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the risk of bias table. We will summarise the risk of bias judgments across different studies for each of the domains listed. We will consider blinding separately for different key outcomes, and will judge self-reported outcomes and assessor-reported outcomes separately. In addition, we will consider the impact of missing data by key outcomes.

Our effect of interest is assignment to the intervention at baseline (the ITT effect). When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

We will present the figures generated by the risk of bias tool to provide summary assessments of the risk of bias.

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will present simple summary data for each intervention group: number of events and number of participants per group for dichotomous outcomes, mean and standard deviation and number of participants per group for continuous outcomes in forest plots.

We will analyse dichotomous data as risk ratios (RRs) and use 95% confidence intervals (CIs). For continuous data, we will use the mean difference (MD) or standardised mean difference (SMD), depending on whether studies use the same scale to measure an outcome, and 95% CIs. When different scales are used to measure the same conceptual outcome (e.g. physical function), we will calculate SMDs with corresponding 95% CIs and back-translate them to a typical scale (e.g. 0 to 10 for pain) by multiplying the SMD by a typical among-person standard deviation (e.g. the standard deviation of the control group at baseline from the most representative trial.[42] We will enter data presented as a scale with a consistent direction of effect across studies.

If an RCT does not report a result as a measure that can directly be entered into a meta-analysis, we will compute that measure using the information in Chapter 6 of the Cochrane Handbook for Systematic Reviews of Interventions.[43]

Minimally important differences

Rather than using minimally important differences, which are not well-defined for knee osteoarthritis, we will judge the magnitude of the effect based upon mean between-group differences for continuous measures based on a similar approach used in the American College of Physicians 2017 guidelines for low back pain.[44] For pain measured on a 0 to 10-point scale, we will consider a difference of 0.5 to 1.0 points as slight to small, a difference of > 1 to 2 points as moderate and a difference of > 2 points as large. Similarly, for function and health-related quality of life measured on a 0 to 100-point scale, we will consider a difference of 5 to 10 points as slight/small, a difference of > 10 to 20 points as moderate and a difference of > 20 points as large.

Unit of analysis issues

Where a single trial reports multiple trial arms, we will include only the relevant arms. If two comparisons (e.g. treatment A versus placebo and treatment B versus placebo) are combined in the same meta-analysis, we will halve the control group to avoid double-counting if possible.

We believe that the carry-over effect may persist beyond the cross-over phase; therefore, we will only include data from the first period of cross-over RCTs.

To address unit of analysis issues in cluster-RCTs, we will extract a direct estimate of the required effect measure (e.g. a risk ratio with its confidence interval) from an analysis that properly accounts for the cluster design.[45] Such an analysis might be

based on a multilevel model or may use generalised estimating equations, among other techniques. When the study authors have not conducted such an analysis, we will use approximately correct analyses to adjust the results. Therefore, we will extract the following information:

- the number of clusters (or groups) randomised to each intervention group and the total number of participants in the study; or the average (mean) size of each cluster;
- the outcome data ignoring the cluster design for the total number of individuals (e.g. the number or proportion of individuals with events, or means and standard deviations for continuous data); and
- an estimate of the intracluster (or intraclass) correlation coefficient (ICC).

If the ICC is not available in the published report, we will use external estimates obtained from similar studies or use an estimate based on known patterns in ICCs for particular types of clusters or outcomes.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only or when data are not available for all participants). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by using a sensitivity analysis. We will clearly describe any assumptions and imputations to handle missing data, and will explore the effect of imputation in a sensitivity analysis.

For dichotomous outcomes (e.g. number of withdrawals due to adverse events), we will calculate the withdrawal rate using the number of participants randomised to the group as the denominator. For continuous outcomes (e.g. mean change in pain score), we will calculate the MD or SMD based on the number of participants analysed at that time point. If the study does not present the number of participants analysed for each time point, we will use the number of randomised participants in each group at baseline.

Where possible, we will calculate missing standard deviations from other statistics, such as standard errors, confidence intervals or P values, according to the methods recommended in Chapter 6 of the Cochrane Handbook for Systematic Reviews of Interventions.[43] If we cannot calculate standard deviations, we will impute them (e.g. from other studies in the meta-analysis). We will conduct sensitivity analyses to evaluate bias arising from missing values.

Assessment of heterogeneity
We will assess the clinical and methodological diversity of included studies in terms of participants, interventions, outcomes and study characteristics (e.g. study design, outcome measurement tools, etc.) to determine whether a meta-analysis is appropriate. We will observe the data in the characteristics of included studies table to do this. To evaluate statistical heterogeneity, we will visually inspect the forest plot to assess the direction and magnitude of effects and the degree of overlap between CIs.

Moreover, we will use the I^2 statistic to quantify between-study heterogeneity in each analysis. We will also report the P value from the Chi^2 test. If we identify substantial heterogeneity, we will report it and explore possible causes by prespecified subgroup analysis. When there are few studies, we will use caution in applying the thresholds below to interpret statistical heterogeneity.

We will use this approximate guide for the interpretation of an I^2 value[46]:
- 0% to 40% might 'not be important';
- 30% to 60% may represent 'moderate' heterogeneity;
- 50% to 90% may represent 'substantial' heterogeneity;
- 75% to 100% represents 'considerable' heterogeneity.

We will keep in mind that the observed value of I^2 depends on: (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a CI for the I^2 statistic: uncertainty in the value of the I^2 statistic is substantial when the number of studies is small).

Our interpretation of the Chi^2 test will be that $p \leq 0.10$ indicates evidence of statistical heterogeneity. If we identify substantial heterogeneity, we will report it and investigate possible causes by following the recommendations in section 10.10 of the Cochrane Handbook for Systematic Reviews of Interventions.[46]

Assessment of reporting biases
We will create and examine a funnel plot to explore possible small study biases if we have at least 10 studies eligible to be pooled in a meta-analysis. When interpreting funnel plots, we will examine the different possible reasons for funnel plot asymmetry as outlined in chapter 13 of the Cochrane Handbook for Systematic Reviews of Interventions and relate this to the results of the review.[47]

If we are able to pool more than 10 trials, we will undertake formal statistical tests to investigate funnel plot asymmetry, and will follow the recommendations in section 13.3 of the Cochrane Handbook for Systematic Reviews of Interventions.[48,47]

To assess outcome reporting bias, we will check trial protocols against published reports. For studies published after 1 July 2005, we will screen ClinicalTrials.gov and WHO ICTRP trial registers to identify the prepublished trial protocol. We will evaluate whether selective reporting of outcomes is present.

Data synthesis

Main planned comparisons

Our primary comparison will be radiofrequency treatment of the genicular nerves versus a placebo (inactive control group). This is defined as any intervention on the genicular nerves where there is no lesion or long-term effect. This includes injections of saline or only needle placement without any injection. Injection of glucocorticoids is not considered a placebo.

Our other main comparisons are grouped as follows.

- Radiofrequency treatment versus no treatment (usual care).
- Radiofrequency treatment versus intra-articular glucocorticoid injections.

Meta-analysis of numerical data

We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense. Forest plots will be presented for each of the three comparisons: radiofrequency treatment versus placebo, radiofrequency treatment versus no treatment and radiofrequency treatment versus intra-articular glucocorticoid injections. As previously mentioned, the forest plots for pain, function and quality of life will be stratified based on the timing of the outcome into short-term (less than 3 months), intermediate-term (three months to one year) and long-term (one year or longer).

We will use a random-effects model that estimates intervention effects that follow a distribution across studies (random effects), as we anticipate substantial clinical between-study heterogeneity.

In the primary analysis, we will include all trials regardless of their risk of bias. We will perform sensitivity analyses to assess the effects of studies with a high risk of bias and with missing data on the pain outcome.

Subgroup analysis and investigation of heterogeneity
We will perform the following three subgroup analyses for pain. For the main comparison between radiofrequency versus placebo.

1. Radiographic mild to moderate osteoarthritis compared to severe disease. Radiographic mild to moderate osteoarthritis is defined as knee osteoarthritis that corresponds to a Kellgren-Lawrence grade 1, 2, or 3 based on imaging. Radiographic severe osteoarthritis corresponds to a Kellgren-Lawrence grade 4. It is unknown whether radiofrequency treatment is more effective in mild to moderate or severe osteoarthritis.
2. 'Prognostic block' (Yes/No). With a prognostic block, the targeted genicular nerves are anaesthetised with a local anaesthetic to confirm the diagnosis and be able to predict radiofrequency treatment response. Until now, no evidence-based algorithm has been established that can properly select which patients would benefit from genicular nerve radiofrequency treatment. A recent study was unable to show a difference in outcomes between participants randomised to receive either a prior prognostic block or no prognostic block at all.[49] It is unclear whether any prognostic block of the genicular nerves is needed, given that they increase health-care costs and the potential for complications as compared with immediate treatment.

For the comparison between different radiofrequency modalities if sufficient study reports are available.

3. Conventional compared to cooled radiofrequency

We will use the formal test for subgroup interactions in RevMan, and will use caution in the interpretation of subgroup analyses as advised in chapter 10 of the Cochrane Handbook for Systematic Reviews of Interventions.[39,46]

Sensitivity analysis
We will investigate the robustness of the treatment effect on pain to potential selection bias and potential detection bias by performing the following sensitivity analyses.

1. Selection bias: remove the trials that reported inadequate or unclear allocation concealment from the meta-analysis to see if this changes the overall treatment effect.

2. Selection bias: include only the trials that reported on participants with chronic knee pain who suffer from moderate to severe knee pain and have a radiographic diagnosis of osteoarthritis that includes grades 2 to 4 according to the Kellgren-Lawrence classification.
3. Detection bias: remove the trials that reported inadequate or unclear participant blinding from the meta-analysis to see if this changes the overall treatment effect.

Sensitivity analyses will be restricted to the 'placebo' and 'no treatment' comparisons.

Summary of findings and assessment of the certainty of the evidence
We will follow the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions, Chapters 14 and 15, when interpreting results, and will be aware of distinguishing a lack of evidence of effect from a lack of effect.[50,51] We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice, and our implications for research will suggest priorities for future research and outline what the remaining uncertainties are in the area.

We will create summary of findings tables using the following outcomes at the intermediate term (three months to one year).
- Pain
- Physical function
- Participant global assessment of treatment effect
- Health-related quality of life
- Adverse events
- Serious adverse events
- Withdrawals due to adverse events

The main comparisons expressed in the summary of findings tables will be:
- Table 1. Radiofrequency treatment versus placebo
- Table 2. Radiofrequency treatment versus no treatment
- Table 3. Radiofrequency treatment versus intra-articular glucocorticoid injections

Two people (BA and VL) will independently assess the certainty of the evidence, with disagreements resolved by discussion or involving a third review author (VT). We will use the five GRADE considerations (study limitations (overall risk of bias), consistency of effect, imprecision, indirectness and publication bias) to assess the

certainty of a body of evidence as it relates to the studies which contribute data to the analyses for the prespecified outcomes, and report the certainty of evidence as high, moderate, low, or very low. We will justify, document and incorporate judgments into reporting of results for each outcome.

We will use GRADEpro software to prepare the summary of findings tables.[52] We will use version 3 of the GRADEPro view to display our summary of findings tables, which has the 'What happens' column. We will justify all decisions to downgrade the certainty of evidence for each outcome using footnotes, and we will make comments to aid the reader's understanding of the review where necessary.

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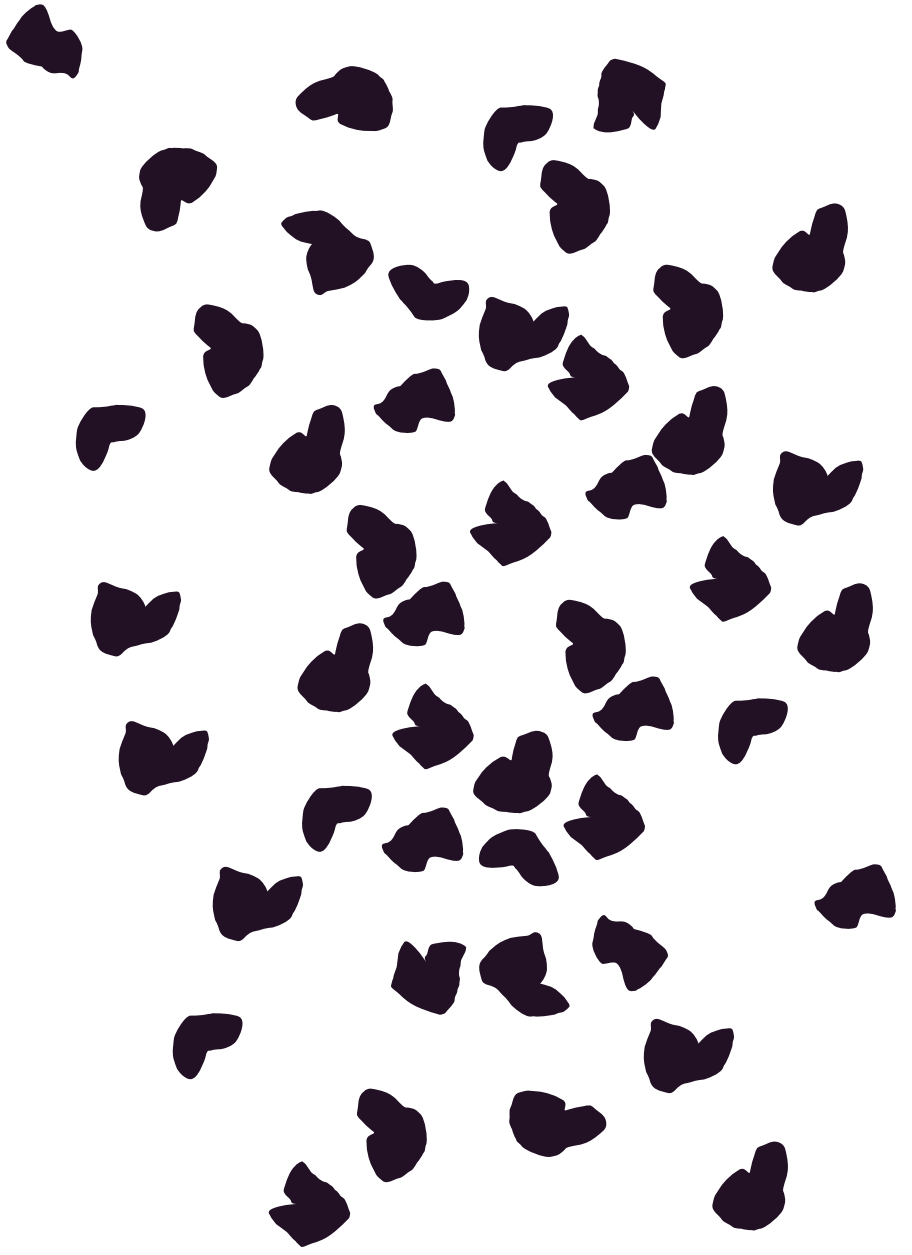
Appendix

Preliminary MEDLINE search strategy

Ovid MEDLINE

1 exp Osteoarthritis/
2 osteoarthr$.tw.
3 (degenerative adj2 arthritis).tw.
4 arthrosis.tw.
5 or/1-4
6 exp knee/
7 exp Knee Joint/
8 knee$.tw.
9 or/6-8
10 exp Radiofrequency Therapy/
11 exp Pulsed Radiofrequency Treatment/
12 exp Radiofrequency Ablation/
13 radiofrequency.tw.
14 (radiofrequency adj3 ablation).tw.
15 or/10-14
16 exp randomized controlled trial/
17 controlled clinical trial.pt.
18 randomised.ab.
19 placebo.ab.
20 drug therapy.fs.
21 randomly.ab.
22 trial.ab.
23 groups.ab.
24 or/16-23
25 exp animals/ not humans.sh.
26 24 not 25
27 5 and 9 and 15 and 26



Chapter 5

Complex regional pain syndrome of the knee after conventional radiofrequency ablation of the genicular nerves treated successfully with dorsal root ganglion stimulation: a case report

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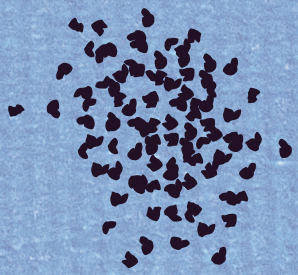

Abstract

Background

Radiofrequency (RF) treatment of the genicular nerves offers pain relief in patients suffering from chronic knee pain, including persistent post-surgical knee pain (PPSP). We present the first case report of the development of complex regional pain syndrome (CRPS) in a chronic knee pain patient after an RF ablation of the genicular nerves that was successfully treated with dorsal root ganglion (DRG) stimulation.

Case presentation

The patient developed increased pain, sympathetic and dysmorphic changes of the index knee 10 weeks after RF treatment for PPSP. Diagnosis of CRPS type II was made using positive clinical findings and the Budapest diagnostic tool. Laboratory workup and PET-CT were negative. The patient was refractory to usual care, and she was treated successfully with dorsal ganglion root stimulation.

Conclusions

Complex regional pain syndrome is a possible complication of RF ablation of the genicular nerves in patients with chronic knee pain, and DRG stimulation may be a treatment option. Physicians should be aware of this complication, especially when patients have a medical history of CRPS.

Introduction

Radiofrequency (RF) ablation of the genicular nerves is a minimally invasive technique used to treat chronic knee pain, including persistent post-surgical knee pain (PPSP) that has been unresponsive to usual care.[1,2] Until now, only temporary and infrequent complications were reported with this treatment.[3]

Complex regional pain syndrome (CRPS) type II is a rare neuropathic pain condition associated with autonomic features caused by nerve tissue trauma of the extremities.[4] We report the first case of a patient developing CRPS after an RF ablation of the genicular nerves. This case study will describe this rare adverse event of RF ablation and its treatment using dorsal root ganglion (DRG) stimulation.

Case report

Patient information

A Caucasian woman in her mid-thirties presented at the pain clinic with a history of more than 20 years of chronic right knee pain. The knee pain originated post-traumatically at the age of 14 years. The patient underwent multiple right knee arthroscopies, one chondrocyte transplantation, and eventually a patellofemoral knee prosthesis. After a temporary resolution of the symptoms, the patient experienced recurrent patellar subluxations treated with medial patellofemoral ligament reconstruction with an allogenic Achilles tendon. After this last operation, the patient developed PPSP and developed pain over a 150 cm^2 area anterior to the patella, accompanied by paraesthesia. Conservative care had resulted in insufficient pain relief, and an orthopaedic workup revealed no correctable causes.

The patient was treated with a conventional RF ablation of the right knee's superomedial, superolateral, and inferomedial genicular nerves at a temperature of 70°C for 90 s per nerve after a positive diagnostic block (lidocaine 2%, 1 ml per genicular nerve). Both procedures were tolerated well and were uneventful. She reported transient neuritis during the first month after RF ablation. The patient informed the physician of anterior knee pain, fluctuating episodes of knee oedema, local increase in temperature, and hair growth on the knee 2.5 months after the RF treatment. Symptoms were more present during knee mobilisation. The patient used the following painkillers when she first presented with the CRPS-like symptoms: Paracetamol 1 g 2–3 times daily PO, Tramadol extended-release 100 mg twice daily PO, and transdermal Lidocaine 5% applied to the knee once daily for 12 hours. The patient's medical history was limited to the mentioned orthopaedic surgeries and a temporary episode of CRPS after knee arthroscopy more than 15 years ago. At that time, the patient experienced oedema, increased pain, and colour changes. The diagnosis of CRPS was made by the orthopaedic surgeon, and the patient was successfully treated with the standard therapy of that moment. Recovery lasted a couple of months.

Clinical findings

The physical examination at diagnosis of CRPS type II was non-remarkable of knee oedema or temperature changes of the knee. Modest colour changes and hair growth were present on the superolateral right knee. Motor function was preserved; however, the patient's gait was antalgic. The patient presented photographs showing significant knee oedema and colour changes (**Figure 1**). The sensory, vasomotor, and trophic changes were limited to the innervation pattern of the genicular nerves.

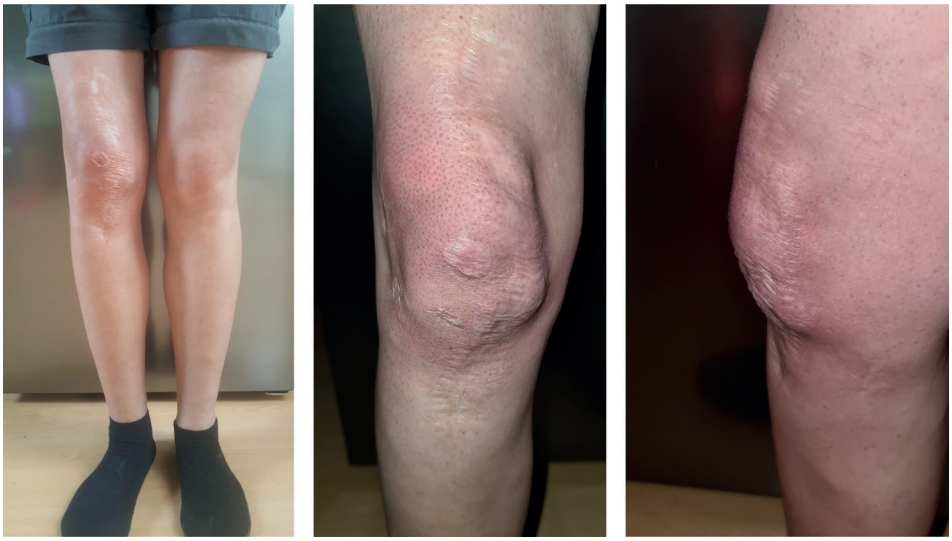

Figure 1. View of index knee at diagnosis of CRPS.

Diagnostic assessment

The diagnosis of CRPS type II, presenting a "primarily warm" phenotype, was made clinically using the diagnostic criteria of the International Association for the Study of Pain (IASP), more commonly known as the "Budapest criteria."[5] SPECT–CT and laboratory tests did not point toward an infection. There was a moderately increased uptake of the proximal knee in SPECT–CT, probably corresponding with CRPS. The orthopaedic surgeon excluded other differential diagnoses.

Diagnosis

CRPS type II.

Therapeutic interventions

The patient was approached multimodally. Pharmacological therapy was initiated with the following medications: Vitamin C 500 mg once daily PO, and Acetylcysteine 600 mg once daily PO for 6 weeks. The previously mentioned painkillers were continued. Physical therapy and rehabilitation, together with mirror therapy, were conducted by a physiotherapist specialised in CRPS. Because of the failure of conservative therapy in achieving tolerable pain, the patient was treated with a pulsed radiofrequency of the fourth lumbar nerve after a positive diagnostic block with local anaesthetics. The treatment resulted only in the temporary improvement of knee pain. A trial with Amitriptyline 10 mg once daily PO was made without effect. After 7 months of therapy-resistant CRPS, the patient was referred for DRG stimulation.

Follow-up and outcomes

Following a positive test stimulation during 3 weeks with right DRG L3 and L4 leads, she received a definitive pulse generator implant (Proclaim DRG non-rechargeable IPG) in the lower abdomen with two SlimTip DRG leads approximately 8 months after the first diagnosis of CRPS (**Figure 2**). The patient described full recovery at 2 months and resumption of work at 5 months after DRG implantation. Symptom relief was present at 8 months of follow-up. **Figure 3** demonstrates the diseased knee after DRG treatment, while **Figure 4** represents the timeline of the patient's medical care.

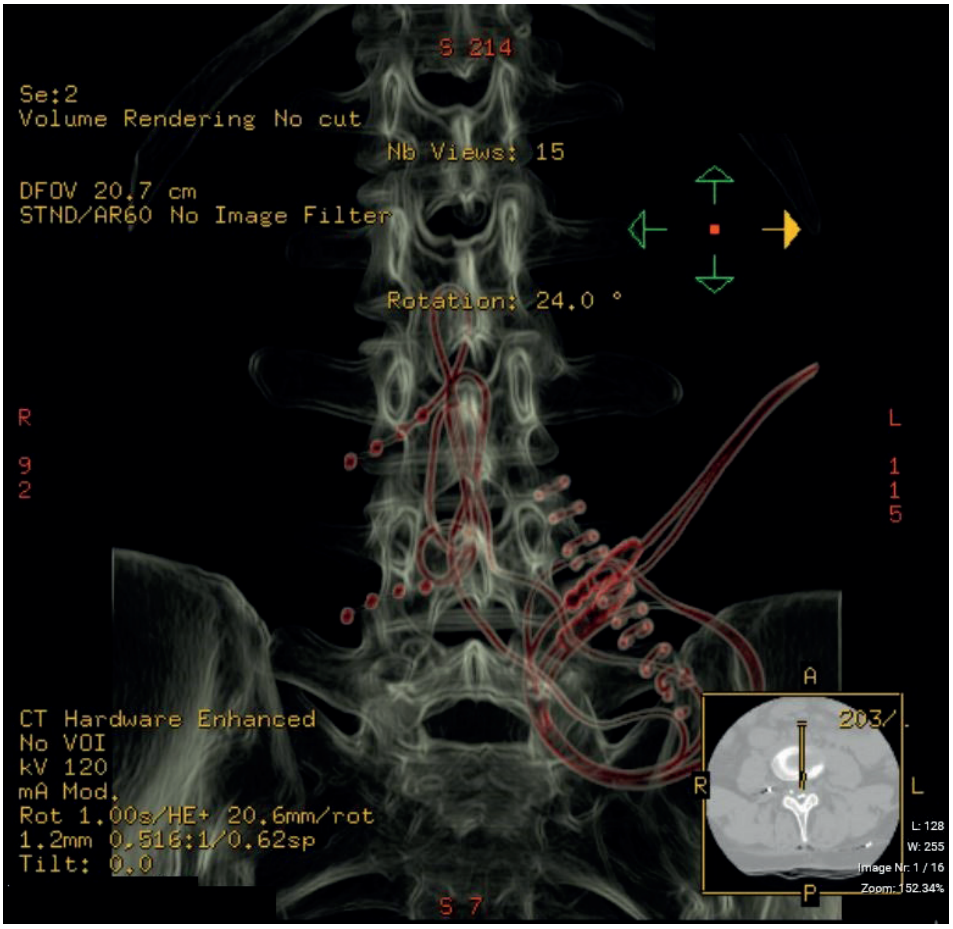

Figure 2. Computed tomography of the lumbar spine of the patient demonstrating the placed DRG L3 and L4 leads.



Figure 3. View of the index knee after DRG implantation.

Patient's perspective

"I feel an important change in my knee after the DRG implantation. I don't experience any acute flare-ups; my knee does not swell any more. I can do eight km-long walks, which was previously not possible. Before the treatment, I had to rest all day and take painkillers for the pain. Now I am working full-time, and usually a light painkiller or changes in the neurostimulator settings are sufficient to perform my daily activities. I am very thankful to the pain team for the help. I was in the long walks, which were previously not possible. Before the treatment, I had to rest all day and take painkillers for the pain. Now I am working full-time and usually a light painkiller or changes in the neurostimulator settings are sufficient to perform my daily activities. I am very thankful to the pain team for the help. I was in the beginning reluctant to the treatment but now I can say that the implant has decreased my pain and brought a lot of comfort to my life."

The patient provided permission for the presentation of this report.

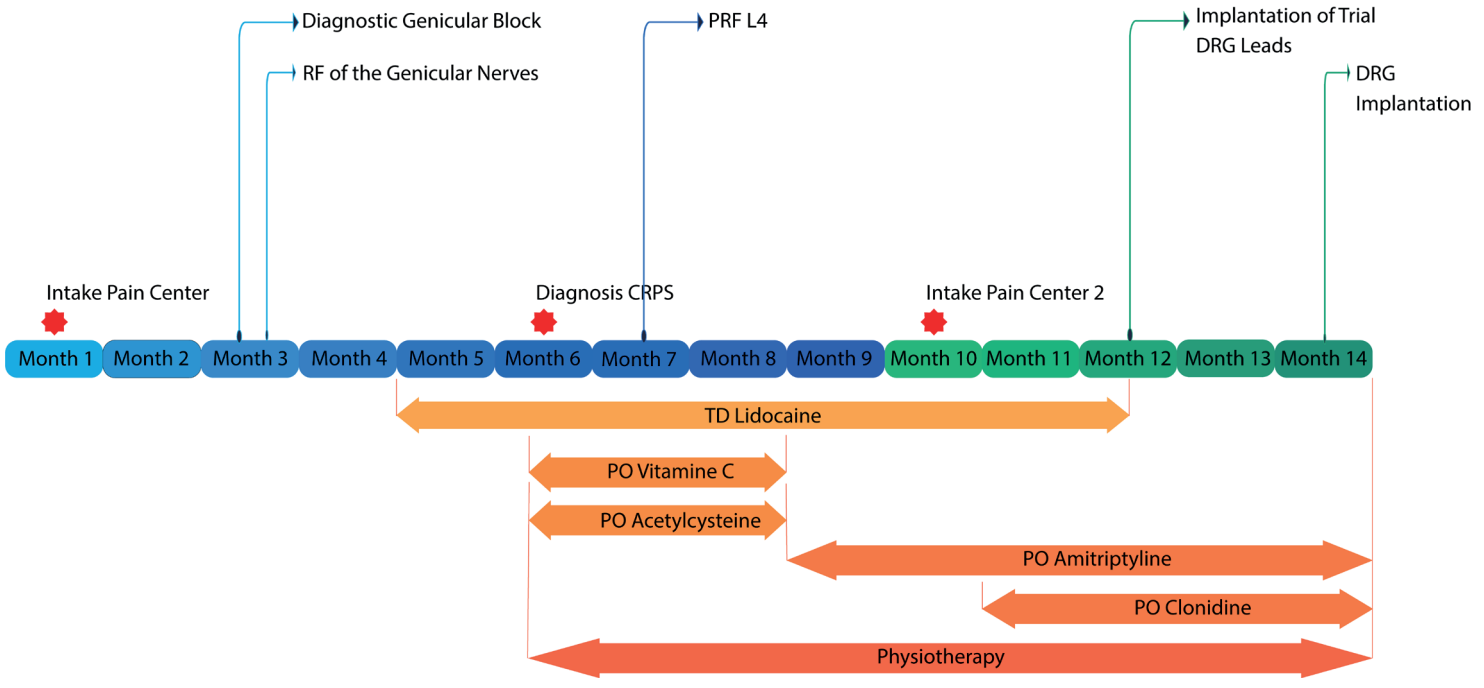

Figure 4. Timeline of the patient's medical care.

CRPS, Complex regional pain syndrome; DRG, Dorsal root ganglion stimulation; PO, Per os; PRF L4, Pulsed radiofrequency ablation of lumbar nerve 4; RF, Radiofrequency ablation; TD, Transdermal.

Discussion

Radiofrequency of the genicular nerves has gained popularity for treating invalidating chronic knee pain in osteoarthritis and PPSP patients. Pain relief is the result of blocking the propagation of nociceptive input from the knee to the central nervous system by thermocoagulation of the genicular nerves. RF treatment is reported to have self-limiting and potentially transient adverse events in RCTs and cohort studies.[5,6] Only a few case reports describe serious complications of the RF procedure, including knee joint infection, pes anserine damage, bleeding, hemarthrosis and third-degree burns.[7] Lack of knowledge on the exact incidence of serious and non-serious complications of RF ablation, mainly long-term ones, creates an obstacle for the large-scale implementation of the RF treatment in chronic knee pain.[8]

In the presented case study, RF ablation of the genicular nerves performed for PPSP was complicated with an episode of CRPS type II. CRPS type II is a disease that develops after documented nerve injury in the patient's extremities. The pathophysiology of CRPS is, despite being convoluted and multifactorial, dominated in the acute phase by a posttraumatic inflammatory reaction.[4] Timely recognition and treatment of the disease are crucial and could prevent dramatic motor dysfunction, fixed dystonia, and limb neglect.[4] We suspect that the genicular nerve lesion caused by RF is the trigger of the mentioned inflammatory reaction and the further development of autonomic changes and peripheral and central sensitisation. A factor that potentially could delay the diagnosis of CRPS is the frequent transient neuritis that patients experience after RF of the genicular nerves. Pain is often the most essential symptom of transient neuritis and CRPS.[4] Dysesthesia and impairment of thermal perception due to transient neuritis, unfortunately, additionally overlap with CRPS symptomatology. Nevertheless, other accompanying symptoms such as temperature, skin colour, and trophic changes should prompt further testing for CRPS. The patient's medical history, such as previous episodes of CRPS, should prompt a faster diagnosis.

Treatment of CRPS is multimodal.[4] Despite adequate pharmacological and physiotherapy treatments, the patient was therapy-resistant. Sympathetic nerve blocks and neurostimulation are considered alternative treatments for CRPS. Chemical or radiofrequency sympathetic neurolysis at the lumbar level has been reported to successfully reduce CRPS symptoms.[9] While pulsed RF of the fourth lumbar nerve performed in this case study did not cause reduction of the sympathetic tonus in the lower limb, the rationale behind this treatment is that neuromodulation of the lumbar nerve could diminish neuropathic pain transmission from the knee.

DRG and spinal cord stimulation (SCS) are two forms of neurostimulation that should be considered after failure of non-invasive treatment in CRPS.[10,11] Most research focuses primarily on CRPS type I (no evident nerve damage); nevertheless, SCS and DRG stimulation have been described as successful in CRPS type II.[4,12] DRG stimulation provides better pain and quality of life outcomes than SCS in CRPS patients, as presented in one RCT of Deer et al.[12] SCS is reported to be successful for up to 5 years in low extremity CRPS type I, while DRG stimulation data for CRPS are limited to 12 months.[4,12,13] DRG stimulation resulted in complete symptom regression up to 8 months after treatment in the present case report.

Conclusions

CRPS type II is a rare but possible complication of RF ablation of the genicular nerves. The lesion caused by the RF ablation can precipitate episodes of CRPS, especially in patients with a previous history of CRPS. Awareness of this occurrence is crucial as anticipation, timely recognition and treatment of acute CRPS can prevent its development into a chronic therapy-resistant pain condition. DRG stimulation resulted in full recovery of the patient at 2 months after treatment, and it may thus be an alternative treatment option for therapy-resistant CRPS.

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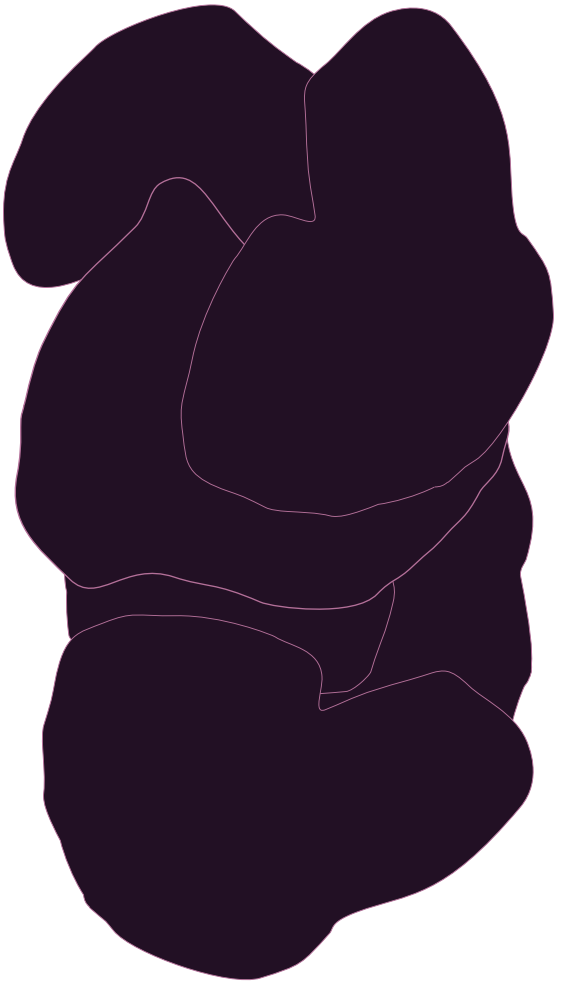

Chapter 6

The GENIFEM pilot randomised trial: genicular nerve block vs femoral triangle block vs local infiltration analgesia for total knee arthroplasty

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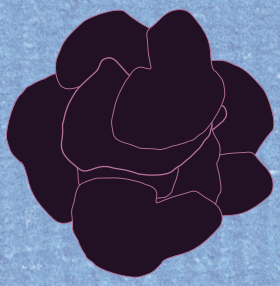

Introduction

Motor-sparing nerve blocks are recommended for total knee arthroplasty (TKA), including femoral triangle block (FTB), genicular nerve block (GNB), infiltration between the popliteal artery and capsule of the knee (iPACK), and local infiltration analgesia (LIA).[1] We designed a pilot study on postoperative pain and functionality using 3 regional anaesthetic approaches (GNB & iPACK, FTB & iPACK, and LIA) for TKA. The objective was to (1) assess feasibility of a future definitive trial, (2) estimate the adequacy of the efficacy outcome, and (3) gather preliminary data.

Methods

This single-centre pilot randomised trial assessed feasibility and compared pain during ambulation in 36 adult patients undergoing primary TKA until 1 post-operative month.[2] The Ethical Committee of Hospital Oost-Limburg (Z-2021085) and the Federal Agency for Medicines and Health Products approved the study, and written informed consent was obtained from all patients in the trial. The trial was registered before patient enrolment at clinicaltrials.gov (NCT05156476, principal investigator: T. Vanneste, registration date: September 20, 2021). Inclusion criteria were the ability to ambulate and fill the questionnaires, grade I-III of the American Society of Anaesthesiologists classification. Exclusion criteria were previous open knee surgery, body mass index >40 kg/m2, contraindication to trial medications, chronic widespread pain, uncontrolled psychiatric disorder, chronic neuromuscular deficit including radicular pain, and use of opioids (excl. tramadol) within 3 days before surgery. Patients were randomised in a parallel manner to one of 3 study arms (GNB & iPACK versus FTB & iPACK versus LIA) after a 1:1:1 randomisation ratio with varying block sizes of 3 and 6 using Castor EDC software. Patients, outcome assessors, and the investigators were blinded to the allocation. GNB & iPACK was the experimental group, while both FTB & iPACK and LIA were control groups.

The nerve blocks (excl. LIA) were performed using ultrasound under periprocedural sedation before general anaesthesia. LIA was performed by the orthopedist. The medication used per nerve block was: GNB, 5 ml of ropivacaine 0.5% for each of the superomedial, superolateral, inferomedial and inferolateral genicular nerves; FTB, 20 ml of ropivacaine 0.5%, iPACK, 10 ml of ropivacaine 0.5%; LIA, 200 ml of ropivacaine 0.2% (50 mL pure, 150 mL + adrenaline [1 mg]). The sham procedure, performed without needle placement or injection of an anaesthetic, mimicked the procedures that the patient was not assigned to. Patients underwent robotically assisted TKA (ROSA Knee System [Zimmer Biomet]) under general anaesthesia and perioperative multimodal analgesics (dexamethasone 5 mg, acetaminophen 15 mg/kg (maximum of 1000 mg) and ketorolac 30 mg). Postoperative analgesia consisted of acetaminophen (15 mg/kg, max. 1 g every 6 hours IV/PO), ketorolac (0.5 mg/kg, max.30 mg IV every 8 hours), Patient Controlled Intravenous Analgesia (bolus of 1.5 mg Morphine, 7-minute lockout interval, maximum dosage of 30 mg/4 hours), oral tramadol and oxycodone.

Data was collected at baseline, perioperative period, 4 to 6 hours, 24 hours, 48 hours, 72 hours, and 1-month follow-up. The efficacy outcome was the proportion of patients with a numeric rating scale (NRS 0–10) ≤4 during mobilisation (walking 10m) without morphine use at 4 to 6 hours of follow-up. Other outcomes include NRS at rest and

during mobilisation, opioid use, the Western Ontario and McMaster Universities Osteoarthritis Index; health-related quality of life (EuroQol 5- Dimension 3-Level); Hospital Anxiety and Depression Scale, Pain Catastrophizing Scale, Maximum voluntary isometric contraction of the quadriceps muscle, timed-up-and-go test (TUG), and 6-minute walking test.

Feasibility outcomes were inclusion rate/month, retention rate, adequacy of the efficacy outcome, and implementation of the study.

Efficacy outcomes were compared using a linear mixed model (R version 4.3.3).

Results

From February 2022 to June 2023, 37 of 102 screened patients were included. Three patients were excluded before randomisation due to protocol violations (**Figure**). Baseline data revealed a higher proportion of females (72%) in the FTB & iPACK group and a shorter mean preoperative pain duration in the GNB & iPACK group.

Feasibility outcomes

The recruitment rate was 6.8 patients/month. The retention rate for the efficacy outcome was 100%. No crossovers occurred. Interventions and trial design were well accepted by patients and clinicians. Approximately 27% of all patients were discharged before the 72-hour evaluation leading to considerable missing data.

Efficacy endpoints

One patient (LIA) met the efficacy endpoint. No statistically significant differences were found when comparing NRS during movement, morphine consumption and knee functionality across the 3 groups at all time points. The evolution of these outcomes is depicted in the **Table**.

- Mean differences (95% CI) at 4 to 6 hours postoperatively: GNB & iPACK versus FTB & iPACK: NRS at movement: 2.8 (3.8); Morphine use: 10 (45.9).
- GNB & iPACK versus LIA: NRS at movement: 3.1 (3.7); Morphine use: 9.4 (46.6).

Sixteen patients ambulated (TUG test) at 4 to 6 hours of follow-up (3/10 GNB & iPACK, 5/11 FTB & iPACK, and 8/13 LIA).
No adverse events were reported.

Sample size calculation for a powered trial

Sample size was calculated using G*Power software (ver. 3.1.9.7; Heinrich-Heine-Universität Düsseldorf) for a 1-way analysis of variance (ANOVA) statistical method ($\alpha = 0.05$, $\beta = 0.2$, number of groups 3). The effect size (eta-squared point estimate of 0.055) translates to a sample size of 171 patients.

Table. Evolution of the Components of the Primary Outcome and of the Functionality Test at Different Timepoints Reported Per Treatment Arm.

	GNB and iPACK	FTB and iPACK	LIA
Mean NRS at mobilisation (95% CI)[a]			
Baseline	4.0 (1.9–6.1)	3.8 (2.5–5.2)	4.7 (3.2–6.2)
4–6 h	7.3 (5.1–9.5)	4.5 (2.6–6.3)	2.6 (1.4–4.0)
24 h	5.6 (3.8–7.4)	4.3 (3.0–5.6)	5.0 (3.8–6.2)
48 h	3.4 (1.6–5.3)	3.2 (1.8–4.5)	4.5 (2.9–6.1)
72 h	2.0 (0.7–3.3)	2.0 (0.4–3.6)	2.0 (0.7–3.3)
1 m	2.0 (0.5–3.5)	1.6 (–0.2–3.3)	2.6 (0.5–3.5)
Mean cumulative morphine consumption in mg (95% CI)			
4–6 h	19.3 (10.4–28.2)	9.4 (4.5–14.3)	9.9 (4.9–14.9)
24 h	32.6 (18.1–47.2)	18.1 (11.8–24.4)	23.7 (14.4–33.2)
48 h	43.0 (27.9–58.0)	29.8 (17.1–42.6)	37.4 (21.4–53.3)
72 h	42.1 (25.9–58.2)	29.8 (17.1–42.6)	37.4 (21.4–53.3).
Mean MVIC in kg of force (95% CI)			
Baseline	14.8 (8.9–20.7)	10.0 (6.3–13.7)	9.2 (6.2–12.3)
4–6 h	2.6 (–1.3–6.5)	2.5 (0.2–4.8)	4.3 (2.4–6.2)
24 h	4.5 (1.9–7.1)	4.5 (1.6–7.3)	2.4 (1.0–3.8)
48 h	3.9 (1.9–5.9)	5.5 (3.1–7.9)	4.7 (2.9–6.5)
72 h	9.2 (5.1–13.2)	8.4 (3.8–13.1)	9.9 (3.4–16.5)
Mean 6MWT in meters (95% CI)			
Baseline	322.1 (250.0–394.2)	320.4 (263.5–377.2)	313.2 (263.7–362.8)
24 h	52.4 (12.9–91.8)	29.4 (7.3–51.4)	52.4 (3.6–101.2)
48 h	100.0 (64.3–135.6)	99.3 (65.1–133.5)	111.4 (62.6–160.2)
72 h	164.9 (95.8–234.0)	137.6 (102.0–173.2)	160.7 (109.1–212.2)
Mean TUG in seconds (95% CI)			
Baseline	13.5 (8.5–18.5)	13.4 (9.8–17.0)	14.3 (11.5–17.1)
4–6 h	197.2 (145.7–248.7)	175.1 (122.5–227.8)	124.3 (68.5–180.1)
24 h	88.0 (44.2–131.8)	77.4 (38.3–116.4)	138.1 (71.1–205.0)
48 h	55.5 (40.9–70.1)	46.4 (34.9–57.8)	58.4 (19.9–96.9)
72 h	27.7 (15.7–40.0)	29.7 (21.5–38.0)	30.7 (23.4–38.0)

Abbreviations: CI, confidence interval; GBN, genicular nerve block; iPACK, infiltration between the popliteal artery and capsule of the knee; FTB, femoral triangle block; LIA, local anaesthetics for infiltration analgesia; NRS, numeric rating scale; MVIC, maximum voluntary isometric contraction of the quadriceps muscle; 6MWT, 6-minute walking test; TUG, timed up and go test.

[a]Mobilization is defined as a minimal effort of walking 10 m.

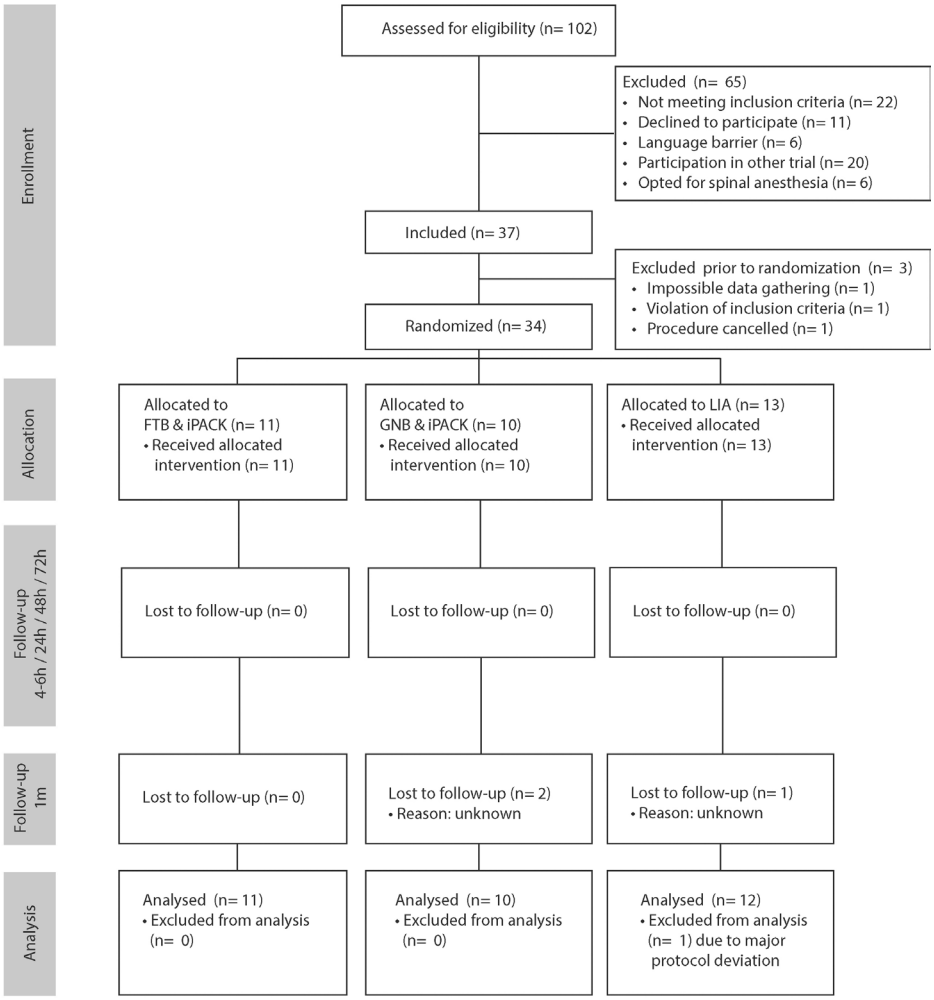

Figure. CONSORT diagram showing the flow of participants at each stage of the GENIFEM trial. CONSORT indicates Consolidated Standards of Reporting Trials; FTB, femoral triangle block; GBN, genicular nerve block; iPACK, infiltration between the popliteal artery and capsule of the knee; LIA, local anaesthetics for infiltration analgesia.

Discussion

In this pilot trial, the comparison of the 3 regional anaesthetic approaches was feasible. Based on the primary outcome, the total sample size for a powered trial would be 171 patients. Switching to a continuous score or adopting a less stringent morphine cutoff could improve feasibility.

Randomised trials on GNB primarily evaluate it in combination with the adductor canal block.[3–6] GNB was noninferior to LIA for TKA.[7] Our study is the first to directly compare the GNB & iPACK to FTB & iPACK and LIA.[8] No statistically significant differences were observed between the groups over time for all outcomes. Roughly half of the patients could ambulate at 4 to 6 hours after surgery.

Limitations

As this study is underpowered, we are unable to conclude on efficacy outcomes. Two components of this protocol, general anaesthesia and IV patient-controlled analgesia, diverge from best practice, which entails multimodal oral analgesia and often spinal anaesthesia.[9] Local anaesthetic dosage was different: 150 mg ropivacaine for the GNB & iPACK and FTB & iPACK, and 400mg for LIA. This reflected our hospital's practice, and while similar doses have been reported for LIA, they exceed the maximum recommended dose.[9] Lastly, we performed no sensory test after the nerve blocks.

In conclusion, a powered comparative study testing the different motor-sparing approaches is feasible in patients undergoing TKA after adaptation of the efficacy outcome.

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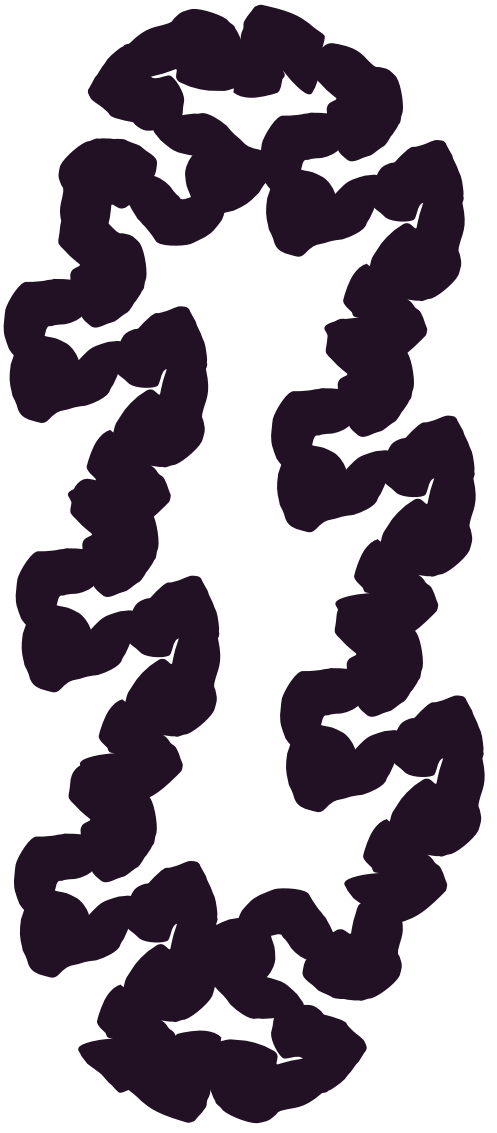

Chapter 7

Patient perspectives on radiofrequency treatment for chronic knee pain: a qualitative study embedded in the COGENIUS-Trial

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Abstract

Background

The COGENIUS trial is an ongoing double-blinded randomised trial evaluating the effectiveness, cost-effectiveness, and safety of radiofrequency (RF) of the genicular nerves, an emerging minimally invasive treatment for chronic knee pain due to osteoarthritis (OA).

Objectives

This qualitative study, embedded within the COGENIUS trial, explored how individuals with knee OA perceive their current treatment options, including RF.

Design & methods

Twelve semi-structured interviews were conducted with COGENIUS participants diagnosed with therapy-resistant knee OA pain of ≥1 year. The sample included seven males and five females (mean age of 66 years, SD 10.5). An interpretive paradigm and descriptive qualitative design guided data collection and analysis.

Setting

17 Belgian hospitals

Results

Participants described a substantial burden of knee OA, characterised by pain, functional limitations, sleep disturbances, and emotional impact. Treatment trajectories were long, heterogeneous, and often inconsistent with guideline-based care. RF was perceived as feasible, acceptable, and credible in the setting of the COGENIUS trial. Sedation was considered important to minimise discomfort. The run-in phase was generally seen as offering little added value. Participants emphasised functionality alongside pain as key treatment outcomes. They were open to targeting multiple genicular nerves to improve treatment effectiveness and expressed willingness to repeat the procedure.

Conclusions

This qualitative study highlights the substantial burden of knee OA and the variability of treatment trajectories in Belgium. Participants regarded genicular nerve RF as a meaningful option for therapy-resistant knee pain, particularly when sedation is tailored to individual needs. Their perspectives provide direction for optimising RF delivery, enhancing patient education, and informing future research, including studies with larger samples, clinician input, and qualitative evaluation of RF in persistent postsurgical knee pain.

Introduction

Chronic knee pain due to osteoarthritis (OA) is a rapidly growing public health concern and a leading cause of disability and reduced quality of life.[1] Its prevalence has doubled in recent generations, contributing to rising levels of pain, functional limitation, psychological distress, and decreased social participation.[2,3] The cornerstone for treatment of knee OA is education, physiotherapy, weight management, and self-management, aided by medications and intra-articular injections. [4,5] When symptoms persist, patients resort to surgical interventions such as a total knee arthroplasty (TKA), but up to one in five individuals continue to experience pain after a TKA.[6] Radiofrequency (RF) treatment of the genicular nerves is a relatively novel, minimally invasive technique with the potential to reduce knee OA burden and has seen increasing clinical use.[7] Emerging evidence suggests that RF can provide meaningful pain relief in knee OA.[8]

Current care for individuals with knee OA in Belgium is highly variable, with patients often following treatment trajectories that do not align with clinical practice guidelines.[9] The 2018 Evikey report identified the underuse of conservative treatments and the tendency for early referral to surgery as key issues.[9] Recently, the RF treatment has been reimbursed in Belgium for patients with therapy-resistant knee OA. As ongoing research continues to refine optimal RF treatment protocols, considerable variation exists in procedural approaches and image-guidance methods. [8,10,11] Standardisation of the RF technique would likely improve consistency and quality of clinical care.

The COGENIUS trial is an ongoing double-blinded randomised trial conducted in 17 Belgian centres and 2 Dutch centres, designed to evaluate the effectiveness, cost-effectiveness, and safety of the RF treatment in 200 knee OA patients.[12] Patients are required to undergo an initial run-in phase where conservative care is optimised following Belgian Health Care knowledge centre quality standards and international guidelines.[13] Participants with persistent pain after the run-in period are randomised to either an RF treatment of the genicular nerves (conventional or cooled RF) (80% of the participants) or a sham procedure (20% of the participants). Patients are followed up at 1-, 3-, 6-, 9 months-, one year, and two years after the intervention.

This multicentre trial provides a valuable opportunity to explore participants' experiences of the current treatment trajectories in Belgium, including the RF treatment. As such, we designed a qualitative trial embedded in the COGENIUS study. The aims are threefold. Firstly, to document the experiences and reflections

on the current treatment modalities in individuals suffering from knee OA in Belgium. Secondly, to document participants' experiences on the RF treatment of the genicular nerves. And thirdly, to examine participants' preferences and expectations on future developments on the RF intervention, enabling them to influence future research.

Methods

Study design

A qualitative descriptive design using individual interviews with semi-structured and structured topics was employed to explore participants' reflections on treatment modalities both before and during the COGENIUS trial, as well as their preferences and expectations for future research on RF treatment. This qualitative study was embedded within the COGENIUS trial, which evaluates the effectiveness, cost-effectiveness and safety of RF of the genicular nerves. Ethics approval was obtained alongside the COGENIUS trial from the central Ethics Committee of the University of Antwerp (Number Project ID 3069-Edge 002190-BUN B3002022000025) and the separate ethics committees of each participating hospital.

Recruitment

Potential participants were initially approached by their treating physician. After expressing interest, they were contacted by the qualitative research team. Written informed consent was obtained before participation.

Participants

Sampled participants were enrolled across 17 Belgian hospital sites. Eligible participants were adults (≥18 years) with knee osteoarthritis (Kellgren–Lawrence grade II–IV) who had exhausted at least one year of conservative treatment, including education, physiotherapy, self-management strategies, medication, and at least one intra-articular injection. No participant had undergone a knee arthroplasty. Participants had completed the run-in phase of the COGENIUS trial and had a minimum follow-up of four months after the study intervention. Purposive sampling was used to include a heterogeneous population in terms of age, language, and study treatment received, without aiming for data saturation. Participants were as such chosen to ensure variation in age (<65 and ≥65 years), and language (Dutch and French). All patients had undergone the study intervention and were chosen to have undergone RF treatment versus placebo following a 4:1 randomisation ratio. The age stratification was used to include both working-age and retired individuals. Exclusion criteria were limited to language barriers and the inability to provide informed consent. After purposive sampling, participants were chosen at random using Microsoft Excel.

Interviews were conducted by two interviewers with medical backgrounds: AB (female, MD) conducted interviews in Dutch, and MD (male, medical student) conducted interviews in French. Neither interviewer had a prior relationship with the participants. Both received external training in qualitative research methods and followed a standardised interview approach.

Data collection

Twelve individual interviews took place in June, July, and August 2025, either face-to-face or via Microsoft Teams, at participants' homes, clinics, or a public setting (e.g., a café). Interviews were semi-structured (topic 1) and structured (topic 2) (see **Appendix**) and were audio-recorded. Some partners were present during the interviews. The topic guide was piloted with a participant of the COGENIUS trial before data collection. Field notes were taken during the interviews. Two interviewers with a background in medical science conducted the interviews: AB (female, MD) in Dutch and MD (male, MD) in French. AB and MD had no previous relationship with the participants.

Data analysis

The audio-recordings were transcribed verbatim using the Amberscript AI transcription software.[14] Patient names were coded similarly to the COGENIUS trial.

Descriptive statistics were used for participant and interview characteristics. Interview data were analysed thematically, combining deductive and inductive coding, in the interviewees' language (Dutch and French) by authors TV, JVZ, VB, AB, DL, and MD using Microsoft Excel. We used an interpretive paradigm and a descriptive design for the interviews.

Rigor

The quality criteria used for this study followed the framework described by Lincoln and Guba, and the methodology was based on the 'Handboek kwalitatieve onderzoeksmethoden' from Dimitri Mortelmans.[15,16] Credibility was enhanced through listening to the audio recording along with the transcripts, by repeated reading of the transcripts before coding, and through ongoing comparison across data segments. Dependability was supported by having all interviews conducted by two researchers, one in each language, ensuring consistency in data collection. Confirmability was strengthened through participant checking of the findings. Authenticity was illustrated by the inclusion of verbatim participant quotations, while transferability was facilitated by providing detailed participant characteristics and verbatim transcriptions. The planned external audit was not conducted due to time and resource constraints. This manuscript conforms to the Consolidated criteria for Reporting Qualitative research (COREQ) and Standards for Reporting Qualitative Research checklists.[17,18]

Results

Participant characteristics

Twelve participants, 5 females and 7 males, belonging to the OA group of the COGENIUS trial, were included, aged from 43 to 84 years old (average age 66) from 5 medical hospitals in Belgium (see **Table 1**). Five individuals declined to be interviewed (due to a lack of time or unsuitable scheduling), and three could not be reached or had language barriers. The duration of interviews was on average 38 min (range 10 – 76 min).

Thematic analysis

Four major themes and 17 subthemes emerged from the analysis. The four themes were: Experience of living with knee OA, Experience of treatments for knee OA, Experience of the COGENIUS study, and Participants' preferences on RF treatment. The first theme was emergent.

Theme 1: Experience of living with knee OA

Subtheme 1.1: The perceived causes of knee OA

Participants attributed knee OA to intrinsic factors (the knee being a weak joint, genetic predisposition, and ageing) and external factors (heavy manual work, repetitive trauma). Participants perceived the disease to be spontaneously progressive; however, they voiced beliefs that sport, trauma, and manual labour were strong determinants of disease acceleration. The discrepancy between the grade of osteoarthritis in imaging techniques and the perceived symptoms was also noted. Participants understood that the symptoms did not only derive from a diseased bone, but that OA is a disease of the whole joint and the surrounding tissue (e.g., tendons and nerves).

> I used to do a lot of triathlons and marathons, so I was very sporty. And that was also partly because of my job. I had the opportunity to train six to eight hours a day... But then you start having trouble with your knees, with your back. (Participant 3, 63y, NL)

> No, not really, because I know that it [sport] would have continued to worsen the osteoarthritis. So I didn't expect to be able to start doing sports again. (Participant 7, 52y, FR)

Subtheme 1.2: Burden of disease

Pain and limitation in functionality emerged as a dominant constant feature of experienced knee OA burden. Participants expressed that the limitations they encountered influenced their sleep, their work, and their emotional well-being. They

reported that this burden was central in their life, that it, in certain periods, resulted in work discontinuation and limited social engagement. Despite this, social engagement was also identified as a distraction to pain. Participants stated that living with knee OA resulted in feelings of frustration, frequent complaining, and uncertainty about the future. They reported that knee pain required life adjustments such as not carrying heavy objects, using fewer stairs, and switching to an automated car.

> For example, if I take a break to stop and eat, when I start again [walking], I feel like an old diesel engine. Everything has to get going again. (Participant 7, 52y, FR)

> I was crying from pain all the time. It's like when you have a toothache, it's the same thing. … When you have a cavity, you're very nervous, you can't even touch the skin. (Participant 8, 60y, FR)

> But what if it gets worse? That's what I wonder. What are they going to do then? They always say, 'We don't want to put in a prosthesis, we don't want to put in a prosthesis.' What are they going to do in my case?! (Participant 2, 63y, NL)

Theme 2: Experience of treatments for knee OA

Participants conveyed having undergone different treatment trajectories. Participants generally recalled active non-interventional care; however, application of physical therapy specifically for knee OA was inconsistent. They understood treatments to be divided into symptomatic treatments (e.g., medications) and disease targeting (e.g., intra-articular injections and surgery). There were differences in the number of received infiltrations, with participants having undergone a minimum of three and an estimated maximum of more than twenty, with variable effects. Participants had consistently considered the need for a TKA and had consulted orthopaedic surgeons; they expressed uncertainty about the appropriateness of the proposed treatments, especially when second or third opinions recommended different approaches. Another recurring topic during the interviews was participants' wish for new treatments for knee OA.

> I went to see a specialist. Right away, he advised me to get a prosthesis. I was a bit shocked because immediately—after five minutes, after looking at the X-rays—he said that a full prosthesis was needed. I had been told that a partial prosthesis was possible. So I went to see a second specialist. In the end, out of the three specialists I consulted, one said a full prosthesis, one a partial one, and the other said, 'Whatever you want.' That didn't reassure me at all. I wondered whether this is medical care or medical business. (Participant 10, 65y, FR)

(AB: What could be improved?) That they could control the pain better. When I hear about athletes, they are always treated immediately... they get operated on and shortly after that—boom—and they're back at it. That can't be right, can it? Couldn't they help ordinary people a bit more? (Participant 1, 73y, NL)

Subtheme 2.1: Non-pharmacological treatments

Participants reported varied beliefs on the value of physiotherapy for knee OA. Physiotherapy was described as having positive attributes (e.g., important for improvement in function and experience of less pain, to improve equilibrium, as a preventive treatment, and valuable for the general health) and negative attributes (e.g., as painful, as a deteriorator for the knee pain, and as being ineffective). There appeared to be distinct participant groups: some had not engaged in knee OA-specific physiotherapy at all, while others had undergone years of physiotherapy and adhered to exercise programs.

Participants generally understood the importance and implemented other self-management strategies, including staying active, activity modification (e.g., pacing), using assistive devices, and weight management. Knee braces and canes were reported to help improve equilibrium and provide support during walking or running, but they were also reported to limit movement and cause discomfort. Need for education on the disease cause and prognosis was not acknowledged in the interviews, except for the need for education on the RF treatment of the genicular nerves.

I found the second operation by Dr. [name omitted] to be very successful. But because of the physiotherapist's actions, the improvement was undone again. (Participant 2, 63y, NL)

Subtheme 2.2: Medication

Participants articulated strong views on medication use, mentioning that medication was not viewed as a solution to their problem, medication was a final recourse when all other treatments did not work, and when used, it was perceived as having a short effect and undesirable complications (addiction and constipation). Medications recurrently mentioned were paracetamol, non-steroidal anti-inflammatory drugs, and tramadol. When strong opioids were mentioned, they were used for knee OA pain in a setting of generalised arthrosis.

I can tolerate pain very well, but at a certain point you say, well... because taking painkillers, I did that as little as possible. And after a while... it's an addiction too. (Participant 2, 63y, NL)

> In fact, I don't take any [painkillers], except during real crisis moments, when for a few days I've overdone it a bit. Or if I make a wrong movement and really put pressure on it, I hurt my knee quite badly. Then, for several days, I sometimes have moments when I can't walk anymore, and so then I take some anti-inflammatories. But otherwise, I try not to take them continuously, painkillers either, and I try to live in a way that avoids hurting myself. (Participant 7, 52y, FR)

Subtheme 2.3: Minimally invasive treatments (intra-articular injections)

Interviewees expressed willingness to undergo articular infiltrations (intra-articular corticosteroids, intra-articular hyaluronic acid); however, an aversion to glucocorticoid injections was also mentioned as they were viewed to have systemic adverse events, especially when the person was suffering from diabetes mellitus. For intra-articular injections, participants reasoned the effect to be more valuable in the early stages of knee OA than in the end-stage disease. The effect of intra-articular injections varied from ineffective to initially effective, with a duration of action of a single infiltration of up to 3 months; however, the effect would diminish after repeated injections. Participants had also undergone Platelet-Rich Plasma infiltrations and considered them painful and not very effective.

> That gel is then absorbed by the cartilage. But if the cartilage is gone? Well, yes, then it can't penetrate that space, can it? (Participant 2, 63y, NL)

> I tried knee supplementation, it worked, it worked, but over time it wasn't as effective anymore. (Participant 8, 60y, FR)

> .. and corticosteroids, I prefer to avoid them because I've heard a lot of negative things about them. That really puts you off. There's an exceptional improvement with the first injections, and then the improvement decreases over the injections, so it deteriorates—the improvement deteriorates over the injections. (Participant 11, 43y, FR)

Subtheme 2.4: Surgery

The possibility of a surgical intervention was a topic that participants had discussed with an orthopedist, and the wish to have undergone a surgical procedure at an earlier age was commonly mentioned. Five reasons were mentioned for not having undergone an operation: the perception that a TKA is a heavy operation, anxiety about the operation, diabetes as a risk factor for surgical wound healing, anxiety about persistent post-surgical pain, and advanced age. The decision did not rest solely with the patient; orthopaedists determined whether a participant was an

appropriate candidate by considering the individual's general health and degree of physical condition (such as low muscle mass), rather than basing the decision solely on the radiological grade of osteoarthritis. Participants also reported inconsistent surgical advice, which heavily influenced their decision to undergo a TKA. One of the participants underwent an unicondylar knee arthroplasty during the study and was very content with their decision.

> But when they explained to me how a total prosthesis works, there were people who were satisfied and others who weren't. That was terrible for me. Yeah, I wasn't laughing about that, as they say. (Participant 10, 65y, FR)

> It's unfortunate that when something is worn out, you can't do anything about that, can you? Or put in prostheses, right? What is that? Prostheses for everything. Yes. A robot man. (Participant 4, 66y, NL)

> The best treatment I've had done is that operation now. I'll say it again, from the first day I came back to my room, I didn't have any pain anymore. (Participant 5, 75y, NL)

Theme 3. Experience of the COGENIUS study

Subtheme 3.1: Study organisation and run-in phase

Participants reported high overall satisfaction with the study, independent of treatment outcomes. Study personnel were described as friendly, supportive, and thorough in their explanations, and the study's organisation—particularly short waiting times—was viewed positively. Participants, however, expressed some scepticism and difficulty when reporting the NRS pain score, noting individual differences in pain interpretation and daily fluctuations influenced by activity, sleep, and emotional state. Certain questionnaire items were also identified as repetitive or irrelevant - such as functionality questions that did not apply to the participant's situation - and had trouble with not knowing the randomisation group. Participants suggested conducting walking tests in a straight line to avoid turns, which can increase the measured time, provoke pain, and discomfort.

Participants were frequently unaware of the study's run-in phase and perceived it as offering little added value, given their extensive prior conservative treatments. This phase was recalled primarily as a waiting period before receiving the study intervention—either following a recent intra-articular injection, while trying a new medication, or as time to reflect on whether they wished to proceed with the intervention. Differences in the type of exercises for knee OA received during physiotherapy went unnoticed.

> So I was eligible for that study. I said that I had already had an injection before, but it had to be at least three months without an injection in my knee before I could even take part. (Participant 3, 63y, NL)

> I actually found it nice that I could talk about it with my family in the meantime. (Participant 4, 66y, NL)

Subtheme 3.2: Experienced effect of the study intervention

Participants reported improvement in pain, functionality, sleep, emotional well-being, and social participation. The reduction in pain was meaningful, even though it did not result in full recovery. The onset of improvement varied considerably from two days to several months after treatment. In some cases, the perceived improvement was not clearly attributable to the study intervention itself but may have been influenced by concurrent physiotherapy, additional injections, or surgery. Participants highlighted a synergistic effect between the study intervention and weight loss. One participant who knew they had received the placebo intervention and yet experienced notable improvement emphasised the role of mindset in influencing treatment outcomes.

> But before, sometimes I had to get up in the middle of the night to take a painkiller. I don't have to do that anymore. It's very, very exceptional now if I take something [painkiller]. I can cycle. I go walking. (Participant 2, 63y, NL)

> After the treatment, I also went to the physiotherapist. Yes, and then I could feel that things were getting a bit better. Yes, those exercises became a bit easier. (Participant 4, 66y, NL)

Subtheme 3.3: Experienced burden of the study intervention

When asked about the burden of the intervention during and after the procedure, participants reported a wide range of experiences. The intervention was described as causing no or only minimal discomfort, but also as very painful. The intervention was also perceived as requiring additional logistical planning due to the use of periprocedural sedation, when, for example, compared to an IA injection, which is performed during a consultation. Notably, even among those who found the procedure painful, all indicated they would be willing to undergo it again if there were a possibility of improvement, despite the actual effect they experienced from the intervention. Participants shared the perception that sedation, individually titrated, can diminish periprocedural pain.

> Yeah, there was a preparation like you would prepare an operating room. They prepared me as if they were going to do something to me, and they pressed the laser against my leg. (Participant 8, 60y, FR)

> The only thing that you feel is when they give those little injections beforehand to numb it. But that's minimal, right? (Participant 3, 63y, NL)

> The more the seconds passed, the more I was in agony. It was really, honestly horrible. And then the anaesthesiologist said, 'Can't we put me a little bit under gas anyway?' Can't we add'—I don't remember what anymore. And when they did the external part [of the knee], then it was much better, it was—well, I didn't have that much pain anymore. … I suppose they added an anaesthetic. (Participant 7, 52y, FR)

Subtheme 3.4: Participants' perceptions of the RF treatment

Participants on multiple occasions perceived that the RF treatment is not a well-known treatment for knee osteoarthritis and felt that the option of undergoing the treatment and participating in the study was not offered by their treating physician. Input from treating physicians and family members was also identified as an important factor in participants' decision-making regarding whether to undergo the intervention.

Participants shared the perception that the intervention was invasive due to logistic factors, such as day-hospitalisation, preparations before intervention, and peri-procedural sedation, finally comparing it to a surgical intervention. The RF treatment was believed to work symptomatically, possibly reducing their disease burden without being disease-modifying. One participant explained that, for her, the RF treatment was a good alternative to surgical intervention. Participants raised significant concerns about possible adverse events and possible joint degradation when the RF treatment is repeated. They also reflected on the reasons for the diminishing effect after several months, such as nerve regeneration.

> Yes, of course it would be easier if a general practitioner or an orthopaedic surgeon said, 'Why don't you go and do that and try it [RF] instead of getting another injection again! (Participant 4, 66y, NL)

> But my question is: how is it that for those two months you're practically, practically pain-free, and then it comes back? I then imagined, for example, when you go to the dentist—well, those are nerves too, right?—that they sometimes burn. But when I go to the dentist and they burn my nerve, that pain doesn't come back. So how come in my knee it came back? (Participant 5, 75y, NL)

> Well, I think four, five years at least, that it will work [RF], I hope. Four, five years—yes, up to seven, eight years. Yes, then it should, right? Because I thought, well, eventually it's been burned. Or well, if you're allowed to say it like that. Yes, that nerve will probably sooner or later come back to life. (Participant 3, 63y, NL)

Theme 4: Participants' preferences on RF treatment

Subtheme 4.1: Optimal timing of the RF treatment

When asked about the optimal timing of RF treatment within their care pathway, participants expressed a range of opinions. These varied between the following: the RF should be offered earlier, though the exact timing varied; the RF was best performed after intra-articular injections or instead of intra-articular hyaluronic acid in more advanced OA; the timing was appropriate; and RF should be proposed before total knee arthroplasty (TKA). Despite the previous answer, they reported feeling that they had waited a long time before being informed about RF or the opportunity to participate in the study.

> I think after a year or two [of knee pain]. I wouldn't wait that long anymore, honestly. I wouldn't wait that long. I would have it done earlier and see what the result is. (Participant 5, 75y, NL)

> I would have been very happy if that had been years earlier. So before I had pain for such a long time. Because I really had pain for a very long time." (Participant 4, 66y, NL)

> Right, I would have done it, because those interventions [RF] are good alternatives to putting in a prosthesis. (Participant 10, 65y, FR)

Subtheme 4.2: Definition of treatment success

Participants defined a successful treatment as diminished pain, improved functionality, and recurrently as less pain during movement (such as standing up from a chair, cooking, walking, jogging, and gardening). Upon inquiry about the degree of relief, participants recognized 50% and 70% improvement as a very good result. When prompted on the duration of relief, perspectives were mixed, ranging from any duration of relief to a one-year effect to be considered important. One participant reported a 2-month effect as not important.

> Yes, I just want to be properly mobile again. To be able to go jogging, go walking. (Participant 2, 63y, NL)

> Let's say about 70% [improvement]. But still, I can live with that. (Participant 5, 75y, NL)

> Preferably forever, right? … But yes, if I had to have it done every year or so, then I would do it. Yes, yes, if that meant that I could—well—have less pain. (Participant 5, 75y, NL)

Subtheme 4.3: Willingness to undergo a repeat RF treatment

Nearly all participants were willing to undergo a repeat of the RF treatment in the future if they experienced increased burden of knee OA or if the intervention could offer additional pain relief (e.g., if additional nerves were to be targeted). One participant was indecisive about a reintervention due to the possibility of adverse events and uncertainty about the possible additional effect. Participants mentioned repeatedly that they were willing to undergo the treatment every few months, yearly, or every two years. This inquiry also triggered some questions on possible adverse events and possible joint degradation after repeated treatment.

> I'm ready to do it again in two years because it gives me quality of life. (Participant 10, 65y, FR)

> I really hope it's once every… once a year. Well, not too often anyway. Yes, yes, I know, now it's ten months [of improvement], that's not what's going to change the world, right. But still, yes, it would be worth it [every 10 months]. (Participant 12, 84, FR)

> But well, if after several months we see that it [pain] comes back and we talk about it again, then after all, why not. Yeah, I think I would do it, but if I had to do it every year, then I think I would start asking myself questions. Clearly, I would be thinking: it's true that there is effectiveness, so that tells you that there is something in my body that's doing that. So, yeah… I would ask myself questions because it's a resistance at the level of the body, meaning there's probably something going on. And maybe it deteriorates more than it improves. (Participant 11, 43y, FR)

Subtheme 4.4: Willingness to undergo treatment of more than 3 genicular nerves

Participants were predominantly open to treating more than 3 genicular nerves, believing that any additional periprocedural burden (such as longer treatment time or increased discomfort) could be compensated for by the potential for greater effectiveness. Participants felt that there should be a limitation on the number of

needles used without specifying this number. Those who opposed targeting more nerves felt that it would increase the risk of adverse events and doubted any added benefit, particularly in cases where treatment of three nerves had not produced improvement.

> If I knew that it would help? Absolutely. I would try anything to have a bit less pain. (Participant 1, 73y, NL)

> If there are no negative side effects, why not? … The pain mustn't be multiplied by—by three. Well yes, why not, if it brings something extra. If at the beginning I have to suffer a bit more, well then, that's the price to pay. But if the result is even better, why not? (Participant 10, 65y, FR)

> Yes, but it's like everything—at some point, there's always a limit. The advantages will no longer be compensated by the disadvantages. The disadvantages become far too bothersome or far too present to justify the benefit alone. (Participant 11, 43y, FR)

> No, it really becomes microsurgery. It only takes one needle that isn't placed properly. (Participant 8, 60y, FR)

No significant variation in answers to the topics related to participant characteristics was seen.

Table 1. Participant characteristics and study-related outcomes.

Participant number	Age (years)	Sex (Male/ Female)	Employment status (Working/ Retired)	Knee Pain Compared to Baseline (Better/ Same/Worse)	Relation Between Improvement and Study Intervention (Yes/No/Unclear)
1	73	Female	Retired	Worse	No
2	63	Female	Retired	Better	Yes[a]
3	63	Male	Retired	Better	Yes
4	66	Female	Retired	Better	unclear
5	75	Male	Retired	Better	No
6	72	Male	Retired	Better	Yes
7	52	Female	Working	Same	No
8	60	Male	Retired	Better	Yes
9	74	Male	Working	Better	Yes
10	65	Female	Retired	Better	Yes
11	43	Male	Working	Better	Yes
12	84	Male	Retired	Same	No

Legend:

[a] Sham procedure.

The relation between improvement and study intervention reflected whether the participant felt the improvement was a direct consequence of the study intervention.

Discussion

This qualitative study provides insight into how individuals with knee OA in Belgium experience and navigate treatment strategies, with particular attention to RF treatment of the genicular nerves administered during the COGENIUS trial. Part of the findings can be interpreted within the FAME framework (Feasibility, Appropriateness, Meaningfulness, and Effectiveness).[19] The main finding is that participants perceived RF treatment as both meaningful and appropriate. In terms of meaningfulness, participants expressed confidence that RF could diminish the burden of knee OA, at least for a subgroup of patients. Outcomes currently used in clinical research, pain, function, and quality of life, were considered relevant, with functionality repeatedly emphasised as a central treatment goal. Regarding appropriateness, participants felt that RF aligns well with their priorities within the context of the COGENIUS trial. They indicated that patients with chronic knee pain who do not improve with standard conservative treatments should be considered eligible for RF. The treatment context, a day hospitalisation procedure performed by a pain specialist under periprocedural sedation, was also viewed as acceptable. Participants also addressed aspects of feasibility, emphasising that the overall burden of the RF treatment is acceptable under periprocedural sedation. To minimise discomfort, systematic use of sedation, individually titrated, should be considered.

If the COGENIUS trial demonstrates positive effectiveness and supports broader implementation of RF in Belgium, several challenges may arise. These include limited awareness of RF treatment among patients, their families, and clinicians, as well as the fact that many individuals with chronic knee pain do not routinely consult pain specialists. Additionally, RF may be perceived as more invasive than other minimally invasive treatments, such as intra-articular injections, because it typically requires a day-hospital admission rather than standard consultation-based procedures. Together, these findings highlight the need for improved patient education and stronger interprofessional collaboration.

Another key finding of this trial was the confirmation of the substantial burden of living with knee OA. Participants described significant pain, functional limitations, sleep disturbances, reduced work capacity, and emotional strain. These accounts are consistent with findings reported in other OA populations and highlight the need to optimise care for this growing patient group.[2,20]

This trial demonstrates that individuals with knee OA in Belgium undergo long and highly variable treatment trajectories, typically managed by general practitioners, physiotherapists, and orthopaedic surgeons. Based on this study,

future initiatives should focus on expanding standardisation of these treatment trajectories, with emphasis on active patient education regarding exercise and exercise adherence, with special attention to the minimal risks of contributing to disease progression, referral to a dietician or psychologist when necessary, and education about treatment options in the multidisciplinary pain clinic, such as RF of the genicular nerves. All treatment trajectories should incorporate a biopsychosocial approach.[21,22] Variation was also evident in the use of intra-articular injections, with participants reporting anywhere from three injections to more than twenty, with inconsistent benefit. Participants generally agreed that infiltrations were effective in the early to mid-stages of the disease and that their effect diminished. This suggests that continuing with repeated injections at that stage may be unwarranted, opening a potential window in which RF treatment of the genicular nerves could be more appropriate.

An important strength of this study is the exploration of participant preferences for future RF-related research. Participants expressed varied views on the optimal timing of RF within the treatment pathway, but agreed that therapy-resistant patients should be referred to a pain clinic to evaluate suitability for RF. A 50% improvement in pain, function, or pain during activity was considered a meaningful treatment outcome, sustained over several months to a year. Of note, although previous surveys report that nearly nine out of ten patients with osteoarthritis identify pain as the main impact of the disease, participants in our interviews repeatedly highlighted functionality as a major concern.[3] This indicates that future RF research should include both pain outcomes and functional measures, such as in combined pain and functionality patient-reported scores, as important endpoints. Participants generally supported repeat RF treatment if initial benefit was observed and were open to targeting multiple genicular nerves when procedural risks were minimal.

Strengths and limitations

As this is the first study to report patient perceptions of RF treatment for knee OA, we undertook multiple measures to increase the transferability of findings, including purposive sampling, investigator triangulation, and inductive analysis. Many identified themes converge with prior qualitative research on other knee OA interventions—such as the heavy disease burden, variable care trajectories, and desire for clearer treatment guidance—supporting the credibility of our findings.

Limitations of this trial include potential recall bias, as participants had long-standing symptoms and had exhausted conservative options, as required by the COGENIUS inclusion criteria. The sample, while heterogeneous, included slightly more men than

women and more non-working participants. Another limitation is that interviews were conducted by a physician and a medical student, whose differing levels of clinical experience may have influenced participants' responses.

Implications and future directions

Further research should explore whether these thematic patterns hold in other cultural contexts, healthcare systems, and in additional clinical groups, such as individuals with persistent postsurgical pain, which is another indication for RF of the genicular nerves.

Conclusions

This qualitative study highlights the substantial burden experienced by individuals with knee OA and the variability of treatment trajectories in Belgium. Participants viewed RF treatment of the genicular nerves as an appropriate and meaningful component of care when knee pain is therapy-resistant, and periprocedural sedation is titrated according to need. The reported patient perspectives offer important direction for optimising RF delivery, improving patient education, and guiding future research to better align the intervention with patient needs and preferences. Future studies should incorporate larger sample sizes, strive for data saturation, integrate clinicians' perspectives, and include qualitative investigations into patients' experiences with genicular nerve RF treatment for patients suffering from persistent postsurgical knee pain.

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Appendix
INTERVIEW LEIDRAAD (NL)

Dit interviewprotocol is geschreven als richtlijn. De interviewers worden aangemoedigd om verdere vragen te stellen op basis van de antwoorden van de deelnemers om een vollediger inzicht in de onderzoeksonderwerpen te krijgen.

Introductie: Ik ben ..... , onderzoeker aan het Ziekenhuis Oost-Limburg. Dit interview vindt plaats in het kader van de COGENIUS-studie. De bedoeling van het onderzoek is om, aan de hand van interviews met chronische kniepijnpatiënten, een duidelijk beeld te krijgen van hoe zij de behandelingsmogelijkheden voor kniepijn ervaren. Er is immers relatief weinig wetenschappelijke informatie daarover beschikbaar in België. Verder zouden wij graag nagaan hoe u uw deelname aan de COGENIUS-studie hebt ervaren. Het interview zal ongeveer één uur duren. De vragen die ik u ga stellen hebben geen juiste of foute antwoorden. Het is de bedoeling dat u de vragen zo uitgebreid mogelijk beantwoordt. Alles wat u denkt of voelt en wat volgens u met de vraag te maken heeft, mag u aanhalen.

Alle informatie uit dit interview zal strikt vertrouwelijk worden behandeld en uw anonimiteit is zeker gewaarborgd. Alle interviews worden samen verwerkt en enkel het eindrapport is publiek toegankelijk. Ik ga het gesprek wel opnemen, maar dit dient enkel en alleen om de latere verwerking van het interview te vergemakkelijken.

Heb u hierover nog vragen of bedenkingen?

Voordat we met het gesprek beginnen, zou ik u eerst een paar korte vragen willen bespreken. Het gaat om enkele algemene gegevens die belangrijk zijn bij de verwerking van de resultaten en het mogelijk maken om algemene conclusies te trekken uit de interviews.

Topic 1:
Subtopic 1: Ervaring met de verschillende mogelijke behandelingen voor de start van de studie

- Ten eerste, kunt u me vertellen hoe het gaat met uw knie nu? (probes: ernst van pijn, niveau van activiteit, welke activiteiten worden gewaardeerd, impact op anderen)
- Als u terugdenkt in de tijd, kunt u mij dan vertellen over uw ervaring met de verschillende behandelingen van artrose in uw knie vóór uw deelname aan de studie? (probes: kinesitherapie, gewichtsreductie, zelf-management, medicatie in pilvorm, injecties in de knie, braces, operaties aan de knie)

Subtopic 2: Ervaring met de COGENIUS-trial

- U was uitgenodigd om deel te nemen aan de COGENIUS-studie en dus om naar het pijncentrum te komen ter behandeling van uw kniepijn. Hoe hebt u tot nu toe de studie ervaren?
- Hoe vond u het om deel te nemen aan de studie? Denk aan de afspraken, vragenlijsten en wachttijden? (probes: afspraken, vragenlijsten, wachttijden)
- De studie start met een inloopperiode van maximaal 3 maanden waarin de standaardbehandelingen van uw kniepijn werden geoptimaliseerd. Wat vond u daarvan? (probes: verschil met standaardbehandeling buiten de studie)
- Tijdens de studie hebt u een van de drie behandelingen voor de knie ondergaan (de conventionele radiofrequente behandeling, de gekoelde radiofrequente behandeling of de schijnbehandeling). Hoe hebt u deze behandeling ervaren? (probes: pijn/ongemak tijdens en na de interventie, behoefte aan sedatie)
- Hebt u feedback voor de organisatie van deze studie?

Topic 2: De voorkeuren van de patienten omtrent de radiofrequente behandeling en toekomstig onderzoek

- Wij zouden graag de radiofrequente behandeling willen verbeteren op basis van uw voorkeuren. Wij zouden graag de behandeling optimaliseren zodra uw ervaring tijdens de procedure en de effectiviteit daarvan verbeterd kunnen worden.
- Momenteel wordt de behandeling aangeboden aan personen met gevorderde artrose en die ernstige pijn blijven ervaren ondanks de standaardbehandelingen. Op welk moment in uw behandelingstraject denkt u het meest baat te hebben bij deze procedure?
- Wij weten dat verschillende mensen heel andere doeleinden hebben als ze een procedure nagaan, i.e., minder pijn ervaren, maar ook kunnen wandelen en beter slapen. Wat is voor u persoonlijk een geslaagde radiofrequente behandeling? (probes: tijd, activiteiten, pijn)
- Stel u voor dat de studiebehandeling succesvol is voor u. Zou u dezelfde procedure opnieuw ondergaan? Hoe vaak? (probes: RF voor een tweede of derde keer)
- Op dit moment zijn er andere onderzoekers bezig met het onderzoeken van radiofrequente behandeling van meer dan 3 zenuwen rond de knie. Dit wordt gedaan om het effect van de behandeling te vergroten. Er zouden dan tot 7 naalden meer kunnen worden geplaatst tijdens de behandeling. Wat denkt u daarover?

Conclusie:

Voordat we ons gesprek beëindigen, zou ik willen vragen of er bepaalde zaken volgens u niet aan bod zijn gekomen. Is er nog iets dat u wilt vertellen over uw ervaringen?

Dan wil ik u van harte bedanken voor uw medewerking aan dit onderzoek. U zult een e-mail krijgen van ons om de transcriptie van het interview nog eens na te lezen en u heeft dan ook de mogelijkheid om antwoorden aan te passen of aanvullende informatie te geven. Als u graag op de hoogte wilt worden gehouden van de resultaten, wil ik u zeker een exemplaar van ons rapport bezorgen. Ik wens u het allerbeste.

GUIDE D'INTERVIEW (FR)

Ce protocole d'interview est rédigé comme une directive. Les intervieweurs sont encouragés à poser d'autres questions basées sur les réponses des participants afin d'obtenir une compréhension plus complète des sujets de recherche.

Introduction : Je suis ....., chercheur à CHU de Liège. Cette interview se déroule dans le cadre de l'étude COGENIUS. L'objectif de la recherche est d'obtenir, à travers des interviews avec des patients souffrant de douleurs chroniques au genou, une image claire de la façon dont ils perçoivent les options de traitement pour la douleur au genou. En effet, il y a relativement peu d'informations scientifiques à ce sujet disponibles en Belgique. De plus, nous aimerions savoir comment vous avez vécu votre participation à l'étude COGENIUS. L'interview durera environ une heure. Les questions que je vais vous poser n'ont pas de bonnes ou de mauvaises réponses. Il est prévu que vous répondiez aux questions de manière aussi détaillée que possible. Tout ce que vous pensez ou ressentez et qui, selon vous, est lié à la question, peut être mentionné.

Toutes les informations de cette interview seront traitées de manière strictement confidentielle et votre anonymat est garanti. Toutes les interviews seront traitées collectivement et seul le rapport final sera accessible au public. Je vais enregistrer la conversation, mais cela sert uniquement à faciliter le traitement ultérieur de l'interview.

Avez-vous des questions ou des préoccupations à ce sujet ?

Avant de commencer notre conversation, je voudrais d'abord vous demander de répondre à quelques questions. Il s'agit de quelques données générales, qui sont importantes pour le traitement des résultats et qui permettent de tirer des conclusions générales des interviews.

Sujet 1:

Sous-sujet 1: Expérience avec les différents traitements possibles avant le début de l'étude

- Tout d'abord, pouvez-vous me dire comment va votre genou maintenant ? (indices: gravité de la douleur, niveau d'activité, quelles activités sont appréciées, impact sur les autres)

- En repensant au passé, pouvez-vous me parler de votre expérience avec les différents traitements de l'arthrose de votre genou avant votre participation à l'étude ? (indices: kinésithérapie, réduction de poids, autogestion, médicaments sous forme de pilule, injections dans le genou, attelles, interventions chirurgicales au genou)

Sous-sujet 2: Expérience avec l'étude COGENIUS
- Vous avez été invité à participer à l'étude COGENIUS et donc à vous rendre au centre de douleur pour traiter votre douleur au genou. Comment avez-vous vécu l'étude jusqu'à présent ?
- Comment avez-vous trouvé votre participation à l'étude ? Pensez aux rendez-vous, aux questionnaires et au temps d'attente. (indices: rendez-vous, questionnaires, temps d'attente)
- L'étude commence par une période d'introduction de 3 mois maximum pendant laquelle les traitements standard de votre douleur au genou ont été optimisés. Qu'en avez-vous pensé ? (indices: différence avec le traitement standard en dehors de l'étude)
- Au cours de l'étude, vous avez reçu l'un des trois traitements pour le genou (le traitement conventionnel par radiofréquence, le traitement par radiofréquence refroidie ou le traitement simulé). Comment avez-vous vécu ce traitement ? (indices: douleur/inconfort pendant et après l'intervention, besoin de sédation)
- Avez-vous des retours pour l'organisation de cette étude?

Sujet 2: Les préférences des patients concernant le traitement par radiofréquence et les recherches futures
- Nous aimerions améliorer le traitement par radiofréquence sur la base de vos préférences. Sur la base de votre expérience, nous aimerions optimiser la procédure et améliorer l'efficacité du traitement.
- Actuellement, le traitement est proposé aux personnes souffrant d'arthrose avancée et qui éprouvent des douleurs sévères malgré les traitements standards. À quel moment de votre parcours de traitement pensez-vous bénéficier le plus de cette procédure ?
- Nous savons que différentes personnes ont des objectifs très différents lorsqu'elles envisagent une procédure, à savoir ressentir moins de douleur, mais aussi pouvoir marcher, mieux dormir. Qu'est-ce qui constitue pour vous un traitement par radiofréquence réussi ? (indices: temps, activités, douleur)
- Imaginez que le traitement de l'étude soit réussi pour vous. Seriez-vous prêt à subir la même procédure à nouveau? Combien de fois ? (indices: RF pour une deuxième ou troisième fois)

- Actuellement, d'autres chercheurs étudient le traitement par radiofréquence de plus de 3 nerfs autour du genou. Ceci est fait pour augmenter l'effet du traitement. Jusqu'à 7 aiguilles supplémentaires pourraient donc être placées pendant le traitement. Que pensez-vous de cela ?

Conclusion:
Avant de terminer notre conversation, je voudrais vous demander s'il y a certains points que vous pensez n'avoir pas abordés ? Y a-t-il quelque chose que vous aimeriez partager sur vos expériences?

Je tiens à vous remercier chaleureusement pour votre participation à cette recherche. Vous recevrez un e-mail de notre part pour relire la transcription de l'interview, et vous aurez également la possibilité d'ajuster vos réponses ou de fournir des informations supplémentaires. Si vous souhaitez être informé des résultats, je serai ravi de vous envoyer une copie de notre rapport. Je vous souhaite le meilleur.



Chapter 8

General discussion and conclusion



Introduction

In this General discussion, the research questions are addressed by integrating the results of each study and critically reflecting on the methodological choices opted for. Each question and respective answer addresses one or more of the Joanna Briggs Institute (JBI) FAME approach elements (Feasibility, Appropriateness, Meaningfulness, and Effectiveness).

Question 1, along with the respective RECORGEN and COCOGEN studies, and the protocol for a systematic review, aim to address the Effectiveness and Feasibility domain of the JBI FAME framework. The RECORGEN study was a single-centre retrospective cohort study evaluating the effectiveness and safety of conventional genicular nerve radiofrequency (RF) treatment in 59 patients with osteoarthritis (OA) and persistent post-surgical pain (PPSP) (2020). The COCOGEN trial was a multicentre, double-blind, non-inferiority pilot randomised controlled trial (RCT) (n=48; 2020–2021) comparing cooled and conventional RF in patients with chronic OA pain and PPSP. This pilot informed the ongoing COGENIUS trial (initiated in 2022), a double-blind, prospective superiority RCT across 17 centres in Belgium and the Netherlands, assessing the effectiveness and cost-effectiveness of cooled versus conventional RF versus sham in 200 OA and 200 PPSP patients. The Cochrane systematic review protocol aims to assess the benefits and harms of RF in chronic OA knee pain when compared to sham, usual care, and intra-articular glucocorticoid injections.

Question 2, which focuses on adverse events of the RF, is also part of the Effectiveness topic of the framework. The data on the adverse events of the RF treatment in the RECORGEN and COCOGEN trials, together with a case report article of a patient who developed Complex Regional Pain syndrome (CRPS) described in Chapter 5, will be used to examine safety concerns associated with the RF treatment.

Question 3 elaborates on the perioperative use of genicular nerve block (GNB) in the GENIFEM trial, evaluating questions on the effectiveness of this procedure in the setting of acute pain. The GENIFEM study was a single-centre, double-blind pilot RCT conducted at Hospital Oost-Limburg (Feb 2022–Jun 2023). It compared analgesia and ambulation in 34 patients undergoing total knee arthroplasty (TKA) receiving three regional anaesthetic approaches, including the GNB, for 1 postoperative month.

Question 4 includes a qualitative trial that addresses the Feasibility domain of the JBI FAME framework, specifically the implementation of RF (patient education, willingness of participants to undergo the same procedure, periprocedural burden),

Appropriateness, and Meaningfulness of the RF in participants of the COGENIUS trial diagnosed with OA. This qualitative study, embedded in the COGENIUS, documents the experiences and perceptions of 12 Belgian knee OA patients.

The last section of the discussion critically examines the **methodological strengths and limitations of the included studies.** In the upcoming chapter, the findings of this thesis are then interpreted from the perspectives of researchers, clinicians, and health policymakers, emphasising their practical relevance and implications. This valorisation is interwoven with directions for future research and potential initiatives emerging from the results.

Research questions

Q1. What is the clinical effectiveness and cost-effectiveness of radiofrequency treatment for chronic knee pain, and how do different radiofrequency modalities compare in terms of effectiveness and cost-effectiveness?

The value of genicular nerve RF depends on its clinical effectiveness, durability of effect, safety, and repeatability. However, its integration into clinical guidelines also requires evidence of comparative effectiveness and cost-effectiveness relative to existing treatment options. Key areas of uncertainty on the RF of the genicular nerves remain long-term durability of effect, long-term safety, its cost-effectiveness, and comparative effectiveness. This section therefore addresses: (1) clinical effectiveness, and (2) comparative and cost-effectiveness of RF in relation to alternative interventions on chronic knee pain.

The effectiveness of the RF of the genicular nerves

Across published trials, genicular nerve RF has demonstrated **statistically and clinically meaningful pain reduction** for up to 12 months, with some studies reporting benefits lasting up to two years in patients with chronic knee pain.[1-4] The RECORGEN and COCOGEN studies confirm the meaningful analgesic improvement in both OA and PPSP, on average, up to 8 months. However, the observed effect sizes were at the lower end of the range reported in the literature. The observed pain reduction was not accompanied by improvements in functional or patient-reported outcomes.[5] Possible explanations for these results include small patient samples, inclusion of a large PPSP population compared to OA, the choice of a three-nerve protocol, and the decision not to include a diagnostic block.

When **RF of the genicular nerves is compared to a sham procedure** in six sham-controlled trials and three systematic reviews, RF results in moderate short- to mid-term pain reduction with low certainty of this evidence.[6-8] Combined with the effect sizes of around 30% reported in the RECORGEN and COCOGEN studies, these results highlight the pressing need for a large-scale, adequately powered sham-controlled trial of genicular nerve RF.

While the RF treatment outcomes are known to be influenced by both patient-related and technical factors, clinically, three major factors can be identified: the aetiology of pain, with specifically PPSP as a predictor of decreased RF effectiveness; RF lesion size/modality, with theoretically a larger lesion created by cooled RF/bipolar RF/trident needle as a predictor of increased effectiveness; and the number of targeted nerves, with more nerves possibly resulting in higher effectiveness. All these three areas

have recently been extensively debated. The COCOGEN pilot trial, comparing cooled and conventional RF using a three-nerve protocol, found no statistically significant differences between the RF modalities. Subgroup analyses suggested that PPSP may not necessarily predict reduced responsiveness when larger-lesion techniques are used. These findings differ from indirect comparisons of the effect size after cooled RF and conventional RF in other published trials, and from the trial by Nayak et al., a head-to-head comparison of cooled and conventional RF, which indicates a larger effect size of cooled RF.[9] While the COCOGEN and the trial from Nayak et al. are small trials, the larger and powered COGENIUS trial will further strongly inform on the possible superiority of cooled RF when using a three-nerve protocol.

In the **long-term follow-up of more than 2 years,** observational data from a large U.S. national database study suggest that genicular nerve interventions may reduce subsequent knee arthroplasty rates. This analyse however, includes mixed genicular nerve interventions and cannot therefore be attributed only to RF.[3] Repeat RF procedures also appear feasible and safe in patients who initially respond but later experience recurrence of pain.[10]

Summing up, the available evidence provides low to moderate evidence for the use of RF in chronic knee pain due to OA, whereas evidence remains limited for PPSP. Larger lesions and targeting multiple genicular nerves may improve outcomes, although head-to-head comparisons between RF protocols remain scarce, and results are inconclusive.

Comparative effectiveness and cost-effectiveness of RF in chronic knee pain care
Comparative effectiveness of RF to other minimally invasive treatments for chronic knee pain, based on systematic reviews and meta-analyses, suggests that genicular nerve RF may provide superior pain relief and functional improvement compared to oral nonsteroidal anti-inflammatory drugs, intra-articular injections, and chemical neurolysis, across follow-up intervals of three to twelve months.[2,4,11-13] However, much of this evidence is derived from Bayesian network meta-analyses rather than direct head-to-head trials. The limited number of direct comparisons generally supports these findings but remains sparse. This lack of direct evidence also applies to comparisons between minimally invasive treatments and knee arthroplasty. [14]

The aforementioned systematic reviews differ methodologically from the Cochrane systematic review protocol presented in Chapter 4 of this thesis. The current protocol adopts a rigorous methodological framework and focuses specifically on comparisons between RF treatment and placebo, conservative management, or intra-articular

corticosteroids. Furthermore, all image-guidance techniques are included, with predefined subgroup analyses based on OA severity, use of a prognostic block, and RF modality, which represent key areas of ongoing debate regarding RF treatment. This approach is expected to provide a comprehensive and robust synthesis of the available evidence and may support the translation of RF research into clinical practice.

When the evidence on the **cost-effectiveness of RF treatment of the genicular nerves** is evaluated, it becomes clear that robust economic data are essential for the integration of RF treatment into national chronic knee pain care pathways and for informing health economic decision-making. This is particularly relevant for higher-cost techniques such as cooled RF, which must demonstrate clear clinical or economic advantages over less expensive alternatives, including conventional RF or chemical neurolysis. Overall, the current cost-effectiveness evidence remains limited to three trials that directly compare interventions on chronic knee pain.

Two head-to-head cost-effectiveness studies comparing cooled RF with intra-articular hyaluronic acid or corticosteroid injections have strongly favoured cooled RF in patients with knee OA.[15,16] In contrast, the cost-effectiveness analysis of the COCOGEN trial indicated that cooled RF is highly likely to be cost-effective in patients with PPSP, whereas in patients with OA, cooled RF had a very low probability of being cost-effective compared with conventional RF at commonly applied willingness-to-pay thresholds. In another interesting network meta-analysis comparing genicular nerve RF, genicular artery embolisation, and intra-articular corticosteroids, results suggested that genicular artery embolisation may be the intervention most likely to be cost-effective, although the limited number of comparative studies warrants cautious interpretation.[17]

From a clinical perspective, RF may nonetheless be economically favourable compared with repeated intra-articular injections. Although RF involves higher upfront procedural costs, the longer duration of analgesic benefit may reduce the need for repeated treatments, potentially lowering cumulative healthcare costs over a 12-month horizon. Importantly, when considering the potential of the RF procedure to delay knee arthroplasty, the main cost-driver in OA, genicular nerve ablation could provide an option with lower cost to manage chronic pain due to OA.

In conclusion, despite heterogeneity in RF techniques and treatment protocols, the available evidence suggests that genicular nerve RF represents a valuable treatment option for chronic knee pain due to OA and, to a lesser extent, PPSP.

Further research is required to strengthen the comparative evidence base, optimise RF techniques, and clarify RF's position within treatment pathways relative to other minimally invasive interventions. The ongoing COGENIUS trial, which evaluates RF in the setting of optimised conservative care in OA and PPSP, will provide powered evidence on the additive value of RF compared with a true sham treatment and on the role of cooled RF when targeting three genicular nerves.[18]

Q2. What is the safety profile of radiofrequency treatment for chronic knee pain?
Based on evidence from systematic reviews and clinical trials with large cohorts, RF ablation of the genicular nerves is a safe, minimally invasive procedure with mostly mild and transient adverse events (AEs).[7,19-21] Most of the available evidence arises from articles on fluoroscopy-guided conventional RF of three genicular nerves (SMGN, IMGN, and SLGN) in patients suffering from knee OA.

The reported cumulative incidence of all AEs after RF of the genicular nerves ranges from 0 to 38%; however, precise estimates for overall and individual AEs remain unavailable. The most reported short-term AEs after RF, in order of prevalence, include peri-and postoperative pain (possibly related to transient neuritis), dysesthesia, and local bruising or hematoma, allergic reaction to local anaesthetics, and superficial skin burns.[22] When present, these AE resolve spontaneously within the mid-term follow-up period (3-12 months).[22] AEs reported in the RECORGEN and COCOGEN study align with the already published data. Evidence suggests that genicular nerve ablation has a more favourable safety profile than knee arthroplasty, which carries risks such as postoperative bleeding, thromboembolism, vascular injury, deep periprosthetic infection, medial collateral ligament injury, and anaesthesia-related complications.[23]

To date, data on long-term AEs are limited to a small number of trials with follow-up up to a year, and one up to two years.[24] Theoretical long-term risks include deafferentation dysesthesia and accelerated OA progression due to reduced pain perception and unrecognised joint overload.[25,26] Given that two years is a relatively short timeframe to assess OA progression – this is optimally evaluated around 5 years after intervention - no firm conclusions can be drawn regarding long-term safety. A recently published cohort of 6035 reported that interventions on genicular nerves, albeit not only RF interventions, delayed or deferred knee arthroplasty in knee OA, indicating that genicular nerve interventions are safe in the long term.[3] Limited knowledge about long-term AEs remains a key barrier to broader endorsement of this treatment in international guidelines, as noted for example, by the American College of Rheumatology in 2020.[27]

Serious AEs reported after RF ablation are rare and mostly stem from case reports. They include skin burns, knee hematoma, septic arthritis of the knee, and damage to ligaments, e.g., the pes anserine.[28-32] Another theoretical and not yet reported severe short-term AE of RF is motor nerve damage, especially when the recurrent fibular genicular nerve is targeted, and a higher chance of intra-articular needle placement with a possibility of resulting septic arthritis when targeting the ILGN. A retrospective trial on 30 RFs of the inferolateral quadrant of the knee (ILGN, recurrent fibular GN) reported similar safety to RF of the other knee quadrants.[33]

In this doctoral thesis, a case report of CRPS was included, describing the first incidence of this AE. The case report describes the clinical evolution of the flare of CRPS and treatment possibilities. Despite this case report, the history of CRPS is not a contraindication to RF treatment; however, patient information and precautions are imperative.

Several factors may influence the safety profile of genicular nerve RF, including patient selection, RF modality, image-guidance, and the number and type of genicular nerves targeted. In patients with PPSP, safety concerns mainly relate to infection, particularly deep periprosthetic infection. Prophylactic antibiotic administration approximately 30 minutes before the procedure may be considered to reduce this risk. In the COCOGEN trial, the number and severity of AE were similar in patients with PPSP and OA. Among RF modalities, pulsed RF is generally considered to carry the lowest risk due to its non-destructive mechanism. Despite the intrinsically larger lesion size produced by cooled RF, the incidence and severity of AEs after cooled RF appear comparable to those of conventional RF, both in the literature and in the COCOGEN trial. Ultrasound guidance may theoretically reduce complications by improving visualisation of needle trajectory, genicular vessels, and surrounding ligaments, thereby potentially limiting vascular injury, inadvertent intra-articular or intra-ligamentous placement, and radiation exposure. However, these potential advantages have not yet been confirmed in clinical trials and will likely require larger cohorts to be demonstrated.

The ongoing COGENIUS trial is expected to provide more robust data on short-, mid-, and long-term AEs, although follow-up is limited to two years. Future approaches involving a broader denervation strategy, such as targeting additional genicular branches, may increase complication risk due to a higher number of needle placements, a higher likelihood of intra-articular needle placement (e.g., when targeting the inferior lateral genicular nerve), and of an unintended motor block (e.g., the recurrence nerve), particularly when using cooled or bipolar RF techniques with larger lesion size. These considerations underscore the need for careful trial design and meticulous long-term follow-up, ideally including reassessment with long-term imaging.

In conclusion, current evidence supports a favourable short- and mid-term safety profile of genicular nerve RF; however, uncertainty remains regarding rare and long-term adverse events. Future trials with standardised adverse event reporting and longer follow-up are therefore essential, particularly as more extensive denervation strategies are being explored.

Q3. Does the genicular nerve block provide adequate perioperative analgesia in patients undergoing a total knee arthroplasty?

The pure sensory nature of the genicular nerves makes them particularly attractive targets beyond the chronic pain setting. As such, a genicular nerve intervention has three potential "windows" of intervention in a knee pain patient's pathway: the preoperative care (in the setting of chronic pain management and/or pre-emptive analgesia), perioperative care (as a regional anaesthetic technique), and postoperative care (in the treatment of PPSP).

In the acute perioperative setting, when combined with other motor-sparing regional anaesthetic techniques, GNB aligns well with the motor-sparing requirements of fast tract pathways.[34,35] In the pilot GENIFEM trial included in this thesis, three regional anaesthetic approaches were compared (the GNB & iPACK to FTB & iPACK and LIA) regarding pain during ambulation in the setting of TKA. The value of this trial lies in the fact that it is the first published comparison of these approaches, and in the fact that a combined primary outcome of analgesia during ambulation was used. Consequent to the pilot nature of the study, the effectiveness results were not statistically significantly different, and the results cautiously suggest a potentially modest analgesic effect of the GNB. Importantly, available perioperative trials, including the GENIFEM, report a favourable safety profile of the GNB, which also included a block of the ILGN, without apparent delays in rehabilitation or increased risk of falls.

A key unresolved question is whether genicular nerve interventions could reduce the risk of pain chronification after arthroplasty. PPSP is one of the most frequent long-term complications following knee arthroplasty, and its prevention is increasingly important as procedure volumes rise. While reducing acute nociceptive input could theoretically reduce short-term postoperative pain, attenuate central sensitisation and long-term pain chronification, current evidence does not support a clear preventive effect of regional blocks on PPSP, and early data on preoperative genicular RF performed in the weeks preceding TKA have been negative or inconclusive.[36-39] Therefore, at present, genicular nerve interventions should primarily be regarded as part of multimodal analgesia rather than a proven strategy to prevent acute and chronic postoperative pain.

In conclusion, the evaluation of GNB for acute perioperative pain during TKA is still in its initial stages. Current data suggest that use of a GNB in their perioperative phase is feasible and safe, but its analgesic value may be moderate, positioning the GNB as an additive block in a multimodal protocol. Future studies should provide stronger comparative evidence and address implementation of aspects within standardised care pathways, including timing, resource use, and identification of subgroups most likely to benefit.

Q4. How do patients with chronic knee pain experience the current treatment options, with particular attention to radiofrequency treatment?

Patient-centred care, rooted in mid-20th-century medical and psychological thought, emphasises the patient as an active partner whose lived experience, values, and goals are central to care. Its early operationalisation through patient-reported outcome measures reflected a shift toward recognising patient-important outcomes as legitimate indicators of treatment effect. Contemporary patient-centred frameworks extend this perspective by redefining effectiveness in terms of quality of life, functional outcomes, treatment burden, and goal-concordant care, while accounting for social, cultural, and structural contexts and promoting equity and shared decision-making. In research, these principles necessitate approaches that move beyond quantitative endpoints alone, supporting the use of qualitative and mixed-methods studies to capture contextual factors, patient meaning, and implementation challenges that directly inform real-world clinical practice.

In this thesis, we attempted to design the COGENIUS trial from a patient-centred framework. The COGENIUS trial, while still being clinician-initiated research, collaborated with three Belgian patient organisations (Vlaamse Reumaliga, VMCP and ReumaNet vzw) and six individual chronic knee pain patients for formulation of the research question, study design, study governance, participant inclusion and dissemination of results. The qualitative trial embedded in the COGENIUS and elaborated in chapter 7 documented OA disease experience, RF treatment burden and acceptability, and patient preference on RF for future decision making and research. This is, to our knowledge, the first trial evaluating patient perspectives on the RF treatment in OA.

The results of the qualitative trial evidenced that individuals with knee OA experience a substantial burden of disease, including pain, functional limitations, sleep disturbance, and reduced work capacity, while also describing long and variable treatment pathways often involving repeated injections with diminishing benefit. Participants viewed RF treatment of the genicular nerves as an appropriate and meaningful option

for patients with chronic knee pain who do not respond to conservative treatments. Functionality, alongside pain and quality of life, was considered a key treatment goal, and the procedural burden of RF—particularly with sedation—was seen as acceptable. Evaluation of patient preferences indicated that participants considered repeat RF treatment acceptable when initial benefit was observed and were generally open to targeting multiple genicular nerves if procedural risks were minimal.

In conclusion, the qualitative study included in this thesis represents an initial step in understanding patient perceptions of RF treatment of the genicular nerves. Future qualitative research should include diverse cultural and ethnic groups, explore the perceptions of the PPSP population, and incorporate perspectives of both patients and healthcare professionals. The findings also highlight the need for improved patient education, stronger multidisciplinary collaboration, and more standardised biopsychosocial care pathways, with RF potentially filling a treatment gap when other conservative options lose effectiveness. Finally, the results of this qualitative trial will additionally aid the interpretation of the quantitative outcomes of the COGENIUS trial, estimated to be published in Q1 2028.

Methodological strengths and limitations

General methodological approach

This thesis follows a **FAME-based framework** (Feasibility, Appropriateness, Meaningfulness, and Effectiveness) by evaluating RF of the genicular nerves through multiple complementary perspectives, including clinical effectiveness, safety, cost-effectiveness, feasibility, and patient relevance. The included studies were deliberately selected to address these different dimensions.

Methodological strengths

A major strength of this thesis is the methodological diversity of the included studies. Quantitative designs (retrospective cohort study, feasibility randomised controlled trials, and a health-economic analysis) are complemented by qualitative research using patient interviews. This multi-perspective approach integrates clinical, economic, perioperative, and patient-centred evidence.

Another strength is the specific inclusion of patients with PPSP, a population for which considerably less evidence exists compared with knee OA.

Across the included studies, several methodological aspects were consistent, improving comparability. OA and PPSP populations were analysed separately, which is important given differences in pain aetiology and phenotype. Baseline characteristics of participants prior to RF were also relatively comparable.

In all studies evaluating RF in the setting of chronic pain, the same three genicular nerves (SMGN, SLGN, IMGN) were targeted. In the acute pain setting, and thus in the GENIFEM trial, the ILGN was also targeted. RF technical parameters were also largely comparable, including lesion temperature (70–80 °C for conventional RF, 60 °C at the probe tip for cooled RF) and lesion duration (90s for conventional RF and 150s for cooled RF), with some variation in needle gauge and active tip length, mainly in the RECORGEN study (RECORGEN: 21G and 5mm active tip, while in the rest 18G and 10mm active tip for conventional RF and 17G and 4mm active tip for cooled RF). Imaging guidance differed per setting, with simultaneous ultrasound and fluoroscopy used in the chronic pain settings, and ultrasound used in the acute setting.

Finally, core clinical outcomes were consistently reported across quantitative studies, including pain intensity, functional outcomes, patient-reported outcome measures, and adverse events. Follow-up timing was also relatively consistent, generally including short-term (4–6 weeks), mid-term (3–12 months), and long-term follow-up (up to 24 months only in the COGENIUS trial).

Methodological limitations

Despite these strengths, interpretation of the findings is to some extent limited by heterogeneity across studies, including variability in patient populations, RF techniques, outcome measures, and follow-up duration, which complicates direct comparison.

Clinical heterogeneity is present, particularly in the RECORGEN study, which included a mixed population with different pain aetiologies. In contrast, the COCOGEN and COGENIUS trials evaluated RF within more clearly defined patient groups. This may limit generalisability, although subgroup analyses were performed where possible.

There is also heterogeneity in the RF intervention itself, as the technique has evolved over time with advances in anatomical knowledge. For example, the COCOGEN and COGENIUS trials used updated anatomical targets for genicular nerve blocks, while the RECORGEN did not.

In addition, outcome measures differed across studies, with different primary outcomes and time points (e.g., GPE at 6 weeks in RECORGEN, OKS at 3 months in COCOGEN, and WOMAC at 6 months in COGENIUS). Pain and functional outcomes were also assessed using different scales, and follow-up duration varied between studies.

Finally, economic heterogeneity limits the transferability of cost-effectiveness findings. The COCOGEN trial included patients from both Belgium and the Netherlands, but the economic evaluation was conducted from a Dutch healthcare perspective. Differences between healthcare systems and reimbursement structures, therefore, restrict the direct transferability of economic results between national contexts.

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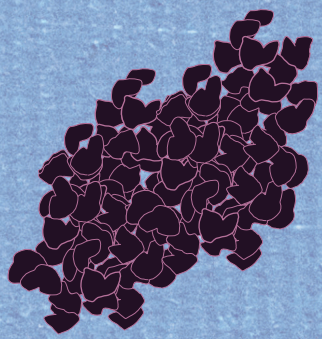
Chapter 9

Summary



English summary

This doctoral thesis aimed to improve the treatment of individuals with chronic knee pain by targeting the genicular nerves, using a rigorous mixed-methods, patient-centred approach. In the context of the growing burden of osteoarthritis (OA) and persistent postsurgical pain (PPSP), genicular nerve interventions, first described in 2011, have the potential to reduce disease burden. The evidence base for radiofrequency (RF) treatment of the genicular nerves is currently advancing from effectiveness trials toward cost-effectiveness and implementation studies in OA, while research in PPSP is still limited. For this thesis, 5 studies were designed between 2017 and 2026 to address effectiveness, cost-effectiveness, and treatment relevance in OA and PPPS. This thesis was structured using the Joanna Briggs Institute (JBI) FAME framework—Feasibility, Appropriateness, Meaningfulness, and Effectiveness— providing a structured approach for generation of clinically and socially relevant evidence.

In **chapters 1, 2, and 3**, evidence from the observational cohort and prospective pilot randomized trial supports the fact that RF of the genicular nerves is effective in patients suffering from therapy-resistant knee OA and PPSP in relation to pain and patient-reported outcomes. The effect size of the primary outcomes, however, points toward the need for adequate patient selection and a possibly important placebo effect that should not be dismissed in future trials. When compared to OA, the evidence on RF of the genicular nerves on PPSP is scarcer. This PhD also lays the groundwork for a cost-effectiveness analysis, where preliminary data indicate that cooled RF, compared to conventional RF, could be more cost-effective in PPSP; with conventional RF being more cost-effective in OA. Effectiveness and cost-effectiveness results from the COCOGEN trial will be translated to stronger evidence by the COGENIUS trial. Future studies need to focus on the evaluation and clinical comparison of protocols involving more nerves as a means of improving effectiveness.

In **chapters 4 and 7**, alongside the two previously mentioned trials, evidence is gathered on the potential adverse events after RF of the genicular nerves and the general perceived periprocedural burden. Data from studies from this doctoral thesis are congruent with the literature and identify RF to be a well-tolerated, minimally invasive treatment with an acceptable burden. The prevalence of adverse events is relatively low at 15%, and when present, they are typically temporary and self-resolving. Specific severe adverse events, such as the development of a complex regional pain syndrome, as in the case report included in this thesis, might, despite being rare,

require immediate and adequate treatment. Acknowledgement that queries on long-term safety, especially in the case of a repeated procedure or when more nerves are targeted, form a large obstacle in the large-scale implementation of this technique should prompt research programs in the form of long-term real-world cohorts.

Chapter 5 explores the genicular nerve block in the setting of acute knee pain, as a valuable derivate from the chronic pain equivalent. The genicular nerve block, due to its motor-sparing qualities, could find a place in enhanced recovery protocols for knee surgery. The GENIFEM pilot trial laid the groundwork for a larger powered trial using the genicular nerve block along a posterior knee capsule block for pain during placement of a knee prosthesis. This trial is the first to evaluate the analgesic capabilities of the block for the anterior aspect of the knee. Larger scale powered trials are needed, to assess the value of the genicular nerve block for acute knee pain.

In **Chapter 6**, the first qualitative study is presented on patient perceptions on the RF treatment in knee OA patients included in the COGENIUS trial. Patient identify experiencing an important disease burden and they experience the RF of the genicular nerves as an appropriate and meaningful treatment option. This study identifies that knee patients in Belgium undergo a long and highly variable treatment trajectory that does not systematically include a bio-psychosocial approach. Education and information of patient and health care providers on the treatment possibilities is an essential starting point. An important strength of this study is the exploration of patient preferences on future research trials and identifies that patients are open to multiple nerve treatment protocols when appropriate sedation is used and the periprocedural burden is acceptable. As such, data from this qualitative trial will further aid the interpretation of the results of the COGENIUS trial, creates a bases for shared decision making and for patient driven research.

In conclusion, this doctoral thesis shows that radiofrequency ablation of the genicular nerves is an effective and possibly cost-effective intervention for chronic knee pain, with a relatively low incidence of adverse events and potential applicability in both chronic and acute pain settings, including postoperative pain after knee arthroplasty. At the same time, the combined findings on effectiveness, cost-effectiveness, safety, and patient experience suggest that the added value of RF lies in its potential role within a broader knee pain care pathway, rather than in the intervention as a stand-alone treatment. As the evidence base strengthens—particularly through large trials such as COGENIUS—the next step lies in a health technology assessment–driven evaluation of how RF can be responsibly implemented in routine care. Rather than being offered as a stand-alone solution, RF should be embedded within a carefully

designed, integrated care pathway for knee pain that supports personalized decision-making, interdisciplinary collaboration, and a focus on functioning and participation alongside pain relief. Such an approach aligns technological innovation with an integral vision on health and maximizes the likelihood that RF contributes to sustainable, high-value care for people with knee osteoarthritis.

Nederlandse samenvatting

Dit promotietraject had als doel de behandeling van personen met chronische kniepijn te verbeteren door zich te richten op de geniculaire zenuwen, met behulp van een rigoureuze mixed-methods, patiëntgerichte benadering. In de context van de toenemende ziektelast van osteoartritis (OA) en persisterende postoperatieve pijn (PPSP), hebben interventies op de geniculaire zenuwen, voor het eerst beschreven in 2011, het potentieel om de ziektelast te verminderen. De evidentie voor radiofrequente (RF) behandeling van de geniculaire zenuwen evolueert momenteel van effectiviteitsstudies naar studies over kosteneffectiviteit en implementatie bij OA, terwijl onderzoek bij PPSP zich nog in een vroeger klinisch stadium bevindt. Voor dit proefschrift werden tussen 2017 en 2026 vijf studies ontworpen om effectiviteit, kosteneffectiviteit en behandelingsrelevantie bij OA en PPSP te onderzoeken. Dit proefschrift werd gestructureerd volgens het Joanna Briggs Institute (JBI) FAME-framework—Feasibility, Appropriateness, Meaningfulness en Effectiveness—wat een gestructureerde benadering biedt voor het genereren van klinisch en maatschappelijk relevante evidentie.

In **hoofdstukken 1, 2 en 3** ondersteunen evidentie uit een observationele cohortstudie en een prospectieve pilootgerandomiseerde studie dat RF van de geniculaire zenuwen effectief is bij patiënten met therapieresistente knie-OA en PPSP, zowel wat betreft pijn als patiëntgerapporteerde uitkomsten. De effectgrootte van de primaire uitkomsten wijst echter op de noodzaak van een adequate patiëntselectie en een mogelijk belangrijk placebo-effect dat in toekomstige studies niet genegeerd mag worden. In vergelijking met OA is de evidentie voor RF van de geniculaire zenuwen bij PPSP beperkter. Dit doctoraat legt ook de basis voor een kosteneffectiviteitsanalyse, waarbij voorlopige gegevens aangeven dat gekoelde RF, vergeleken met conventionele RF, mogelijk kosteneffectiever is bij PPSP, terwijl conventionele RF kosteneffectiever lijkt bij OA. De resultaten inzake effectiviteit en kosteneffectiviteit van de COCOGEN-studie zullen verder versterkt worden door de COGENIUS-studie. Toekomstige studies dienen zich te richten op de evaluatie en klinische vergelijking van protocollen waarbij meer zenuwen worden behandeld, als middel om de effectiviteit te verbeteren.

In **hoofdstukken 4 en 7** wordt, naast de twee eerder vermelde studies, evidentie verzameld over mogelijke neveneffecten na RF van de geniculaire zenuwen en de algemeen ervaren periprocedurele belasting. Gegevens uit de studies in dit doctoraat zijn in overeenstemming met de literatuur en identificeren RF als een goed verdragen, minimaal invasieve behandeling met een aanvaardbare belasting. De prevalentie van neveneffecten is relatief laag (15%) en wanneer ze optreden, zijn ze doorgaans tijdelijk

en zelflimiterend. Specifieke ernstige neveneffecten, zoals het ontwikkelen van een complex regionaal pijnsyndroom, zoals beschreven in de casus in dit proefschrift, vereisen, ondanks hun zeldzaamheid, onmiddellijke en adequate behandeling. De vaststelling dat vragen rond de langetermijnveiligheid, vooral bij herhaalde procedures of wanneer meerdere zenuwen worden behandeld, een belangrijke hinderpaal vormen voor grootschalige implementatie van deze techniek, zou aanleiding moeten geven tot onderzoeksprogramma's in de vorm van langetermijn real-world cohorten.

Hoofdstuk 5 onderzoekt de geniculaire zenuwblokkade in de context van acute kniepijn, als een waardevolle afgeleide van de toepassing bij chronische pijn. De geniculaire zenuwblokkade, dankzij haar motor-sparende eigenschappen, zou een plaats kunnen krijgen binnen enhanced recovery-protocollen voor kniechirurgie. De GENIFEM-pilootstudie legde de basis voor een grotere, voldoende gepowerde studie waarbij de geniculaire zenuwblokkade wordt gecombineerd met een blokkade van het posterieure kniekapsel voor pijncontrole tijdens het plaatsen van een knieprothese. Deze studie is de eerste die de analgetische werking van de blokkade voor het anterieure deel van de knie evalueert. Grootschaligere, voldoende gepowerde studies zijn nodig om de waarde van de geniculaire zenuwblokkade bij acute kniepijn te beoordelen.

In **hoofdstuk 6** wordt de eerste kwalitatieve studie gepresenteerd over patiëntpercepties van RF-behandeling bij knie-OA-patiënten geïncludeerd in de COGENIUS-studie. Patiënten geven aan een aanzienlijke ziektelast te ervaren en beschouwen RF van de geniculaire zenuwen als een gepaste en betekenisvolle behandelingsoptie. Deze studie toont aan dat kniepatiënten in België een langdurig en sterk variabel behandeltraject doorlopen waarin een biopsychosociale benadering niet systematisch wordt toegepast. Educatie en informatie voor zowel patiënten als zorgverleners over de behandelingsmogelijkheden vormen een essentieel uitgangspunt. Een belangrijke sterkte van deze studie is de exploratie van patiëntvoorkeuren voor toekomstig onderzoek, waarbij blijkt dat patiënten openstaan voor behandelprotocollen waarbij meerdere zenuwen worden behandeld, mits adequate sedatie en een aanvaardbare periprocedurele belasting. De gegevens uit deze kwalitatieve studie zullen bijdragen aan de interpretatie van de resultaten van de COGENIUS-studie en vormen een basis voor gedeelde besluitvorming en patiëntgestuurd onderzoek.

Concluderend toont dit doctoraat aan dat radiofrequente ablatie van de geniculaire zenuwen een effectieve en mogelijk kosteneffectieve interventie is voor chronische kniepijn, met een relatief lage incidentie van neveneffecten en potentiële toepasbaarheid in zowel chronische als acute pijnsettings, inclusief postoperatieve pijn na knieartroplastiek. Tegelijkertijd suggereren de gecombineerde bevindingen

inzake effectiviteit, kosteneffectiviteit, veiligheid en patiëntervaring dat de meerwaarde van RF vooral ligt in haar rol binnen een breder zorgpad voor kniepijn, eerder dan als een op zichzelf staande behandeling. Naarmate de evidentie verder versterkt wordt—met name door grootschalige studies zoals COGENIUS—ligt de volgende stap in een door health technology assessment (HTA) gedreven evaluatie van hoe RF op een verantwoorde manier kan worden geïmplementeerd in de routinezorg. In plaats van als een op zichzelf staande oplossing te worden aangeboden, dient RF ingebed te worden in een zorgvuldig ontworpen, geïntegreerd zorgpad voor kniepijn dat gepersonaliseerde besluitvorming, interdisciplinaire samenwerking en een focus op functioneren en participatie naast pijnreductie ondersteunt. Een dergelijke benadering stemt technologische innovatie af op een integrale visie op gezondheid en maximaliseert de kans dat RF bijdraagt aan duurzame, hoogwaardige zorg voor personen met knieartrose.



Chapter 10

Impact paragraph



Introduction

Chronic knee pain secondary to osteoarthritis (OA) and persistent post-surgical knee pain (PPSP) represents a substantial global clinical and socioeconomic burden.[1] Individuals with knee OA and PPSP experience a substantial burden of disease, including pain, functional limitations, sleep disturbance, and reduced work capacity.[2,3] Despite the availability of multiple treatment options, an important therapeutic gap persists in both population groups, frequently leading to high rates of total knee arthroplasty (TKA) and revision surgery, resulting in high healthcare costs. Radiofrequency treatment of the genicular nerves has emerged as a potential minimally invasive intermediate treatment option.

This doctoral research aims to optimize pain and quality of life outcomes in patients with chronic knee pain through genicular nerve-targeted interventions, using a rigorous and patient-centred collaborative research approach involving patients, clinicians, and researchers. Beyond their scientific contribution, the findings provide valuable insights for guiding future research, informing clinical practice, and supporting evidence-based decision-making by policymakers regarding the use of radiofrequency (RF) techniques for chronic knee pain.

Guiding academic research

A key priority for future research is to further establish the clinical effectiveness of genicular nerve RF. Current evidence, largely derived from Bayesian network meta-analyses, remains partially indirect, and direct head-to-head comparisons between RF modalities are limited. Well-designed randomized controlled trials comparing conventional and cooled RF, preferably including a sham arm, are required to address remaining uncertainties. Preliminary insights from the COCOGEN trial and the ongoing COGENIUS trial will help clarify whether commonly applied three-nerve RF protocols provide clinically meaningful benefit. Should these approaches demonstrate limited efficacy, expanded nerve-targeting strategies may warrant investigation.

Patient selection represents another important area of focus. Differences in treatment response between patients with knee OA and those with PPSP suggest distinct underlying pain mechanisms, supporting the need for separate evaluation and patient phenotyping in future trials.

The findings of this thesis also highlight the importance of outcome selection. Patients emphasized functional improvement over pain reduction alone, indicating that future studies should incorporate composite patient-reported outcomes and specific measures of physical functioning.

In addition to RF treatment, alternative minimally invasive interventions, including chemical neurolysis, genicular artery embolization, and regenerative therapies, merit further investigation, particularly regarding their position within the disease trajectory. This is especially important for treatments that may have a disease-modifying potential.

Uncertainty regarding the long-term effectiveness and safety of RF persists. In this context, registries of patients undergoing the RF procedure may provide valuable real-world data on durability, complications, and progression to knee arthroplasty.

Economic evaluations assessing the cost-effectiveness of RF strategies in OA and PPSP within specific healthcare systems, together with the integration of qualitative research both as stand-alone studies and alongside clinical trials, will further clarify the value of RF. These approaches may enhance understanding of patient priorities and clinicians' perspectives, thereby supporting the implementation of these interventions in clinical practice.

Finally, the perioperative role of genicular nerve blocks warrants further investigation. Preliminary findings from the GENIFEM trial suggest a potential role in anterior knee analgesia; however, adequately powered studies are needed to determine whether this technique is sufficient as a primary strategy or should be used as an adjunct, such as to an adductor canal block.

Guiding clinical practice

The findings of this thesis may contribute to refining the clinical management and care pathways for patients with chronic knee pain.[4,5] Currently, patient trajectories remain highly variable and are influenced by multiple factors, including clinician awareness of genicular nerve RF, referral pathways to orthopaedic surgery, and both patient and clinician perceptions of RF and chronic pain management within specialized pain clinics.

Based on the conduct of the trials included in this thesis, the broader research of the field, and clinical experience, genicular nerve RF should be considered earlier in the treatment pathway. Despite variations in national guidelines, discussion of RF may be appropriate after approximately six months of unsuccessful conservative management and intra-articular injections in patients with knee OA, and potentially earlier in patients with PPSP. Importantly, genicular nerve RF should not be regarded as a stand-alone intervention. The qualitative findings of this thesis highlight the substantial psychosocial burden associated with chronic knee pain, supporting the need for integration within a broader biopsychosocial framework. Accordingly, RF should be implemented as part of a multidisciplinary treatment strategy, delivered alongside conservative care within a comprehensive pain management approach.

Another important subject is appropriate patient selection. Current evidence suggests that genicular nerve RF is most suitable for patients with knee OA (Kellgren–Lawrence grade II–IV) presenting with predominantly anterior knee pain, as well as for patients with PPSP.

Periprocedural considerations may further optimize the safety and tolerability of genicular nerve RF. In patients with PPSP following knee arthroplasty, antibiotic prophylaxis may be considered to reduce the risk of periprosthetic infection, although no cases of periprosthetic infection were reported in the studies included in this manuscript. In addition, qualitative findings indicate that RF procedures may be painful, supporting the availability of periprocedural sedation where appropriate to improve patient experience. Finally, the clinical data presented suggest that interruption of anticoagulation therapy may not be necessary, as bleeding complications appear to be rare and typically compressible, consistent with recommendations for peripheral nerve blocks.

Guiding policymakers and Health Technology Assessment

The results of this thesis may also inform policy decisions regarding the implementation and reimbursement of genicular nerve interventions. The methodological framework used throughout this research aligns with the principles of the Joanna Briggs Institute (JBI) approach, which integrates evidence on clinical effectiveness, safety, cost-effectiveness, feasibility, and patient experience. These elements correspond closely with the criteria considered in health technology assessments (HTA).

The studies included in this thesis provide several of the building blocks required for such an evaluation, such as clinical effectiveness, patient experience, procedural safety, and economic considerations. However, because several studies represent pilot randomized trials, larger powered studies are necessary before definitive HTA conclusions can be drawn.

The ongoing COGENIUS trial is expected to provide stronger evidence regarding the clinical effectiveness of RF treatment, with particular interest in the cooled RF technique. These results may provide the necessary foundation for HTA evaluations examining whether such interventions should be reimbursed within national healthcare systems.

Importantly, HTA evaluations should consider OA-related pain and PPSP as distinct clinical entities, given the differences in treatment response suggested by current evidence. As most of the research presented in this thesis was conducted within the Belgian healthcare context, the findings may be particularly relevant for HTA evaluations and reimbursement decisions in Belgium. Nevertheless, the broader framework and research directions outlined here may also inform policy discussions in other healthcare systems.

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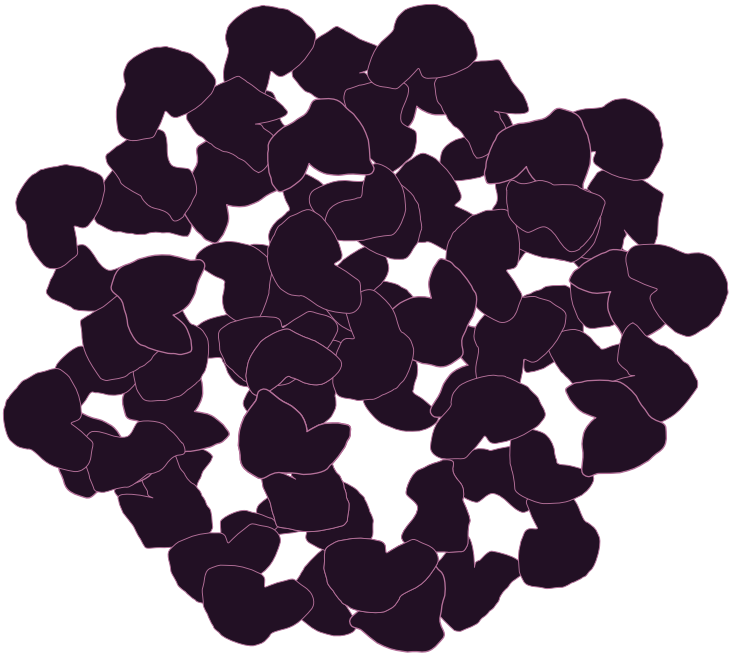
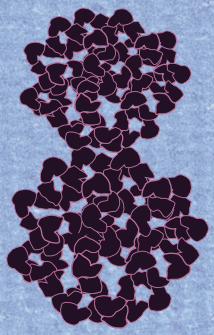


Curriculum vitae and list of publications



Curriculum Vitae

Amy Belba was born on February 4, 1992, in Albania. She completed her secondary education at the high school "Ismail Qemali" in Tirana in 2010. Following her move to Belgium, she obtained a Certificate in Dutch as a Foreign Language at the Leuven Language Institute in 2011. She subsequently pursued medical studies at KU Leuven, where she earned her Bachelor of Medical Sciences in 2014 and completed her Master of Medical Sciences in 2018. During her studies, she developed a strong interest in anaesthesiology, pain medicine, and scientific research. She was actively involved in research at the Research Centre for Skeletal Biology and Engineering under the supervision of Prof. Dr. Christa Maes and Prof. Dr. Patrick Verschueren, contributing to projects in rheumatology and musculoskeletal research.

In 2018, she started her specialist training in anaesthesiology-resuscitation. During her residency, she developed expertise in anaesthesiology, perioperative medicine, and pain management. In parallel, she initiated a PhD project at Maastricht University and Hasselt University in 2021 under the supervision of Prof. Dr. Jan Van Zundert, focusing on radiofrequency treatment of the genicular nerves for chronic knee pain. Her scientific work has resulted in several peer-reviewed publications in the fields of chronic pain and regional anaesthesia.

To further specialize in interventional pain medicine, she completed a fellowship in regional anaesthesia at Ziekenhuis Oost-Limburg (ZOL) Genk in 2024, followed by a fellowship in chronic pain management at ZOL Genk from 2024 until December 2025. The completion of this advanced subspecialty training culminated in successfully obtaining the prestigious 'Fellow of Interventional Pain Practice' (FIPP) certification in 2025, organized by the World Institute of Pain. Since January 2026, she has been working as a staff member in pain medicine and anaesthesiology at Antwerp University Hospital (UZA).

In addition to her clinical and scientific activities, she is actively involved in academic reviewing and professional organizations. She serves as a peer reviewer for several international peer-reviewed journals in anaesthesiology and pain medicine. She was also a representative of the Belgian Anaesthesia Trainees (BAT) within the Belgian Association for Regional Anaesthesia (BARA) and participated in the scientific committee of the Young Researchers Day of the Belgian Pain Society.

Beyond medicine, Amy has a longstanding passion for visual arts and has pursued advanced education in oil painting at the SLAC Academy of Visual Arts in Leuven since 2011. Her artistic work has been exhibited in Leuven, Belgium, and she has participated in several artistic collaborations and workshops.

On a personal note, Amy is married to Diederik de Ceuster and is the proud mother of her son, Elias.

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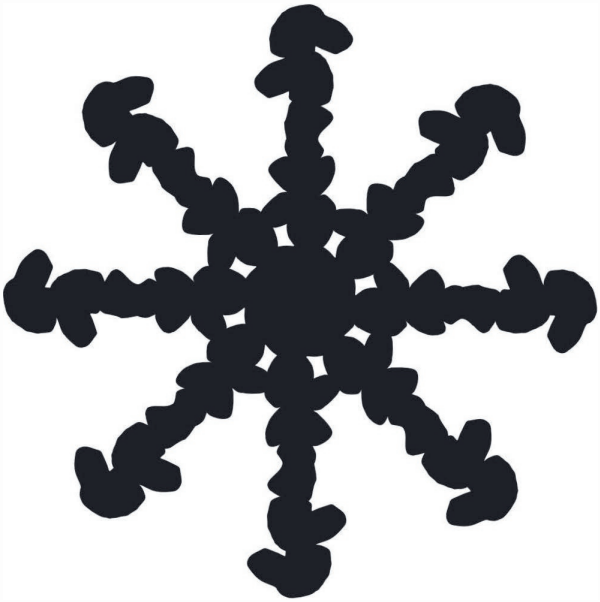

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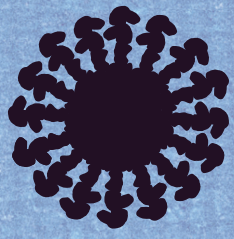

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I would like to finally dedicate this book to my husband, Diederik, and to our son Elias. Diederik, you have taken on so many different roles these last years: that of a loving partner, of a dedicated and joyful father, and of a researcher yourself, challenging my work conceptually. I cherish your goodwill, your outlook on life and especially your love. Elias, I hope that when you read this book, it will spark your curiosity!

