PROTOCOL

A **re**trospective single-center cohort study on patients with chronic knee pain treated with **co**nventional **r**adiofrequency of the **geni**cular nerves.

(Recorgen trial)

Site Investigator:
This study is organized by the Department of Chronic pain of the Hospital of Oost-Limburg (Ziekenhuis Oost-Limburg), Campus Sint-Barbara.

It will be coordinated by Prof. Dr. Van Zundert and Dr. Vanneste.

TITLE: A retrospective single-center cohort study on patients with chronic knee pain treated with conventional radiofrequency of the genicular nerves.

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Sponsor	**ZOL Genk**

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	**Adverse Event**
GPE	**Global Perceived Effect**
IC	**Informed Consent**
IL	**Inferior Lateral**
IM	**Inferior Medial**
NRS	**Numeric Rating Scale**
OKS	**Oxford Knee Score**
PPSP	**Persistent Post-Surgical Pain**
RFA	**Radiofrequency Ablation**
SL	**Superior Lateral**
SM	**Superior Medial**
ZOL	**Ziekenhuis Oost-Limburg**

ABSTRACT

Context: Management of chronic knee pain remains a challenge to the treating physician. Chronic knee pain can be the consequence of osteoarthritis but also of persistent post-surgical knee pain (PPSP). Conservative and surgical treatments may not always be the optimal solution in this diverse population, leading to a need for alternative treatment methods. A radiofrequency treatment of the genicular nerves is a not yet established but promising technique. It employs heat and an electrical field to target sensory knee nerve fibers in order to block them and alleviate chronic knee pain. This procedure is minimal invasive and has few adverse events. For these reasons it can be advantageous and fulfilling the unmet needs of these chronic knee pain patients warranting further research of its efficacy.

Objectives: This project has as primary objective the evaluation of treatment success of a conventional radiofrequency treatment of the genicular nerves in patients diagnosed with chronic knee pain due to osteoarthritis of the knee or PPSP at six weeks post treatment. Secondary objectives are evaluation of treatment effect at a third time point at the end of the inclusion period, subgroup analysis of treatment success based on indication to treatment, evaluation of subjective functional improvement and change in analgesics, estimation of the duration of effect of the treatment and adverse events.

Study Design: This study is a retrospective single-center cohort.

Setting/Participants: This study includes all patients treated with radiofrequency ablation in the multidisciplinary chronic pain center in Ziekenhuis Oost-Limburg, Campus Sint-Barbara between 1 September 2017 and 30 June 2020 with exclusion of patients with chronic widespread pain.

Main study endpoints: The main study outcome is the proportion of patients with a global perceived effect of at least 50% at 6 weeks post intervention. Secondary outcomes include reduction in pain intensity, measured by Numeric Rating Scale (NRS) at six weeks and at a third time point, global perceived effect at a third time point, subjective change in physical functioning, duration effect of the treatment, use of strong opioids, and adverse events.

PROTOCOL SYNOPSIS

Study Title	A retrospective single-center cohort study on patients with chronic knee pain treated with conventional radiofrequency of the genicular nerves.
Funder	ZOL Genk
Study Objectives	**Primary objective** • To evaluate treatment success of the conventional radiofrequency ablation at week 6 **Secondary objective** • Evaluation of treatment effect at a third time point at the end of the inclusion period • Subgroup analysis of treatment success based on indication to treatment • Evaluation of subjective functional improvement • Evaluation of change in analgesics • Estimation of the duration of effect of the treatment • Adverse events
Study Design	Retrospective single-center cohort study
Subject Population **Key criteria for Inclusion and Exclusion:**	**Inclusion Criteria** 1. All patients with chronic knee pain who qualify for a conventional RF treatment of the genicular nerves **Exclusion Criteria** 1. Refusal to participate 2. A negative diagnostic block with lidocaine 2% 1 ml of the three genicular nerves defined as less than 50% pain reduction 3. Chronic widespread pain
Time	Patients treated with conventional RF treatment between 1 September 2017 and 30 June 2020.
Study endpoints	1. **Primary endpoint**: - Proportion of patients with treatment success at 6 weeks defined as GPE of ≥ 50% compared to baseline. 2**. Secondary endpoints:** - Proportion of patients with treatment success at third time point defined as GPE of ≥ 50% compared to baseline. - NRS reduction at week 6 and at the third time point - Subjective physical functioning at week 6 and at the third time point - Duration effect of the treatment defined as period with a GPE of ≥ 50% - Change in strong opioid use at week 6 and at the third time point - Safety: number/type of adverse events

1. BACKGROUND INFORMATION AND RATIONALE

Chronic knee pain is one of the most common disabling joint disorders in the global population.(1) Chronic knee pain can be the consequence of osteoarthritis but also of persistent post-surgical knee pain (PPSP). Osteoarthritis is an active degenerative disease that involves cartilage, subchondral bone and new bone formation leading to a considerable number of patients suffering from disabling symptoms such as chronic pain, stiffness and loss of function. The lifetime risk of developing symptomatic knee osteoarthritis is estimated to be ~45% based upon Johnston County Osteoarthritis Project data.(2)

Treatment strategies for chronic knee pain condition can be divided into surgical and non-surgical. When a conservative treatment fails to treat the symptoms, surgical techniques come to rescue. Total knee arthroplasty or an artificial replacement of the knee is the treatment of choice in multiple clinical situations of osteoarthritis. Despite being a successful treatment, comorbidities frequently hinder its application. Secondly, artificial joint replacement has unfortunately a limited longevity, and pain or discomfort after total knee replacement is frequent. (3-5) The percentage of patients that continues to report clinically significant pain and/or dissatisfaction after total knee arthroplasty mounts up to 19%-20%. (6-8) Residual pain has most commonly been associated with patellofemoral disorders, locating this pain largely in the anterior knee. (9) Due to this number of pitfalls a growing number of patients remain optionless facing disability, decrease in quality of life, extensive opioid consumption and/or polypharmacy. The groups of patients suffering from chronic knee pain including patients with comorbidities, non-geriatric patients and surgically treated patients with remaining knee pain have since the last decade been considered as potential candidates for treatment with radiofrequency ablation.

Radiofrequency treatment is a novel technique implemented on knee pain. This method targets the sensory innervation of the knee, leading to a decrease in the transmission of pain signals. The knee nerves presently targeted are the genicular nerves which are branches of the femoral, saphenous, obturator, common peroneal, tibial and sciatic nerve. This technique has little contraindications and few reported adverse events. As such it is a potential promising solution to persistent knee pain.

The first described conventional radiofrequency ablation of the genicular nerves is presented by Choi and colleagues in 2011. (10) In this double blind randomized trial patients showed significant improvement in pain and functionality scores in comparison with placebo. Since this first positive report, multiple investigations have explored and expanded the use of radiofrequency ablation towards pulsed radiofrequency and cooled radiofrequency treatment as alternatives to the conventional ablation. (11-13)

In the present retrospective cohort study we will analyze patients treated with this novel technique in our chronic pain center. The main aim of this study is to determine treatment success of radiofrequency ablation on patients with chronic knee pain. Furthermore, we aim to gain a better insight in demographics, indications, referring physicians, complications and adverse events that might be beneficial for organizing care for chronic knee pain patients.

2. STUDY DESIGN

2.1 **Study design**

This study is designed as a retrospective longitudinal cohort study of patients treated with a radiofrequency treatment of the genicular nerves in a single-center (ZOL, Genk) between 1 September 2017 and 30 June 2020. Each knee will be considered as a unique observation, and bilateral procedures were assessed specific to each knee treated. Data retrieved from the patient files will be collected at baseline, 6 weeks post-intervention and telephonically at a third time point which ranges from 6 weeks to 3 years after the procedure. The following demographic and clinical data will be collected at baseline: patient age, sex, NRS score, length of symptom duration, indication for the procedure, use of strong opioids, history of previous knee surgery and the referring physician. Strong opioid analgesics are defined as all opioids excluding tramadol and codeine.

Data collected at 6 weeks post-intervention will include: NRS, GPE, adverse events, and concomitant use of strong opioids.

Patient's data will be collected at a third time point. Written informed consent will be obtained by mail prior to contact by phone. After receiving informed consent, patients will be contacted by telephone and data will be gathered on the same variables as at 6 weeks post-intervention and on subjective functional outcome.

2.2 **Questionnaire**

At the third time point patients will be contacted by phone, after receiving written informed consent by mail. The study and its rationality will be introduced together with the main objectives. The input needed from the patients will be communicated and an oral informed consent will be requested. In case of a positive input the following questions will be asked:

- How much pain do you experience at the moment in the knee where the procedure was performed in a scale of zero to ten where zero is 'no pain' and ten is 'unbearable pain'?
- Is the pain in the knee tolerable or not?
- How much effect do you still perceive at the moment expressed in percent between 0 and 100%?
- How long do you think the treatment worked or is there still effect?
- Do you experience at the moment functional improvement in comparison with before the treatment?
- Which pain medication are you using at the moment?
- Did you experience any adverse events?

The conversation will be executed in the Dutch language.

3. STUDY SETTING AND POPULATION

3.1 **Study setting**

The enrollment period will be between 1 September 2017 and 30 June 2020. The patients recruited were treated in an outpatient setting in the multidisciplinary chronic pain center in Lanaken, Campus St. Barbara, ZOL. Patients with chronic knee pain who qualify for an conventional radiofrequency treatment of the genicular nerves were recruited. Prior a diagnostic block was performed and in case of positive results patients were treated with conventional radiofrequency ablation. Follow up in the pain clinic consisted of a minimum of one consultation after treatment at six weeks post procedure. Further follow up was planned according to the needs of the patient at the pain clinic, orthopedist or general practitioner.

3.2 **Population**

3.2.1 Inclusion criteria

1. All patients with chronic knee pain who qualify for a conventional RF treatment of the genicular nerves

3.2.2 Exclusion Criteria

Patients will be excluded from participating in the study if the meet any of the following exclusion criteria:

1. Refusal to participate
2. A negative diagnostic block with lidocaine 2% 1 ml of the three genicular nerves defined as less than 50% pain reduction
3. Chronic widespread pain

4. STUDY OBJECTIVES

4.1 **The primary objective** of this study is to evaluate the treatment success of the conventional radiofrequency treatment of the genicular nerves in patients on patients diagnosed with chronic knee pain due to osteoarthritis of the knee or PPSP at six weeks post treatment. Treatment success is defined as a global perceived effect of at least 50% at measurement time point compared to baseline.

4.2 **The secondary objectives** are:

- Evaluation of treatment effect at a third time point at the end of the inclusion period
- Subgroup analysis of treatment success based on indication to treatment
- Evaluation of subjective functional improvement
- Evaluation of change in analgesics
- Estimation of the duration of effect of the treatment
- Adverse event

5. STUDY ENDPOINTS

5.1 **Primary endpoint**:

Proportion of patient with treatment success at week 6 defined as a global perceived effect of ≥ 50% compared to baseline.

5.2 **Secondary endpoints:**

- Proportion of patients with treatment success at third time point defined as a global perceived effect of ≥ 50% compared to baseline.
- NRS reduction at week 6 and at the third time point.
- Subjective physical functioning at week 6 and at the third time point.
- Duration effect of the treatment defined as the period with a GPE of ≥ 50%.
- Change in use of strong opioids at week 6 and at the third time point.
- Safety: number/type of adverse events.

6. TIME SCHEDULE

Outcome / Time point	**Baseline Consultation prior to inclusion**	**Diagnostic RF treatment**	**RF treatment**	**Consultation 6 weeks post treatment**	**Telephonic contact**
Age	X				
Sex	X				
Duration of symptoms	X				
Previous knee surgery	X				
Referring physician	X				
Indication for treatment	X				
NRS	X			X	X
Strong opioid use	X			X	X
Chronic widespread pain	X				
NRS reduction ≥ 50%		X		X	X
Treating physician			X		
Subjective physical functioning score					X
GPE ≥ 50%				X	X
Adverse events				X	X
Informed consent					X

7. STATISTICAL CONSIDERATIONS

Data will be presented as mean values and standard deviations or as median values and interquartile range (IQR) depending on the distribution of the data. The average post-treatment pain score will be estimated using linear mixed effects regression analysis using time since treatment as independent variable. We will use this multilevel approach as (most) patients contribute more than one post-treatment pain score to the dataset. This way, we will be able to estimate the 3 and 6 months effect of RF treatment. The statistical analysis will be performed using SPSS.

8. INFORMED CONSENT

Patients in accordance with eligibility criteria will be contacted by mail to obtain written informed consent and afterwards by phone by the investigator. At the beginning of the contact oral informed consent will also be obtained.

9. REFERENCES

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APPENDIX

Description of the procedures:

Conventional radiofrequency treatment of the genicular nerves is performed in an outpatient setting. Patients are not required to stop anticoagulation prior to procedure. During the procedure the patient is monitored using pulse oximetry. No sedation is administered so the patient is able to communicate and report the stimulation adequate. The patient is placed in a supine position on a fluoroscopy table with the index knee flexed 10-15° by placing a cushion in the popliteal fossa.

Description of the procedure of the diagnostic nerve block

The eligible patients underwent diagnostic genicular nerve blocks with local anesthetic, which were performed under ultrasound guidance. The targets included the SL, SM and IM genicular nerves which pass periosteal areas connecting the shaft of the femur to bilateral epicondyles and the shaft of the tibia to the medial epicondyle. Lidocaine (1 mL of 2%) was injected at each target site. Responses were recorded as positive if the participant experienced a decrease in numeric pain scores of at least 50%. Patients with a positive response were included in the RF procedures.

Description of the procedure of conventional radiofrequency ablation

The procedure is performed under sterile conditions. A 100 mm long, 22 G straight RF cannula/introducer with a probe/electrode with a 5 mm active tip is used for the procedure. No corticosteroids are injected to decrease the risk of complications such as systemic effects and infection. The superomedial, the superolateral and the inferomedial genicular nerve are targeted using a high frequency linear ultrasound. The inferolateral genicular nerve is not targeted because of its proximity to the common peroneal nerve with its motor branches.

Superomedial genicular nerve

The transducer is placed in a coronal orientation on the medial side of the proximal knee. After identifying the femoral medial epicondyle, the transducer is displaced proximally to image the junction between the epiphysis and diaphysis of the femur and the vastus medialis superficial to it, just anterior to the adductor tubercle. The skin and soft tissue are anesthetized with 1 ml lidocaine2% at the estimated entry point. The superomedial genicular artery may or may not be seen between the deep fascia of the muscle and the femur at this level. If the superomedial genicular artery is visualised just above the bony cortex, the cannula tip is placed next to it using an cephalad to caudad ‘in plane’ approach. If the artery is not visualised, the cannula is advanced until contact is made with the bony cortex at the junction also using an cephalad to caudad ‘in plane’ approach. A RF electrode is introduced in the cannula. Sensory stimulation (50Hz) is applied and produced paresthesia at a threshold of less than 0,5 V. The absence of fasciculations below 1 V is observed after motor stimulation at 2 Hz, confirming sufficient distance to relevant motor branches. If no sensory stimulation threshold is obtained at this position, the transducer is rotated in a transverse view and the needle tip is redirect towards the middle of the femur until sensory threshold is reached.

Inferomedial genicular nerve

The transducer is placed in a coronal orientation on the medial side of the distal knee to visualize the junction of the tibial medial epiphysis and diaphysis, the inferomedial genicular artery and the medial collateral ligament. The skin and soft tissue are anesthetized with 1 ml lidocaine 2% at the estimated entry point. The inferomedial genicular artery may or may not be seen beneath the medial collateral ligament at the midpoint between the tibial medial epicondyle and the tibial insertion of the medial collateral ligament. If the inferomedial genicular artery is visualized just above the bony cortex, the cannula tip is placed next to it using an caudad to cephalad 'in plane' approach. If the artery is not visualized, the cannula is advanced until contact is made with the bony cortex at the junction also using an caudad tot cephalad 'in plane' approach. A RF electrode is introduced in the cannula. Sensory stimulation (50 Hz) is applied and produced paresthesia at a threshold of less than 0,5 V. The absence of fasciculations below 1 V is observed after motor stimulation at 2 Hz, confirming sufficient distance to relevant motor branches. If no sensory stimulation threshold is obtained at this position, the transducer is rotated in a transverse view and the needle tip is redirect towards the middle of the tibia until sensory threshold is reached.

Superolateral genicular nerve

The transducer is placed in a coronal orientation on the lateral side of the proximal knee. After identifying the femoral lateral epicondyle, the transducer is displaced proximally to image the junction between the epiphysis and diaphysis of the femur and the vastus lateralis superficial to it. The skin and soft tissue are anesthetized with 1 ml lidocaine 2% at the estimated entry point. The superolateral genicular artery may or may not be seen between the deep fascia of the muscle and the femur at this level. If the superolateral genicular artery is visualized just above the bony cortex, the cannula tip is placed next to it using an 'in plane' approach. If the artery is not visualized, the cannula is advanced until contact is made with the bony cortex at the junction also using an 'in plane' approach. A RF electrode is introduced in the cannula. Sensory stimulation (50 Hz) is applied and produced paresthesia at a threshold of less than 0,5 V. The absence of fasciculations below 1 V is observed after motor stimulation at 2 Hz, confirming sufficient distance to relevant motor branches. If no sensory stimulation threshold is obtained at this position, the transducer is rotated in a transverse view and the needle tip is redirect towards the middle of the femur until sensory threshold is reached.

If all three target nerves were identified 1 ml of lidocaine 2% is injected before the start of a RF treatment without a fluoroscopic control. A treatment of 70°C at the tip is applied during 90 seconds at each nerve. After the procedure, the patient is transferred to the recovery. After 30 minutes without any events, the patient is discharged at home. Home medication is continued postoperative. Patient is informed about potential transient increase in pain due to neuritis and alarm symptoms (fever, swelling, bleeding and motor weakness).