

STUDY PROTOCOL

Classic vs New Anatomical Targets for Cooled Radiofrequency Ablation of the Genicular Nerves in the Symptomatic Management of Knee Osteoarthritis: A Prospective, Randomized, Double-Blind Clinical Trial

Background

Osteoarthritis (OA) is a degenerative joint disease involving the cartilage and many of its surrounding tissues. In addition to damage and loss of articular cartilage, there is remodeling of subarticular bone, osteophyte formation, ligamentous laxity, weakening of periarticular muscles, and, in some cases, synovial inflammation [1]. While total knee arthroplasty is an effective treatment option for end-stage knee arthritis and persistent severe pain [2], the relatively slow progression of the disease allows for stepwise algorithmic approach in management using non-surgical treatment options [3]. Through the wide array of non-surgical treatment options cooled radiofrequency ablation has been proposed.

Radiofrequency ablation (RFA) is the process of thermal nerve degradation through a probe providing radiofrequency energy [4]. Cooled radiofrequency ablation (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 [5]. The procedure aims to disrupt the transmission of pain signals from the osteoarthritic knee via the genicular nerves.

The classical anatomical targets [6] involve three genicular nerves: (a) the superior lateral genicular (SLGN) – at the confluence of the femoral shaft and the lateral femoral condyle in the AP view and the midpoint of the femur width in the lateral view; (b) the superior medial genicular (SMGN) - at the confluence of the femoral shaft and the medial femoral condyle in the AP view and the midpoint of the femur width in the lateral view; (c) the inferior medial genicular (IMGN) - at the concave transition between the tibial plateau and adjacent metadiaphyseal shaft in the AP view and at the midpoint of the tibia shaft in the lateral view; an additional proposed target (d) is the medial retinacular genicular nerve from vastus intermedius (MRGN) – at the middle of the AP distance of the femur, 3–4 cm above the superior pole of the patella.

Fonkoue et al. [7] has proposed two new anatomical targets: for the SLGN more distal (closer to lateral epicondyle) in the AP view and laterally in the area connecting the posterior cortex of the femur shaft and the superior edge of the lateral condyle and for the SMGN more distal and closer to adductor tubercle (AT) in the AP view and just few millimeters anterior to the AT in the lateral view. Also, safe fluoroscopic ablation of the infrapatellar branch of the saphenous nerve (IPBSN) and the recurrent fibular nerve (RFN) have been proposed recently by Beckwith et al [8] and Sperry et al [9] in respect.

Objective

The primary objective of our proposed randomized trial is to evaluate the efficacy of CRFA at 1-3- and 6-months post-intervention in patients with painful KOA using the Numerical Rating Pain Scale (NRPS). Three groups of patients would be investigated: group CRFA⁴ = classical anatomical targets (4 nerves), group CRFA⁶ = revised and classical anatomical targets (6 nerves) and group CRFA⁸ = Additional (IPBSN & RFN), Revised and Classical anatomical targets (8 nerves).

The secondary objectives are the comparison of safety and tolerability of the interventions, as well as the patient's clinical outcome at 3- and 6-months post-intervention, using the Knee Injury and Osteoarthritis Outcome Score for Joint Replacement (KOOS-JR), the Oxford Knee Score (OKS), the SF-12 and the Forgotten Joint Score (FJS).

Hypothesis

The hypothesis is that groups CRFA⁶ and CRFA⁸ would express greater pain reduction and better PROMs than the classical CRFA⁴ group as more nerve targets would be ablated. Also, there may be a significant difference between groups CRFA⁶ and CRFA⁸.

Methods and analysis

Approximately 300 patients visit our clinic with diagnosed symptomatic KOA each year. A small percentage has end stage disease that needs total knee replacement. Most of the remaining patients require conservative measures to control their symptoms and from those patients a respectable percentage has not been able to respond to oral medications, injections (hyaluronic acid, corticosteroids and PRPs), physiotherapy and loss of weight. This will be the pool of patients that will participate to our randomized trial. All of the participants will receive a well-known and established symptomatic treatment (classical cooled radiofrequency ablation), but some of them will receive extra targeting, thus creating three groups of patients: group CRFA⁴ = classical anatomical targets (4 nerves), group CRFA⁶ = revised and classical anatomical targets (6 nerves) and group CRFA⁸ = Additional (IPBSN & RFN), Revised and Classical anatomical targets (8 nerves). This will allow us to test whether there is a statistically important clinical benefit from the extra targets and compare the three subgroups in terms of efficacy and safety (figure 1)

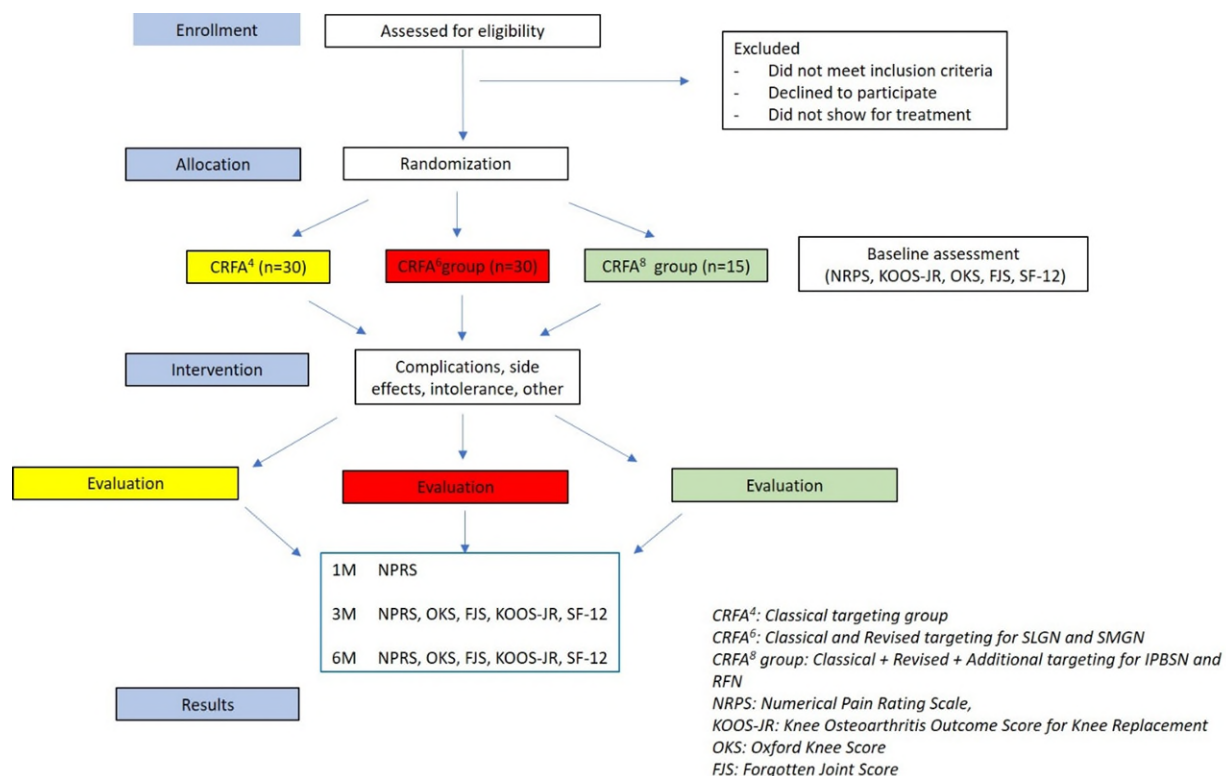


Figure 1. Enrollment of the study

Inclusion criteria

1) age between 30 and 80 years; 2) more than six months of knee pain; 3) lack of pain relief from conventional therapy, including nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, muscle relaxants, oral steroids, physical therapy, and intra-articular injection therapy; 4) numeric rating scale (NRS) pain score of 5 or greater (0 to 10, where 0 is no pain and 10 worst pain imaginable); 5) Kellgren-Lawrence knee osteoarthritis grade of 2 or greater.

Exclusion criteria

1) refusal to participate, provide consent, or provide follow-up information for the six-month duration of the study; 2) pain referral beyond the expected distribution for knee osteoarthritis; 2) focal neurologic signs or symptoms; 3) concomitant radicular pain; 4) clinically significant cognitive deficit; 5) unstable medical or psychiatric illness; 6) previous radiofrequency ablation treatment for similar symptoms; 5) history of total or partial knee arthroplasty; 7) contraindication to genicular nerve block or genicular nerve CRFA (active infection, bleeding disorders, current anticoagulant or antiplatelet medication use, allergy to medications used in the protocol, pregnancy, pacemaker).

Randomization

Most CRFA studies suggest performing a diagnostic nerve block prior to radiofrequency ablation. A reduction of pain > 50% indicates that a meaningful clinical outcome after CRFA will be obtained. McCormick et al [10] presented a prospective randomized trial on the prognostic value of genicular nerve blocking using a local anesthetic volume of 1 mL at each injection site and a threshold of $\geq 50\%$ pain relief for subsequent CRFA eligibility and they didn't find any improvement in the final rate of treatment success. Patients with symptomatic KOA and initial NPRS score > 5 will be 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 into one of the three prementioned groups. 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.

Consent form

Patients will be informed in detail about the procedure. At any point of the clinical trial they have the right to withdraw. In case of adverse effects, group allocation will be unblinded and the patient will receive treatment of the complication. Having these understood the patients who wish to take part in the clinical trial will fill a consent form in order to proceed.

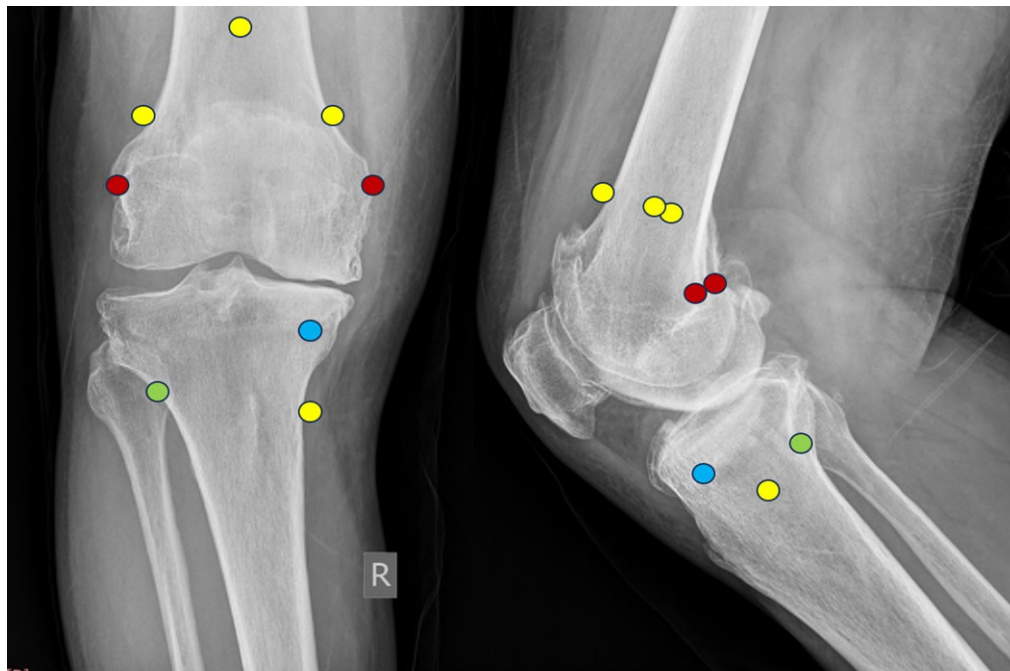
Initial assessment

The baseline assessment will include: a) the medical history of the patient (age, sex, body mass index, duration of pain, comorbidities, use of analgesics, and prior interventions of the knee joint); b) radiological classification using standing AP and lateral x-rays of the knee joint and, c) clinical assessment of the knee OA using the NPRS, the KOOS-JR, the OKS, the SF-12 and the FJS. 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.

Group allocation

Patients will be placed in the radiolucent table at the Department of Interventional Radiology in a supine position with a bolster under the knee to produce 30° of flexion; this position flattens the suprapatellar joint space, thus minimizing needle trespass, and also allows for an unobstructed lateral view of the knee. The treated knee will be draped and sterilized in a standard manner. Patients will be continuously monitored and administered conscious sedation (1–2 mg IV midazolam and/or fentanyl 25–100 mcg IV) and supplemental oxygen. Fluoroscopic images will be obtained to align the femur in an anteroposterior (AP) view in order to target the genicular nerves at locations above the femoral condyles and for the IMGN a greater caudal tilt of the fluoroscope will be obtained to square off the tibial plateau for an appropriate AP view. A sealed and opaque envelope will be brought to the operating theatre, dictating the group of each patient. The location of the nerves (SLGN, SMGN, IMGN, MRGN, IPBSN and RFN) will be identified using fluoroscopy, according to previously described methods. Two to 3 ml of 1% lidocaine is used

to anesthetize the skin and subcutaneous tissues before cannula insertion at each target site under fluoroscopic guidance. Thereafter, a 75 mm, 17-gauge introducer needle will be placed to ablate the targeted nerves. One milliliter of 2% lidocaine will be injected through the introducer needles to anesthetize the area before ablation. After placement of the introducer needle, an 18 gauge, internally cooled 4-mm active tip RFA electrode (Coolief, Halyard Health, Alpharetta, GA, USA) will be placed into the introducer needle, and the positioning is checked again using fluoroscopy. The introducer is connected to COOLIEF* Cooled RF Advanced Generator that allows staggered start, stop and adjusting of 4 independent channels. The CRFA probes will be advanced, and ablation will be performed with lesion settings at 60 °C (80–90 °C adjacent tissue temperature) for 2.5 min. As mentioned before, this type of ablation creates a spherical lesion at the tip of the probe. Cooled RF electrodes include a thermocouple at the active electrode tip to provide a temperature-controlled lesion formation. This involves water-cooling of the active electrode tip during the duration of the process without tissue charring at the electrode tip; this mechanism doubles the lesion radius and increase the lesion volume by 5 times.



GROUP CFRA⁴: classical targets ●

GROUP CFRA⁶: Revised (SLGN and SMGN ●) + classical targets ●

GROUP CFRA⁸: Additional (IPBSN ● and RFN ●) + Revised + classical targets

Patient assessment

Patients will be assessed at 1 month (NPRS), 3 and 6 months post intervention (NRPS, KOOS-JR, OKS, FJS, SF-12). Patients will be asked about what intervention they believe was performed. Possible adverse effects will be looked for.

Timepoint	Allocation	Assessment times				
	-3 w	0	1 m	3 m	6 m	
Enrollment	√					
Eligibility screening	√					
Informed consent	√					
Outcome measures						
NPRS (primary)		√	√	√	√	
KOOS-JR		√	-	√	√	
OKS		√	-	√	√	
SF-12		√		√	√	
FJS		√		√	√	
Complications		During intervention	√	√	√	

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 times, 1 baseline and 3 follow-ups (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 NPRS score is expected to reduce in 2 of the 3

groups approximately 50% more, relatively to the 3rd group. This fact, according to Cohen [11], denotes a large effect size of f approximately equal to 0.75. This 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. 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).

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).

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