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# Management of pain in the arthritic knee

**Submission date**
27/03/2022

**Recruitment status**
No longer recruiting

**Registration date**
29/03/2022

**Overall study status**
Completed

**Last Edited**
12/04/2023

**Condition category**
Musculoskeletal Diseases

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

## Plain English summary of protocol

Background and study aims
Knee osteoarthritis (KOA) is a degenerative joint disease that primarily involves the cartilage and many of the surrounding tissues in the knee joint. In addition to damage and loss of cartilage, it also involves bone remodeling, bone spur formation, hypermobile ligaments, weakening of knee joint muscles, and, in some cases, inflammation. Knee osteoarthritis is increasing in prevalence worldwide. While total knee arthroplasty (knee replacement surgery) is an effective treatment option for end-stage knee arthritis, the relatively slow progression of the disease allows for a stepwise approach using non-surgical or
non-drug treatment options (weight loss, exercise, braces, injections with steroids, hyaluronic acid etc). Through the wide array of non-surgical treatment options, cooled radiofrequency ablation (CRFA) and cryoneurolysis (CRYON) have been proposed. Radiofrequency ablation (RFA) uses radio waves to heat up nerve tissues and disrupt the transmission of pain signals from the knee. Cryoneurolysis uses cold temperatures (-20 to -100°C) to temporarily block nerves, leading to pain relief while the nerve retains its ability to regenerate. There is clinical evidence suggesting that both CRFA and CRYON are safe and effective procedures in the management of knee osteoarthritis pain. The aim of this study is to compare the two techniques (CRYON and CRFA) to a group of patients that will receive sham surgery, in terms of pain relief as well as improvement in several clinical scores.

Who can participate?
Patients aged over 45 with primary knee arthritis

What does the study involve?
Patients with an initial positive response to the diagnostic nerve injection will be randomly allocated into one of the three groups: a SHAMS group, a CRFA group or a CRYON group. During the sham procedures, the probes of either the CRYON or CRFA will be applied in the treated knee as usual and a non-therapeutic signal will be given for treatment simulation. Participants will be followed up for a period of 6 months.

What are the possible benefits and risks of participating?
The main benefit is the relief of knee pain for at least a period of 6 months. Expected side effects and complications (e.g., bruising, swelling, numbness, inflammation and/or erythema

[rash]) involving the access to the nerves and the use of local anesthetic will be assessed at each follow-up visit and documented independently except for the loss of movement outside the treatment area.

Where is the study run from?
Patras University Hospital (Greece)

When is the study starting and how long is it expected to run for?
September 2021 to April 2023

Who is funding the study?
General University Hospital of Patras (Greece)

Who is the main contact?
Prof. Andreas Panagopoulos
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# Contact information

### Type(s)
Principal investigator

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# Additional identifiers

### Clinical Trials Information System (CTIS)
Nil known

### Protocol serial number
11846/5/10/2021

# Study information

### Scientific Title
Cooled radiofrequency ablation versus cryoneurolysis for the symptomatic management of pain in knee osteoarthritis: a prospective, randomized, sham-controlled, double-blind trial

## Acronym
NEurolysis for the ARthritic PAin of the Knee (NE.AR.PA.K)

## Study objectives
The main hypothesis is that a substantial relief of pain would be achieved with both techniques (cooled radiofrequency ablation [CRFA] and cryoneurolysis [CRYON]) compared to SHAMS but their efficacy would be equal.

## Ethics approval required
Old ethics approval format

## Ethics approval(s)
Approved 05/10/2021, Research Ethics Committee, Patras University (26504 Rion-Patras, Greece; +30 (0)2610997841; uprescom@upatras.gr), ref: 11846 / 5/10/2021

## Study design
Single-center interventional double-blinded randomized controlled trial

## Primary study design
Interventional

## Study type(s)
Treatment

## Health condition(s) or problem(s) studied
Relief of pain related to knee osteoarthritis

## Interventions
Approximately 400 patients with symptomatic knee OA visit the clinic each year. A small percentage has an end-stage disease, only amenable for total knee replacement. Most of the remaining patients require conservative measures initially to control their symptoms and from those patients a respectable percentage has not been able to respond to oral medications, physiotherapy, loss of weight and injectable therapies. This will be the pool of patients that will participate in this randomized trial. After establishing the diagnosis of knee arthritis according to the eligibility criteria outlined below, the patients will visit again the Department for diagnostic block (with lidocaine) of the genicular nerves, under ultrasound guidance. Patients would be only enrolled in the study if they report, at least a 50% reduction of their pain (as measured using the NRPS). Eligible patients will then be randomized 2:2:1 to either CRFA, CRYON or SHAMS. This will allow the researchers to test the clinical results of both CRFA and CRYON with the SHAMS group, but also between each other in terms of safety and complication rate.

Patients will be placed in the operating theatre in a supine position with a bolster under the knee to produce 30 degrees of flexion. A sealed and opaque envelope will be brought to the operation theatre, dictating the group of each patient. The treated knee will be draped and sterilized in a standard manner; one dose of third-generation cephalosporin will be given for infection prophylaxis. Patients would be continuously monitored and given conscious sedation (1–2 mg IV and/or fentanyl (25–100 mcg IV)) and supplemental oxygen. The location of the nerves (SLGN, SMGN, IMGN and SPGN) will be identified with the use of ultrasound and/or fluoroscopy according to the standard described methods. The technique deployed to spot the genicular nerves and perform accurate ablation is the one presented by Lash et al. The US

transducer is initially oriented in the coronal plane on the level of the joint line. In order to spot the superior medial and lateral genicular nerves the transducer is moved cephalad towards the diaphyseal/metaphyseal junction in both sides of the femur. As the genicular artery nerve and artery are located in the long axis, the transducer is now turned in an axial orientation in order to visualize them in the short axis. The same principle is applied for the inferior medial genicular nerve, but in order to spot it the transducer is moved caudal from the joint line towards the medial metaphyseal/diaphyseal junction of the tibia. Finally, the SPGN was located 5 cm above the superior pole of the patella at the midportion between the femur and quadriceps muscle according to Wong et al.

CRFA technique
A 50–150 mm, 17-gauge introducer needles will be placed thereafter to ablate the SLG, SMG, IMG and SPG nerves. One milliliter of 2% lidocaine is injected through the introducer needles to anesthetize the area prior to ablation. After placement of the introducer needle, the 18-gauge internally cooled 4-mm active tip RFA electrode (Coolief, Halyard Health, Alpharetta, GA, USA) is placed into the introducer needle and the positioning is again checked with the ultrasound. Motor nerve activity is excluded with testing 2 Hz at 1 mA. Then the CRFA probe is advanced and ablation is performed with lesion settings at 60°C (80–90° adjacent tissue temperature) for 2.5 minutes.

CRYON technique
The cryoneurolysis probe (ICEseed 1.5, Galil Medical Ltd.) is inserted in the proximity of the four target nerves, guided by ultrasound visualization as already has been described. Our study differs from that of Radnovich et al. who targeted only the infrapatellar branch of the saphenous nerve (IPBSN). The machine used for cryoneurolysis is the VisualICE, (Galil Medical Ltd). The procedure is performed with a single freeze cycle; 30s at an effect of 20%, and 2 min 30s at 60% effect. After each freezing cycle, 1 min active thaw and 1 min passive thaw are used.

SHAMS technique
Patients that have been randomized to SHAMS will undergo the same procedures as described above but using a sham probe that does not allow for any ablation or freezing temperatures. Thus, four visible marks on the skin as a result of the procedures will be similar in both groups for the clinical evaluation. During treatment, CRYON or CRFA probes will display the same lights and activation features as the active ones in a similar time frame to ensure blinding of the investigator to the patient's group assignment.

## Intervention Type
Procedure/Surgery

## Primary outcome(s)
Pain associated with knee OA measured using the Numerical Rating Pain Scale (NRPS) at 2-, 4-12- and 24-weeks post-intervention

## Key secondary outcome(s))
Safety, tolerability and the patient’s clinical outcome measured using the Knee Injury and Osteoarthritis Outcome Score (KOOS) the Oxford Knee Score (OKS) and the Patient Global Impression of Change (PGIC) 7-point scale at 12- and 24-weeks post-intervention

## Completion date
15/04/2023

# Eligibility

### Key inclusion criteria
Patients of either sex will participate in the clinical trial as long as they have:
1. The NICE clinical criteria of primary knee OA for one or both knees:
1.1. Age >45 years
1.2. Activity-related joint pain
1.3. No morning joint stiffness or morning stiffness that lasts no longer than 30 minutes
2. Radiological confirmation of knee arthritis (grade ≥2) according to the Kellgren and Lawrence classification
3. Chronic knee pain for a minimum duration of 6 months
4. Pain intensity ≥4 on the (NRPS)
5. A decrease of ≥50% in NRPS scores with diagnostic genicular nerve block
6. The ability to communicate in Greek

### Participant type(s)
Patient

### Healthy volunteers allowed
No

### Age group
Adult

### Sex
All

### Key exclusion criteria
1. inflammatory or post-traumatic knee arthritis
2. Patients who have received CRYON or CRFA treatment in the past
3. Injection of hyaluronic acid or corticosteroid within the previous 3 months
4. Significant structural deformities affecting locomotion and knee function aside from osteoarthritis and which might cause chronic knee pain
5. Body mass index ≥40 kg/m²
6. Uncontrolled serious disease (cancer, diabetes, end-stage heart disease etc)
7. Unstable psychiatric illness
8. Coagulopathy or bleeding disorders
9. Active systemic or local infection
10. Disease-associated with reactions to cold, such as cryoglobulinemia

### Date of first enrolment
15/04/2022

### Date of final enrolment
15/10/2022

# Locations

### Countries of recruitment
Greece

**Study participating centre**
**Patras University Hospital**
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# Sponsor information

**Organisation**
General University Hospital of Patras

**ROR**
https://ror.org/03c3d1v10

# Funder(s)

**Funder type**
University/education

**Funder Name**
University of Patras

**Alternative Name(s)**

**Funding Body Type**
Private sector organisation

**Funding Body Subtype**
Universities (academic only)

**Location**
Greece

# Results and Publications

**Individual participant data (IPD) sharing plan**
The datasets generated and/or analysed during the current study will be published as a supplement to the subsequent results publication

## IPD sharing plan summary

Published as a supplement to the results publication

## Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Protocol article | | 12/04/2023 | 12/04/2023 | Yes | No |
| Participant information sheet | | | 29/03/2022 | No | Yes |
| Protocol file | | | 29/03/2022 | No | No |