

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

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## **Background**

Knee osteoarthritis (KOA) is a degenerative joint disease that primarily involves the articular cartilage and many of the surrounding periarticular tissues. In addition to damage and loss of articular cartilage, there is also remodeling of subchondral bone, osteophyte formation, ligamentous laxity, weakening of periarticular muscles, and, in some cases, synovial inflammation [1]. According to GBD 2015, approximately 85% of the burden of osteoarthritis worldwide is connected with knee OA [2] and this have shown increased prevalence, multimorbidity, and higher number of drug prescriptions [3]. While total knee arthroplasty is an effective treatment option for end-stage knee arthritis and persistent severe pain [4,5], the relatively slow progression of the disease allows for stepwise algorithmic approach using non-surgical or no-pharmacological treatment options [6,7]. Through the wide array of non-surgical treatment options, cooled radiofrequency ablation (CRFA) and cryoneurolysis (CRYON) have been proposed.

Radiofrequency ablation (RFA) is the process of thermal nerve degradation through a probe providing radiofrequency energy. CRFA uses a water supply system to internally cool the RFA probe. While the internally cooled probes operate on a temperature of 60°C, the temperature of the surrounding tissues reach 80°C, thus providing a larger lesion around the probe [8]. The procedure aims to disrupt the transmission of pain signals from the osteoarthritic knee via the genicular nerves. Traditionally, the ablation primarily involves 3 genicular nerves—superolateral (SLGN), superomedial (SMGN), and inferomedial (IMGN) and some reports also include the suprapatellar branch to vastus intermedius (SPGN) [9,10].

Cryoneurolysis is the process of applying cold temperatures (-20 to -100°C) to a peripheral nerve, leading to Wallerian degeneration and subsequent analgesia, while the nerve retains its ability to regenerate [11]. The infrapatellar branch of the saphenous nerve (IPBSN), a sensory nerve that innervates the anterior and inferior part of the knee capsule

as well as the anterior femoral cutaneous nerve (AFCN), have been used as a prime target for nerve blockade to reduce knee pain [12,13]. There is clinical evidence suggesting that both CRFA and CRYON are safe and effective procedures in the management of knee OA pain [12-17].

## **Objective**

The primary objective of our proposed randomized, double-blind, sham controlled trial is to evaluate the efficacy of CRFA or CRYON in comparison to sham surgery (SHAMS) in patients with pain associated with knee OA using the Numerical Rating Pain Scale (NRPS) at 2-, 4- 12- and 24-weeks post intervention (Trial Registry .....).

Secondary objectives will be the comparison of safety and tolerability of the two main interventions as well as the patient's clinical outcome at 12- and 24-weeks post-intervention utilizing the Knee Injury and Osteoarthritis Outcome Score (KOOS) the Oxford Knee Score (OKS) and the Patient Global Impression of Change (PGIC) 7-point scale to capture the patients feel improved following treatment.

Our main hypothesis is that a substantial relief of pain would be achieved with both techniques (CRFA and CRYON) compared to SHAMS but their efficacy would be equal.

## **Methods**

This study protocol describes the design of a parallel-group RCT that will be conducted at the Department of Orthopaedics, University Hospital of Patras, Greece. The institutional review board (IRB) of our University Hospital has approved the study (11846/05/10/2021) and written informed consent from participating patients would be obtained. The study will be conducted in accordance with all applicable laws and regulations as specified in the International Conference on Harmonization Guideline for Good Clinical Practice and the Declaration of Helsinki.

Approximately 400 patients with symptomatic knee OA visit our 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 to our 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 50% reduction of their pain (as it is measured in the NRPS). Eligible patients will then randomize 2:2:1 to either CRFA, CRYON or SHAMS in respect. This will allow us 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.

#### *Inclusion criteria*

Patients of either sex will participate in the clinical trial as long as they have:

- (1) the NICE clinical criteria [18] of primary knee OA for one or both knees [(a) age > 45; (b) activity-related joint pain and (c) no morning joint stiffness or morning stiffness that lasts no longer than 30 minutes].
- (2) Radiological confirmation of knee arthritis (grade  $\geq 2$ ) according to the Kellgren and Lawrence classification [19].
- (3) Chronic knee pain for a minimum duration of 6 months.
- (4) Pain intensity  $\geq 4$  on the (NRPS).
- (5) A decrease of  $\geq 50\%$  in NRPS scores with diagnostic genicular nerve block.
- (6) The ability to communicate in Greek.

#### *Exclusion criteria*

Patients who belong to any of the following groups will be excluded:

- (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  $\geq 40 \text{ kg/m}^2$ .
- (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

#### *Initial assessment*

In this baseline assessment the medical history of the patient will be noted (age, gender, body mass index, duration of pain, comorbidities, use of analgesics, prior interventions in the knee joint). Radiological classification will be performed, as well as clinical evaluation of the knee OA using the OKS and KOOS, as well as the NRPS. Patients who fulfill the inclusion criteria and have no exclusion criteria will be then informed about the clinical trial in detail and a consent form will be signed in order to proceed.

#### *Technique of diagnostic block*

The procedure will be performed after the initial assessment, under sterile conditions. Patient will be placed in the supine position with a bolster under the knee (knee flexed in 30 degrees). The target of the block will be the 3 main genicular nerves; superior medial (SMGN), superior lateral (SLGN) and inferior medial (IMGN) as well as the suprapatellar branch (SPGN). The 3 main nerves will be targeted with the use of ultrasound, using the genicular arteries as landmarks [20] whereas the SPMN will be located with the ultrasound at the midportion of the femur and quadriceps tendon, approximately 5 cm above the superior patella pole [10]. Then, a nerve stimulator will be advanced at the targeted position and a low intensity current (2 Hz up to 1–2 V) will be used to locate the genicular nerves. Nerve structures can be distinguished by its hypoechoic nerve fascicles among the hyperechoic epineurium forming a honeycomb-like structure in short-axis view. Injection of lidocaine follows and the procedure is repeated for the other three nerves.

The patient will be monitored for one hour and a NRPS will be measured for a second time. Patients with a reduction of pain (> 50%) will proceed to the next phase, whereas patients who experience no change in perceived pain will be excluded from the clinical trial.

#### *Randomization*

Patients with an initial positive response ( $> 50\%$  reduction in NRPS) to the diagnostic nerve injection will be then randomized using a number list generated by specific software. The number will arrive to the operation theatre in a sealed and opaque envelope, assigning each patient with a positive diagnostic block into one of the three groups: SHAMS group, CRFA group and 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. Researchers, personnel involved in the clinical trial, statistician and participants will be blinded to the patient allocation. The number will be sealed and transferred to the operation theatre by an external investigator, who will not take part in the clinical trial. Unblinding will only be performed in case of adverse effects directly related to the study and will be stated along with the results of the trial.

### *Surgical Treatment*

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 3<sup>rd</sup> 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 [10, 20-22]. The technique deployed to spot the genicular nerves and perform accurate ablation is the one presented by Lash et al [21]. 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 [10].

*i. 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.

*ii. CRYON technique*

The cryoneurolysis probe (ICEseed 1.5, Galil Medical Ltd.) is inserted in proximity of the four target nerves, guided by ultrasound visualization as already has been described. Our study differs from that of Radnovich et al [12] 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 is used.

*iii. 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 at 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.

### *Medications*

Patients will discontinue all pain medications, supplements, chondroprotective drugs and other alternative therapies for knee OA for a duration of 10 days prior to the screening/baseline visit. During follow-up, patients were prohibited from undergoing any other adjunctive treatment for knee OA, including steroid injections, viscosupplementation, and pain medications other than paracetamol (max 2 g/day) and etoricoxib 90mg/daily for rescue medication. Use of prohibited medications treatments will be recorded as a protocol deviation and patients will allowed to continue in the study until the 3<sup>rd</sup> month.

### *Patient assessment*

Patients will be assessed at baseline, 2 weeks, 1 month, 3 months and 6 months post intervention (Table 1). Clinical evaluation will include NPRS, KOOS, and OKS. Patients will be asked about what intervention they believe was performed. Also, the Patient Global Impression of Change (PGIC) [23] will assess the extent to which the patients feel improved following treatment on a 7-point scale; PGIC responders are the patients who indicated that they were either “very much improved” or “much improved” at each follow-up assessment. Expected side effects and complications (e.g., bruising, swelling, numbness, inflammation and/or erythema) involving the percutaneous access to the nerves and the use of local anesthesia will be assessed at each follow-up visit and documented independently except for loss of motor function outside the treatment area.

### **Statistical design and power analysis**

According to the protocol, the patients will be randomly assigned to 3 groups, and they will all be evaluated (with NPRS and other scores) 4 more times, after the baseline assessment (15 days, 1 month, 3 months, and 6 months post intervention). The objective will be to examine possible diversity in NPRS improvement among patients of different groups. The regular statistical approach to do this is to perform repeated measures ANOVA (rmANOVA), taking as given that all ANOVA assumptions are met (e.g., normality of scores, etc.). Thus, a statistical power analysis for an rmANOVA procedure is as follows:

we a priori assume a number of groups equal to 3 and a number of measurements equal to 4. More specifically, the PNRS score is expected to reduce in 2 groups (CRYON & CRFA) approximately 50% more, relatively to the 3<sup>rd</sup> (SHAMS) group. This fact, according to Cohen [24], denotes a large effect size of  $f$  approximately equal to 0.75. Statistical significance is as usually considered at the 5% level, and the power analysis curve for rmANOVA is demonstrated in Figure 1. This figure illustrates that approximately 30 patients suffice for an achieved power of 80% using rmANOVA, and taking into account a large effect size, as expected. It is proposed by the protocol that an analogy of 2:2:1 of patients allocated to the 3 groups of study is the most proper approach. Thus, a 12:12:6 allocation can be considered as the exact allocation of the patients that suffice for a statistical power of 80%, assuming a large effect size. As for 90% statistical power, the equivalent numbers are 45 patients (18:18:9 true analogy). Finally, even if we consider a medium effect size, which is a relaxation in our assumptions, in order to achieve 80% statistical power, the requested sample size is 60 (i.e., true analogy 24:24:12) which is the one that we intend to use in our study.

Another statistical approach for the study is to evaluate all the follow-up (post intervention) measurements separately against the baseline. This may happen in two possible ways: one with the use of an ANCOVA procedure, the other with the use of ANOVA on the difference of the scores (follow-up minus the baseline). As Borm et al [25] suggests, the ANCOVA approach requires a significantly smaller number of subjects, reduced by a multiplicative factor that depends on the correlation estimate between the prior score and the posterior score, which is usually high. More specifically, a significance level of 5% along with a power of 80% are achieved with 24-45 patients in total, when the correlation estimates between the a priori and the a posteriori score is about 80%-90%, which is a realistic approach.

Statistical power analysis was held with the R language and the RStudio IDE, two well-known open-source products. In specific, the library “WebPower” was utilized in order to obtain the sample sizes that are the minimal ones to ensure 80% statistical power in the 5% significance level using repeated measures ANOVA, which is the main proposed approach (with ANCOVA being the secondary one, also yielding to similar sample sizes).



## Discussion

Knee osteoarthritis is a common disease, yet currently proposed conservative treatments have unsatisfactory overall efficacy and have been linked with elevated risk of complications [7, 26-28]. This has promoted the need of effective non-pharmacological therapies to control chronic arthritic pain [29-32]. In this setting, new techniques like CRFA and CRYON have been developed, aiming in nerve blockage to improve pain and disability produced by knee OA [12,33].

Radnovich et al [12] in their multicenter, randomized, double-blind, sham-controlled trial demonstrated that cryoneurolysis of the IPBSN resulted in statistically significant decreased knee pain and improved symptoms compared to sham treatment for up to 150 days, while appeared a safe and well tolerated intervention. Mihalko et al [17], in a single-center RCT study, assumed that preoperative cryoneurolysis of the superficial genicular nerves (IPBSN and AFCN) in patients with osteoarthritis would decrease postoperative opioid use relative to standard of care (SOC) treatment in patients undergoing TKA; compared with the SOC group, the cryoneurolysis group had improved functional scores and numerical improvements in pain scores across all follow-up assessments, with significant improvements observed in current pain from baseline to the 72-hour and 2-week follow-up assessments. Finally, Nygaard et al [13] presented recently a study protocol of a two-arm, parallel-group RCT, where 94 patients will randomly allocate to a cryoneurolysis intervention group + standardized education and exercise or a sham group + standardized education and exercise. The target nerves would be the IPBSN and the anterior femoral cutaneous nerve (AFCN) and the primary outcome the change of the NPRS at 2 weeks. In our study the CRYON group will be treated in a same manner to CRFA group whereas 4 genicular nerves will be targeted [10].

In contrast to cryoneurolysis treatment, where the literature is scarce, the method of radiofrequency ablation for the treatment of symptomatic knee pain in osteoarthritic knees has been well documented in the past. In a cross-sectional survey, McCormick et al [34] demonstrated a success rate of 35% based on a robust combination of outcome measures, and 19% of procedures resulted in complete relief of pain at a minimum of six months of follow-up using the CRFA technique. They also demonstrated that 80% or greater relief

from diagnostic blocks and duration of pain of less than five years are associated with high accuracy in predicting treatment success. Davis et al [16] in their prospective, multicenter, randomized, cross-over trial investigated the analgesic effect of CRFA in patients with knee osteoarthritis 12 months postintervention and its ability to provide pain relief in patients who experienced unsatisfactory effects of intraarticular steroid injection. They demonstrated that at 12 months, 65% of the original CRFA group had pain reduction  $\geq 50\%$  and the mean overall drop was 4.3 points ( $p < 0.0001$ ) on the numeric rating scale, while 75% reported 'improved' effects. Hunter et al [35] performed an extended evaluation of the patients enrolled in the study of Davis et al [16] at 18- and 24-months post-intervention showing a perceived positive effect with a mean NPRS score of  $3.1 \pm 2.7$ , and  $3.6 \pm 2.8$ , in respect. In another multicenter, randomized clinical trial, Chen et al [15] compared the effectiveness of CRFA and a single injection of hyaluronic acid for the treatment of chronic knee pain; at 12-months, 65.2% of subjects in the CRFA cohort reported  $\geq 50\%$  pain relief from baseline with a mean NPRS of  $2.8 \pm 2.4$  (baseline  $6.9 \pm 0.8$ ). Subjects in the CRFA cohort saw also a 46.2% improvement in total WOMAC score at the 12-month timepoint. Carlone et al [36] in a recent retrospective review of 176 patients who underwent genicular nerve ablation or block or both found that 31.8% of the participants failed to respond to the block procedure, mainly due to the associated psychological comorbidities, smoking history, and diabetes. They also demonstrated that of the subjects that proceeded to genicular nerve ablation, 53.7% reported less than 50% pain relief, and 46.3% reported pain relief greater than or equal to 50% at the first follow-up visit.

Two recent systematic reviews have demonstrated promising results for the treatment of severe chronic knee pain by radiofrequency ablation with minimal complications. Gupta et al [37] reported positive patient outcomes on 17 studies (5 RCT) but the inconsistent procedural methodology, inconsistent patient assessment measures, and small study sizes averted according to the authors the applicability of any specific method to clinical practice. In contrast, Ajrawat et al [33] in their systematic review of 33 studies (13 RCTs) with 1,512 participants (mean age, 64.3 years, 32.5% males) found that in all studies (33/33) the OA-related knee pain was alleviated from baseline until three to 12 months with RF modalities, with six comparative studies reporting 194/296 (65.5%) and 29/150 (19.3%) RF and control patients achieving  $>50\%$  pain relief, respectively.

It is obvious that there is an increasing body of evidence showing the effectiveness of CRFA and cryoneurolysis as treatment modalities for the osteoarthritic knee. Both techniques will be tested at a same manner in our study to investigate their capacity to control the pain and disability in a short time period of 6 months, while we will have the opportunity to record complication rates and failures. Patients included in the SHAMS group will have the opportunity to receive appropriate treatment after the 6-month period if their symptoms persist.

These treatment options may prove to be a significant aid for patients with knee OA that is not end stage and for patients in waiting lists for surgery. Safety could also prove to be favorable, as pharmacological treatments are linked to complications.

### **Strengths and limitations**

This is a blinded randomized control sham trial, with a follow up of 6 months. Effort is given to minimize the strong impact of placebo effect by having a sham group. While the sham group will receive similar sensory input to the groups receiving CRYON or CRFA, some degree of attrition bias may occur, mainly due to patients from the sham group seeking medical treatment elsewhere. Technical limitations also exist, as the effectiveness of these treatments highly rely on accurately spotting the genicular nerves. The extend of the nerve damage and its capacity to regenerate also depend on parameters that cannot be fully controlled in this clinical trial.

### **Conclusions**

### **Legends**

**Figure 1.** Diagram of the proposed power analysis for the 3 groups in 4 different assessment points using rmANOVA.

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