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Study protocol for a randomised controlled trial of ultrasound-guided pulsed radiofrequency of the genicular nerves in the treatment of patients with osteoarthritis knee pain

Javier Mata, Pedro Valentí, Beatriz Hernández, Bartolome Mir, Jose Luis Aguilar

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Department of Anaesthesia, Son Llàtzer University Hospital, Palma de Mallorca, Spain

Correspondence to
Dr Javier Mata; jmata@hsll.es

ABSTRACT

Introduction The goals for the management of patients with osteoarthritis (OA) of the knee are to control pain and to minimise disability. Because the number of patients will increase as the population ages, alternative approaches to alleviate their joint pain other than conventional treatments are necessary. The purpose of this article is to present a refined protocol to determine if there is long-term improvement in pain and function after ultrasound-guided pulsed radiofrequency treatment of the genicular nerves (GNs) in patients with chronic painful knee OA.

Methods and analysis This study is a randomised, double-blind, placebo-controlled, parallel design trial. One hundred and forty-two outpatients with OA of the knee will be recruited from Mallorca, Spain. Participants will be randomly allocated into two groups: ultrasound-guided sham GN pulsed radiofrequency without active treatment and ultrasound-guided real GN pulsed radiofrequency. The primary outcome measures will be the observed changes from baseline pain intensity based on visual analogue scale (VAS). The possible changes in the secondary efficacy variables from the baseline as assessed by the Goldberg Anxiety and Depression Scale, pain medication use, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC subscales) and VAS pain intensity are also to be included in the study. These variables will be assessed at baseline, 1 month, 3 months, 6 months and 1 year after treatment.

Ethics and dissemination The protocol was approved by the Research Ethic Committee of the Balearic Islands (IB 3223/16 PI). The results will be disseminated in peer-reviewed journals and at scientific conferences.

Trial registration Trial registration numberNCT02915120; Pre-results

Strengths and limitations of this study

- Central randomisation and blinded assessment will be used.
- This is a single-centre clinical trial.
- The study design favours patients that respond to the treatment (double diagnostic nerve blocks positive to the inclusion) and exclude patients that experience placebo effects or can be resistant to the treatment (double diagnostic nerve blocks negative to the inclusion).
- Loss to follow-up is possible, particularly those participants who do not respond to treatment. Recruitment period and duration of the study may have to be extended to ensure results of data analysis.
- This study is a randomised, double-blind, placebo-controlled, parallel design trial with large sample size, a long-term follow-up and checklists for gathering information about adverse effects.

INTRODUCTION

Osteoarthritis (OA) of the knee is one of the main causes of disability. Population-based studies revealed that symptomatic knee OA is present in 20%–30% of the elderly population aged >65 years, and its prevalence is increasing due in part to the ageing of the population.[1] According to the Study of Prevalence of Rheumatic Diseases in the Spanish population (EPISER study), symptomatic knee OA prevalence is estimated at 10.2% (14% of women and 5.7% of men) in Spain. The prevalence of radiographic findings of knee OA is increased from 60% among those aged 65 years to 80% among those over 75 years of age.[2]

The goals of management of patients are to control pain and to minimise disability. Evidence-based guidelines from National Institute of Health and Clinical Excellence[3] and Osteoarthritis Research International (OARSI)[4] suggest that the treatment should be multidisciplinary. Optimal management requires a combination of non-pharmacological (changes in lifestyle, pacing of activities, weight reduction, regular aerobic exercise, acupuncture, muscle strengthening and range of motion exercises) and pharmacological modalities when additional treatment is required. Total knee

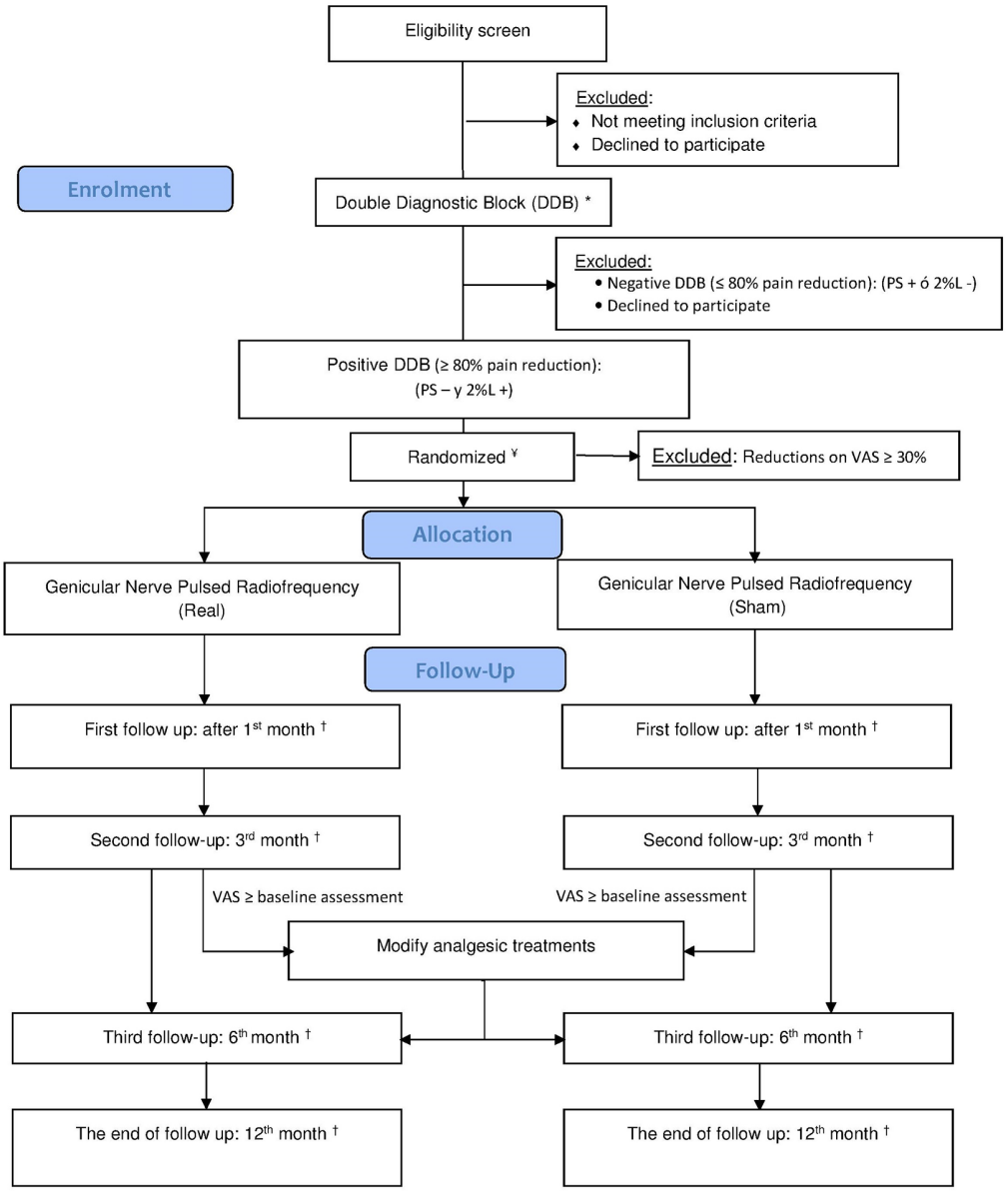

Figure 1 Trial flow. The study trial flow is described, indicating the patient selection process, treatment, and follow-up. †Visual analogue scale, Western Ontario and McMaster Universities Osteoarthritis Index, Goldberg Anxiety and Depression Scale, and medication use are measured on each follow-up visit. VAS, Visual analogue scale. ¥Reductions on VAS scale ≥30% from baseline levels excluded in the Pulsed Radio frequency procedures. *Double Diagnostic Block (DDB): randomised to physiological Saline (PS) or 2% Lidocaine (2%L). First block with PS (+) or 2%L (–), excluded. Second block with 2%L (–) or PS (+), excluded. 3rd month follow-up VAS ≥ baseline assessment, modifies analgesic treatments.

arthroplasty should be considered for patients with significant symptoms and/or functional limitations associated with a reduced health-related quality of life, despite conservative therapy. However, there are some fragile patients who are at high risk during surgery and other patients who are not willing to undergo surgery. Because the number of patients will increase as the population ages, alternative approaches to alleviate their joint pain other than conventional treatments are necessary. Recently, GN ablation with conventional radiofrequency (CoRF) has been used in the management of OA-related knee pain.[5] The tissue is heated grossly by electrical energy dissipation, and it is the tissue heating that leads to localised destruction of the neural tissue and consequent interruption of neural signalling. A variation of CoRF, pulsed radiofrequency (PRF) is often effective without raising the average target tissue temperature above 42°C, which has been traditionally been thought to be below the irreversible tissue destruction threshold (ie, the heat-lesion threshold) of 45°C–50°C.[6] Radiofrequency (RF) treatments on the knee joint have the potential to reduce pain from OA.[7]

As opposed to the traditional approach under fluoroscopy, ultrasound allowed the visualisation of neurovascular bundles, soft tissue structures and, presumably, more accurate nerve identification.[8]

The recommendations for PRF as a treatment of patients with OA knee pain are debated until randomised controlled trials with long-term follow-up confirm the results of current studies.

The purpose of this study is to determine if patients with chronic painful knee OA experience meaningful and long-term improvement in pain, function and analgesic use after ultrasound-guided PRF of the GNs following a double diagnostic GN blocks.

Aims

The primary outcome will be the change from the baseline of the VAS for pain at the completion of treatment at 12 weeks. Secondary variables to be considered are the following: the change in the secondary efficacy variables from the baseline of the scores for the Goldberg Anxiety and Depression Scale (GADS), changes in pain medication use, changes in pain assessment, functional capacity and stiffness (Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscales) and visual analogue scale (VAS) pain scores measured at 1 month, 3 months, 6 months and 1 year after treatment.

Hypothesis

The primary hypothesis is that ultrasound-guided PRF of the GNs will mitigate pain and improve function as compared with placebo.

METHODS AND ANALYSIS

Study design and setting

This study proposes a randomised, double-blind, placebo-controlled, pretest and post-test, parallel design clinical trial, which conforms to the Standard Protocol Items for Randomized Trials recommendations,[9] Consolidated Standards of Reporting Trials guidelines[10] (figure 1) and OARSI Clinical Trials Recommendations.[11]

Approximately between 3000 and 4000 patients visit the Pain Unit at Son Llàtzer University Hospital each year, of which 5% are diagnosed with chronic knee pain. This means that in our clinic 150–200 patients with chronic knee pain are treated each year. To increase the amount of eligible patients for our trial, hospitals and general practitioners in our region we will be approached to help recruit potential participants. The eligibility of prospective participants will be determined by a researcher who is not involved in the assessment or treatment of the participants.

Inclusion criteria

Eligibility requirements will include the following: patients of either sex with primary OA of one or both knees fulfilling diagnostic criteria for OA knee laid down by American College of Rheumatology,[12] Kellgren-Lawrence (radiologic criterion) score of at least 2 with chronic knee pain with pain intensity of at least 4 out 10 on the VAS on most or all days for more than 3 months, resistant to conventional therapy including non-steroidal anti-inflammatory drugs, opioids, muscle relaxants, oral steroids, physical therapy and intra-articular injection. In patients with bilateral knee OA, the most painful side will be studied.

Exclusion criteria

Patients with any of the following will be excluded from the study: patients with secondary OA of knees (ie, rheumatoid arthritis or gouty arthritis); any knee treatment with steroids, methotrexate or azathioprine; previous RF ablation treatment for similar symptoms; intra-articular knee corticosteroid or hyaluronic acid injection in the past 3 months; active systemic or local infections at the site of proposed needle and electrode placement; coagulopathy or other bleeding disorder; cognitive deficit; unstable medical or psychiatric illness; or previous knee joint replacement surgery.

The use of analgesic medicine will be allowed at any time during the study.

Randomisation

Each eligible patient will be randomised twice (the randomiser will be otherwise uninvolved in the study):

- double diagnostic block. Patients will be assigned to one of two groups: 'physiological saline first block' or '2% lidocaine first block'. A random number list generated by SPSS statistical software V.18.0 (balanced for each six cases per study branch) will be used for the allocation to each group. Researchers from the statistical centre will send the randomised list in a numbered, sealed and opaque envelope to the researcher responsible for participant recruitment and group assignment: starting with a sham and ending with a positive versus starting with a positive and ending with a sham.
- RF group. Patients with a double positive response will be included in the PRF procedures. A computer-generated randomisation list will allocate patients in a 1:1 ratio to ultrasound-guided real genicular nerve pulsed radiofrequency (real GENPRF) or ultrasound-guided sham genicular nerve pulsed radiofrequency without active treatment (sham GENPRF) groups. Randomisation is stratified by OA severity using Kellgren-Lawrence grade (2 and 3 vs 4) using random blocks of size 2, 4 and 6.

Concealment of allocation

The patient codes of the double-blind study will be placed in numbered, sealed and opaque envelopes. Researchers, personnel performing the interviews, statisticians and participants will be blinded to patient allocation. The sequence generation will be prepared by a statistician, and the envelopes will be prepared by an external investigator not involved in the trial.

Blinding

All clinical assessments will be conducted by an assessor blinded to treatment allocation. Any occurrence of

unblinding of the assessor will be recorded with its reason and reported along with the trial's results. The researcher executing and supervising the treatments will be blinded to the group allocation. Group allocation will be immediately unblinded if deemed necessary by the chief investigator in the case of serious adverse events potentially related to the study.

Interventions

Study procedures are as follows (table 1).

Trial objectives will be explained, and any questions or doubts with respect to the study will be resolved to all eligible participants. Patients will be informed that they will be receiving a new technique based on RF for knee pain treatment and that they will be allocated to either active or sham treatment (with a strict 50% probability), one will be followed treatment with real PRF and the other will be followed treatment with sham PRF. The necessity of a double diagnostic block for testing the benefits for the RF treatment will be informed. Long-term benefits of treatment will be informed to control patients' expectations and to reduce drop outs. A researcher who is not involved in the assessment or treatment will obtain informed consent from the participants before undergoing any examination or study procedure and will then be assigned a unique sequentially numbered study identifier according to the order in which he or she is enrolled in the trial.

Baseline visit (first visit)

Once eligibility has been confirmed and informed consent has been obtained, a baseline assessment will be undertaken. At the baseline assessment appointment, the researcher will further explain the study and answer any questions. After clinical and radiological assessment, comorbidities, age, gender, body mass index, duration of knee OA symptoms, medication use, previous treatment and surgery for knee OA will be obtained at baseline. Neuropathic Pain Diagnostic Questionnaire, the Spanish version validated by Perez *et al*,[13] will estimate the probability of neuropathic pain (recent studies suggest that neuropathic mechanisms involved in joint pain[14]).

- Overall average knee pain intensity over the last month will be assessed by a continuous scale comprised of a horizontal line, anchored by 'no pain' (score of 0) and 'worst imaginable pain' (score of 100 (100 mm scale)). (VAS pain intensity score)
- Self-reported knee pain and difficulty with physical function will be measured using WOMAC Index (the Spanish version validated by Escobar *et al*).[15]
- Analgesic medicine use will be obtained with a questionnaire elaborated according to the European Health Interview Survey (EUROHIS) recommendations.[16] Subjects will be asked (1) about the prescription medicine their general practitioner may have prescribed for them ('Have you taken any pain medicine prescribed by your general practitioner?') as well as any medication not prescribed by their general practitioner ('Have you taken any pain medicine not prescribed by your general practitioner') and (2) whether their prescribed and non-prescribed pain medication use has increased or decreased.
- Levels of depression and anxiety will be measured with the GADS. The Spanish version validated by Montón *et al* will be used.[17]

Diagnostic block visit (second visit)

Between 7 and 10 days since baseline visit, the eligible patients will be randomised, using a computer-generated randomisation schedule, to undergo diagnostic GN block with local anaesthetic or physiological saline (figure 2). Under sterile conditions and appropriate monitoring, the patient will be placed in a supine position on a table and the knee slightly flexed with a pillow under the popliteal fossa. To find the GNs exact location, the genicular arteries are used as landmarks because they share the same trajectories as the GNs. Other important landmarks are the femoral and tibial cortical surfaces because of their close topographic relation to the genicular neurovascular bundles (figure 3). GNs consist of six branches: superior lateral (SL), superior medial (SM), middle, inferior lateral (IL), inferior medial (IM) and recurrent tibial GN. The targets in this study include the SL, SM and IM. These three branches are easily accessible by percutaneous approach. They lie on the surface of bone at the confluence of the femur with the medial and lateral epicondyles and the confluence of the tibia with the medial epicondyle. The IL genicular nerve is not target due to concerns about inadvertent injury to the common peroneal nerve that lies in close proximity at the neck of the fibula. A 10 cm long, 21-gauge needle (Stimuplex, B. Braun Medical, Bethlehem, Pennsylvania, USA) connected to nerve stimulator (0.5 mA, 0.1 ms and 2 Hz) will be advanced towards the target nerve. When needle is judged to be adequately placed by ultrasound, the current intensity (mA) will be reduced to assure no motor response present at <0.2 mA. Then 2 mL of 2% lidocaine or physiological saline will be injected, in adequate spread, in the desired tissue plane, with an injection resistance normal. The procedure will be repeated at each targeted site.

Block assessment (third visit)

A researcher calls the patient to assess the VAS pain intensity between 2 and 3 hours after procedure. Responses will be recorded as positive if the participants experience a decrease in numeric pain scores of at least 80% with 2% lidocaine or no response with physiological saline. Patients with a positive response will be given a new appointment in a week. Patients with a negative response will be excluded.

Diagnostic block visit (fourth visit)

Between 15 and 20 days since baseline visit, patients with a positive response in the first diagnostic block will be made a second diagnostic block with physiological saline

Table 1 Schedule of enrolment, interventions and assessments

	Visits									
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
	Baseline visit	First diagnostic block	First block assessment	Second diagnostic block	Second block assessment	Radiofrequency	Follow-up 1st month	Follow-up 3rd month*	Follow-up 6th month	Follow-up 12th month
(Schedule since baseline visit)	**(1st day)**	**(10th day)**	**(Phone call)**	**(20th day)**	**(Phone call)**	**(30th day)**	**(2nd month)**	**(4th month)**	**(7th month)**	**(13th month)**
Enrolment										
Patient's evaluation and collection of the relevant data	√									
Inclusion/exclusion criteria	√		√		√					
Explanation of the objectives of the procedure and how it works	√		√		√					
Informed consent	√									
Randomisation, blinding and allocation		√†				√‡				
Interventions										
Double diagnostic block		√		√						
Genicular nerve pulsed radiofrequency real						√				
Genicular nerve pulsed radiofrequency sham						√				
Assessments										
Visual analogue scale (VAS) pain intensity	√		√		√	√	√	√	√	√
McMaster Universities Osteoarthritis Index	√						√	√	√	√
Medication use	√						√	√	√	√
Goldberg Anxiety and Depression Scale	√						√	√	√	√
Adverse event			√		√	√	√	√	√	√
Outcome assessment										√
Reasons of drop-outs or withdrawals							√	√	√	√
Satisfaction and expectations Survey										√

*Third-month follow-up VAS pain intensity≥baseline assessment modifies analgesic treatments.
†Double diagnostic block: randomised to physiological saline (PS) or 2% lidocaine (2% L). First block with PS (+) or 2% L (–), excluded. Second block with 2% L (–) or PS (+), excluded.
‡Patients with a significant reduction in VAS pain scores from baseline levels (reductions on VAS scale ≥30%) will be excluded in the pulsed radiofrequency procedures.

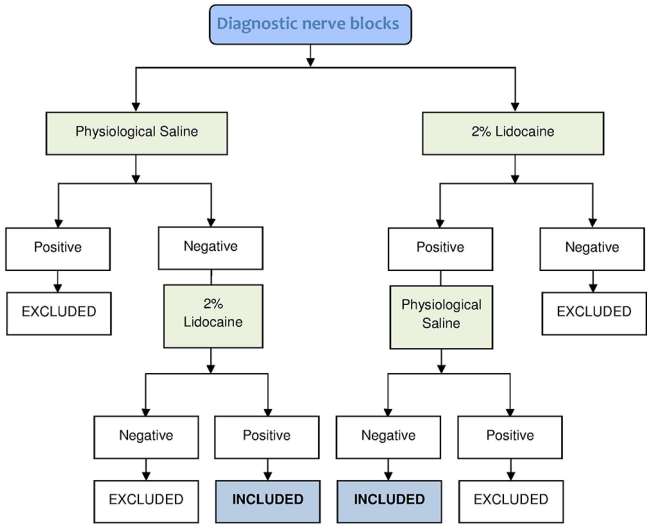

Figure 2 Flow chart showing progression in diagnostic nerve blocks.

if they received 2% lidocaine in the first block or 2% lidocaine if they received physiological saline. This second diagnostic block will be undergone the same procedure.

Block assessment (fifth visit)

Same assessment protocol as after the first diagnostic block. Patients with a double positive response will be included in the PRF procedures.

RF visit (sixth visit)

One month since the baseline visit, the patient will be reviewed. First of all, the interviewers will repeat the assessments for pain level. Patients with a significant reduction in VAS pain scores from baseline levels (reductions on VAS scale of at least 30% reduction to be moderately clinically meaningful[18]) will be excluded in the PRF procedures.

Patients included will be randomly assigned again to receive sham GENPRF (sham GENPRF group, n=71) or real GENPRF (real GENPRF group, n=71) using another computer-generated randomisation schedule. The randomisation sequence will be concealed throughout the study from both the study patients and the investigator who will be an independent physician from the outpatient pain clinic.

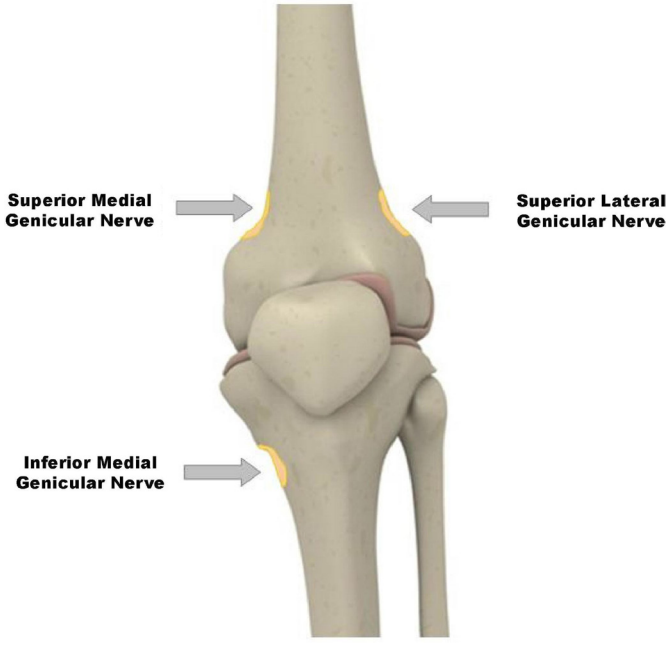

Figure 3 Genicular nerves location.

Real RF group

Under sterile conditions and appropriate monitoring, the patient will be placed in a supine position on a table and the knee slightly flexed with a pillow under the popliteal fossa. Skin and soft tissues will be anaesthetised with 1 mL 2% lidocaine. Before needle insertion, the patient's IM, SM and SL GN branches will be identified under ultrasound guidance. RF needles and probes will be advanced to each of the target nerves under ultrasound guidance. A 10 cm 22-gauge RF cannula with a 10 mm active tip RF (Model SL-S1010-22, NeuroTherm, Croydon Surrey, UK) will be employed for the technique. A 50 Hz frequency sensorial stimulation will be applied with a threshold of <0.5 mA to identify the nerve position, the current intensity (mA) will be reduced at <0.2 mA. During the sensorial stimulation, the patients will be asked if they feel tingling, pain or discomfort inside the knee. The RF probe will be maintained in place until one of those feelings is elicited. In order to avoid inactivating motor nerves, the nerve will be tested for the absence of fasciculation in the corresponding area of the lower extremity on stimulation of 0.5 mA at 2 Hz. with an impedance value between 300 and 700 ohms, when needle is judged to be adequately placed by ultrasound, the current intensity (mA) will be reduced at <0.2 mA. Lidocaine (1 mL of 2%) will be injected before activation of the RF generator (Neurotherm NT1000 radiofrequency generator, NeuroTherm). The RF electrode will be then inserted through the cannula, and RF lesions will be generated by applying PRF treatment (current of 2 Hz at 40 volts with 20 ms active and 480 ms silent periods) to the IM, SM and SL GN branches for 8 min each GN branch, whereby the temperature was below 42°C.[19]

Sham RF group

Control patients will undergo the same procedure. The sensorial and motor stimulations will be applied too. RF lesions will be simulated without applying pulsed RF treatment to the IM, SM and SL GN branches for 8 min each GN branch and the temperature of the electrode tip was not raised.

First, 3rd and 6th month visit since RF (7th, 8th and 9th visit)

Two, 4 and 7 months since baseline, the assessments for pain level, analgesic consumption, WOMAC scale, adverse events and the GADS will be repeated. The interviewers

will also note RF-related adverse effects or complications observed either by the participants or by the interviewers.

The type of treatment that the patient believes he or she is receiving (blinding test) will be asked in the first appointment after RF (seventh visit). If 3rd month follow-up, since RF, VAS pain intensity≥baseline assessment, the analgesic treatments will be modified.

Twelfth month visit since RF (10th visit)

Thirteen months since baseline, at study completion, questions related to patient satisfaction with the treatment received, and their expectations for improvement will also be included in the questionnaires.

Outcomes

The primary outcome measures will be the change from the baseline of the VAS for pain at the completion of treatment at 12 weeks.

Secondary variables to be considered are the following: the change in the secondary efficacy variables from the baseline of the scores for the GADS, changes in pain medication use, changes in pain assessment, functional capacity and stiffness (WOMAC subscales) and VAS pain scores measured at 1 month, 3 months, 6 months and 1 year after treatment.

Adverse events

Any adverse events will be monitored and reported by researchers at each visit since double diagnostic block. All expected and unexpected adverse events potentially related to the study will be monitored, and their progress will be recorded until resolution. The physicians will decide whether trial participation should be discontinued or not based on these reports.

Sample size

A total of 142 patients will be necessary (71 subjects for each treatment group) to detect differences between groups of at least 30% in the pain perception assessment according to VAS pain intensity (scale of 0–100 mm). Accepted values will be for an alpha risk of 0.05 and beta risk of less than 0.2 in a bilateral contrast as well as a value of 2.5 for the SD (size effect of 0.75).[18] It is assumed that 20% of the trial patients will be lost to attrition. Patients will be included in the study by case-consecutive, non-probability sampling after responding to a recruitment visit to the Pain Clinic, then if they sign an informed consent form, they will be allocated randomly into one of the treatment groups.[20]

Statistical analysis

Analysis population

The primary analysis will be conducted on all outcome data obtained from all participants as randomised and regardless of protocol adherence, that is, intention-to-treat analysis.

Continuous normally distributed variables will be presented by their mean and SD, or as medians and their IQR, if not normally distributed. Categorical variables will be expressed as counts (n) and percentages (%). Intergroup comparisons at baseline will be examined using independent samples t-test or Mann-Whitney U test (continuous variables) and χ^2 or Fisher's exact test (categorical variables). Intragroup differences (between baseline and 3 months; between baseline and 1 year) will be analysed using paired samples t-test or Wilcoxon signed rank paired test (continuous variables) and McNemar test (dichotomised variables). Intergroup comparisons at 3 months and at 1 year will be evaluated using analysis of covariance and Fisher's exact test after adjusting changes in categorical and continuous variables for baseline values. The relationship between each possible predictor variables at baseline and VAS change at 3 months and at 1 year will be assessed by Pearson/Spearman (continuous data) and point-biserial (dichotomic data) correlation coefficients. Baseline predictors of VAS reduction at 3 months and at 1 year will be identified with multiple linear regression models. Analysis will be performed using stepwise and backward method for all models.

An interim analysis will be performed on the primary endpoint when 100% of patients have been randomised and have completed the 3-month follow-up. The interim analysis will be performed by an independent statistician, blinded for the treatment allocation. The statistician will report to the Research Ethic Committee of the Balearic Islands (RECIB). The RECIB will have unblinded access to all data.

A two-tailed p value <0.0294 will be considered statistically significant after adjusting according Pocock's method[21] for interim analysis. Statistical analyses will be performed using SPSS V.18.0.

Data collection, management and monitoring

The data will be collected by means of a case report form (CRF) specially designed for the study written by the researchers and outcome assessors and then will be entered into electronic database hosted at the Son Llàtzer University Hospital on the research computer server. Any paper study records will be kept in locked storage cabinets. All electronic participant study records will be stored in the password-protected computer study database accessible to the researchers only.

Entry and coding of clinical data and data management and reporting will be conducted by the clinical data manager. In accordance with European Legislation, all the documentation should be retained for at least 25 years after completion or discontinuation of the trial, as per the new Clinical Trials Regulation EU N° 536/2016.

This study will be monitored by the Research Ethic Committee of the Balearic Islands. During the study period, the clinical research associate will monitor written informed consent documents, recruitment status, protocol compliance and overall trial progress, data quality, timeliness of data collection, treatment administration and other relevant trial aspects and processes.

DISCUSSION

The effect of GN ultrasound-guided PRF treatment of OA knee pain, selected after repeated diagnostic blocks, will be investigated in this study. Effectiveness indicators should be the relief of pain, stiffness and functional disability of the knee and a reduction in medication use.

RF is a type of alternate current that creates heating the target tissues by providing friction between the molecules; thus, a thermal lesion is formed by the heat generated from this current.[22] RF has been used to treat a variety of pain conditions such as trigeminal neuralgia, cervicogenic headaches and spinal pain.[23–25]

Choi *et al* described fluoroscopically guided CoRF neurotomy of the sensory nerves (GNs) supplying the knee joint. The findings of the study showed that there was a significant improvement in pain and satisfaction in the RF treatment group.[5] The GNs are sensory branches of the tibial, common peroneal and obturator nerves. They provide innervation to the capsule of the knee joint, as well as to the intra-articular and extra-articular ligaments.[26]

A recent anatomic studies in cadavers on innervation of the knee[8 27] supports the methodology used by Choi *et al*,[5] who targeted IM, SM and nerves on the SL aspect of the knee joint accompanying genicular vessels because of their proximity to bony structures (junction of the metaphyseal and epiphysial parts of the femur and tibia). The IL genicular nerve is not targeted due to concerns about inadvertent injury to the common peroneal nerve that lies in close proximity at the neck of the fibula.

Use of prognostic nerve blocks at the site of pain generators has generated debate in the interventional pain community.[28] Pain arising from the knee joint is often complex. Nerve blocks with local anaesthetics are frequently used to confirm a joint as the primary pain generator, in predicting the success of RF treatments. A threshold of 80% reduction in pain after diagnostic GN block with 2% lidocaine is used. This protocol is more stringent than that which has been previously reported by Choi *et al*. Eighty per cent or greater relief from diagnostic blocks is associated with high accuracy in predicting treatment success.[29]

Controlled blocks are recommended because of a 25%–41% false-positive response when using only single blocks.[30] It is logical to suggest that ablative RF treatments should be preceded by nerve blocks with local anaesthetics to better prognosticate the likelihood of success and to allow patients to experience temporarily a partly denervated knee joint, but there is no evidence-based algorithm established that provides a means of properly selecting which patients would benefit from genicular nerve RF. The general consensus is to start by diagnostic blocks.

A variation of CoRF, PRF is the technique whereby RF oscillations are gated at a rate of pulses per second (cycles per second, defined as a hertz (Hz)). Current of 2 Hz means two cycles per second (with 20 ms active and 480 ms silent periods per cycle). PRF uses RF current in short (20 ms), high-voltage bursts (with amplitude of 45 V); the 'silent' phase (480 ms) of PRF allows time for heat elimination, generally keeping the target tissue below 42°C: the signal amplitude (volt) or the pulse duration are often modified. PRF also appears to be a relatively safe procedure. Unlike CoRF, which is associated with neuritis-like reactions, motor deficits and the risk of deafferentation pain, PRF seems to have few side effects.

The use of ultrasound-guided GN block offers advantages over fluoroscopically guided techniques: the excellent soft tissue imaging, which enables the use of soft tissue structure as landmarks other than bony landmarks, and the visualisation of neurovascular bundles and identification of the nerves are the most important ones beyond the advantage of no ionising radiation.[8]

PRF has been performed in the above-mentioned CoRF applications, in peripheral joints and in other neuropathic syndromes. Pulsed RF appears to have genuine biological effects in cell morphology, synaptic transmission and pain signalling, which are likely to be temperature independent.[31–33]

The use of PRF to treat mechanical pain is controversial because there are no controlled clinical trials demonstrating efficacy. The long-term effects of PRF on periarticular nerves have not been studied, but the publications on PRF treatments of major nerves for knee pain reported significant analgesic benefit at 10 days–6 months following the interventions.[20 34 35]

To the best of our knowledge, the study of Kesikburun *et al*,[36] a preliminary report, is the first study of ultrasound-guided genicular nerve PRF treatment in patients with OA-related knee pain. The number of participants was limited, the lack of a control group (no double-blind controlled study) and the fact that long-term effect of pulsed RF treatment was not evaluated are limiting factors of this study.

To conclude clinical recommendations for ultrasound-guided PRF as a treatment for severe knee OA should not be written until high-quality (randomised controlled) clinical studies confirm the results and address the safety aspects. In this article, we combine all of the methodological suggestions, attempting to minimise the biases that may result from study design: the number of patients recruited is sufficient to achieve the significant differences, treatment number, long-term treatment, blinding method (from recruitment), patient perception assessment of the type of technique used before and after treatment, the objective and subjective assessment of the technique and sham without applying PRF treatment.

The purpose of this study is to determine if patients with chronic painful knee OA experience meaningful and long-term improvement in pain, function and analgesic use after ultrasound-guided PRF of the GNs following a double diagnostic GN blocks (2% lidocaine and physiological saline solution).

Trial status

The trial is currently in the recruitment phase. Participant recruitment is started in March 2017 and expected to end in December 2017.

Ethics and dissemination

All of the participants will be recruited through voluntary participation, and written informed consent forms from all trial participants will be obtained by researchers in accordance with the Declaration of Helsinki.[37] Trial participation may be terminated during the trial at any time through voluntary refusal to continue or in cases of significant clinical adverse event as judged by the researchers. Participants suffering from trial-related problems or adverse events may be administered medical treatment for compensation. Modifications of the study protocols will be publicly accessible via the US National Institutes Health Clinical Trials Registry, Clinical Trials.gov. (Trial number: NCT02915120). JM and BH will conduct the data management procedures. JM, chief investigator of the study, will have access to the final trial dataset and will be responsible for ensuring that the analysis plan will be remain consistent with the version of the protocol approved by the ethics committee. Dissemination of results will include conference presentations and publications in peer-reviewed journals. Research participants will receive a summary of the results of the completed study.

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REFERENCES

1. Leveille SG. Musculoskeletal aging. *Curr Opin Rheumatol* 2004;16:114–8.
2. Carmona L, Villaverde V, Hernández-García C, *et al*. The prevalence of rheumatoid arthritis in the general population of Spain. *Rheumatology* 2002;41:88–95.
3. Royal College of Physicians. *National Collaborating Centre for Chronic Conditions. Osteoarthritis: national clinical guideline for care and management in adults*. London: Royal College of Physicians, 2008.
4. Zhang W, Moskowitz RW, Nuki G, *et al*. OARSI recommendations for the management of hip and knee osteoarthritis, part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 2008;16:137–62.
5. Choi WJ, Hwang SJ, Song JG, *et al*. Radiofrequency treatment relieves chronic knee osteoarthritis pain: a double-blind randomized controlled trial. *Pain* 2011;152:481–7.
6. Byrd D, Mackey S. Pulsed radiofrequency for chronic pain. *Curr Pain Headache Rep* 2008;12:37–41.
7. Bhatia A, Peng P, Cohen SP. Radiofrequency procedures to relieve chronic knee pain. *Reg Anesth Pain Med* 2016;41:501–10.
8. Yasar E, Kesikburun S, Kılıç C, *et al*. Accuracy of ultrasound-guided genicular nerve block: a cadaveric study. *Pain Physician* 2015;18:E899–904.
9. Chan AW, Tetzlaff JM, Altman DG, *et al*. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
10. Schulz KF, Altman DG, Consort MD. statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;2010:c332.
11. McAlindon TE, Driban JB, Henrotin Y, *et al*. OARSI clinical trials recommendations: design, conduct, and reporting of clinical trials for knee osteoarthritis. *Osteoarthritis Cartilage* 2015;23:747–60.
12. Altman R, Asch E, Bloch D, *et al*. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. *Arthritis & Rheumatism* 1986;29:1039–49.
13. Perez C, Galvez R, Huelbes S, *et al*. Validity and reliability of the Spanish version of the DN4 (Douleur Neuropathique 4 questions) questionnaire for differential diagnosis of pain syndromes associated to a neuropathic or somatic component. *Health Qual Life Outcomes* 2007;5:66.
14. Hochman JR, Davis AM, Elkayam J, *et al*. Neuropathic pain symptoms on the modified painDETECT correlate with signs of central sensitization in knee osteoarthritis. *Osteoarthritis Cartilage* 2013;21:1236–42.
15. Escobar A, Quintana JM, Bilbao A, *et al*. Validation of the Spanish Version of the WOMAC Questionnaire for Patients with Hip or Knee Osteoarthritis. *Clin Rheumatol* 2002;21:466–71.
16. Nosikov A, Gudex C. eds. *EUROHIS: Developing common instruments for health surveys*. Amsterdam: IOS Press, 2003.
17. Montón C, Pérez Echeverría MJ, Campos R, *et al*. [Anxiety scales and goldberg's depression: an efficient interview guide for the detection of psychologic distress]. *Aten Primaria* 1993;12:345–9.
18. Dworkin RH, Turk DC, McDermott MP, *et al*. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. *Pain* 2009;146:238–44.
19. Akbas M, Luleci N, Dere K, *et al*. Efficacy of pulsed radiofrequency treatment on the saphenous nerve in patients with chronic knee pain. *J Back Musculoskelet Rehabil* 2011;24:77–82.
20. Shuster JJ. *Practical handbook of sample size guidelines clinical trials MAC*. Boca Raton, FL: CRC Press, 1992.
21. Pocock SJ. When (not) to stop a clinical trial for benefit. *JAMA* 2005;294:2228–30.
22. Rea W, Kapur S, Mutagi H. Radiofrequency therapies in chronic pain. *Continuing Education in Anaesthesia, Critical Care & Pain* 2011;11:35–8.
23. Niemistö L, Kalso E, Malmivaara A, *et al*. Radiofrequency denervation for neck and back pain: a systematic review within the framework of the cochrane collaboration back review group. *Spine* 2003;28:1877–88.
24. Patel N, Gross A, Brown L, *et al*. A randomized, placebo-controlled study to assess the efficacy of lateral branch neurotomy for chronic sacroiliac joint pain. *Pain Med* 2012;13:383–98.
25. Chua NHL, Vissers KC, Sluijter ME. Pulsed radiofrequency treatment in interventional pain management: mechanisms and potential indications—a review. *Acta Neurochir* 2011;153:763–71.
26. Manzano D, Jimenez F, Blasi M. Ultrasound-guided pain interventions in the knee region. *Tech Reg Anesth Pain Manag* 2013;17:131–9.
27. Franco CD, Buvanendran A, Petersohn JD, *et al*. Innervation of the anterior capsule of the human knee. *Reg Anesth Pain Med* 2015;40:363–8.
28. Cohen SP, Williams KA, Kurihara C, *et al*. Multicenter, randomized, comparative cost-effectiveness study comparing 0, 1, and 2 diagnostic medial branch (facet joint nerve) block treatment paradigms before lumbar facet radiofrequency denervation. *Anesthesiology* 2010;113:395–405.
29. McCormick ZL, Korn M, Reddy R, *et al*. Cooled radiofrequency ablation of the genicular nerves for chronic pain due to knee osteoarthritis: six-month outcomes. *Pain Med* 2017:1631–41.

30. Streitberger K, Müller T, Eichenberger U, *et al*. Factors determining the success of radiofrequency denervation in lumbar facet joint pain: a prospective study. *Eur Spine J* 2011;20:2160–5.
31. Kvarstein G. Pulsed radiofrequency—Time for a clinical pause and more science. *Scand J Pain* 2012;3:124–6.
32. Bogduk N. Pulsed radiofrequency. *Pain Med* 2006;7:396–407.
33. Chua NH, Vissers KC, Sluijter ME. Pulsed radiofrequency treatment in interventional pain management: mechanisms and potential indications-a review. *Acta Neurochir* 2011; 153:763–71.
34. E Djibilian Fucci R, Pascual-Ramírez J, Martínez-Marcos A, *et al*. Ultrasound-guided sciatic nerve pulsed radiofrequency for chronic knee pain treatment: a novel approach. *J Anesth* 2013;27:935–8.
35. Vas L, Pai R, Khandagale N, *et al*. Pulsed radiofrequency of the composite nerve supply to the knee joint as a new technique for relieving osteoarthritic pain: a preliminary report. *Pain Physician* 2014;17:493–506.
36. Kesikburun S, Yaşar E, Uran A, *et al*. Ultrasound-guided genicular nerve pulsed radiofrequency treatment for painful knee osteoarthritis: a preliminary report. *Pain Physician* 2016;19:E751–9.
37. Puri KS, Suresh KR, Gogtay NJ, *et al*. Declaration of Helsinki, 2008: implications for stakeholders in research. *J Postgrad Med* 2009;55:131.