Doctor, why does my hand hurt? The nature, course and treatment of pain in hand osteoarthritis

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CHAPTER 10

PULSED RADIOFREQUENCY THERAPY FOR HAND OSTEOARTHRITIS PAIN (PROAP)

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ABSTRACT

Rationale

Different types of pain may be present in patients with hand osteoarthritis (OA), including nociceptive pain and non-nociceptive pain. This makes adequate pain treatment difficult. New treatment options are needed.

Objective

To assess the efficacy of transcutaneous pulsed radiofrequency therapy (tPRF) as a treatment for pain in hand OA.

Study design

Randomized clinical trial (RCT).

Study population

Patients with hand OA, recruited from the Leiden University Medical Center Rheumatology outpatient clinic, aged 18-80 years and fulfilling hand pain criteria. Patients with known or suspected presence of other rheumatic musculoskeletal diseases or laboratory findings suspect for other inflammatory rheumatic musculoskeletal diseases are excluded. Patients with other conditions known to cause neuropathic or other non-nociceptive pain, or suspicion thereof, that are pregnant or breast-feeding, have had corneal eye surgery recently, have an implantable cardioverter-defibrillator, pacemaker or neurostimulator, or have metal implants in the hand, arm, shoulder or neck in the area to be treated are also excluded.

Intervention

Transcutaneous pulsed radiofrequency therapy of the hand versus sham.

Main study endpoint

Hand pain assessed with the numerical rating scale over 6 weeks after transcutaneous pulsed radiofrequency therapy compared to sham.

Secondary study endpoints

Efficacy of tPRF on NRS hand pain in patients with hand OA over 12 weeks. Efficacy of tPRF on depression and anxiety, health related quality of life, the AUSCAN subscales hand pain, hand function and hand stiffness, painDETECT outcomes, Michigan Hand Outcome Questionnaire outcomes, and joint tenderness in patients with hand OA over 6 and 12 weeks. Global perceived effect of tPRF by patients with hand OA over 6 and 12

weeks. Exploration of association of somatosensory profiles measured by quantitative sensory testing, and local inflammation measured with ultrasound, with efficacy of tPRF

INTRODUCTION

Hand OA is a common condition with pain as a main symptom. (1) No disease modifying treatment is currently available, so treatment aims to relieve pain and to reduce loss of function. The efficacy of most symptom modifying treatments is limited. (2) Unfortunately, the exact aetiology of osteoarthritic joint pain is still unclear. This lack in understanding hampers development of effective treatment of pain in patients with OA in general, including those with OA in the hands. (1) Multiple mechanisms have been suggested to play a role in pain in hand OA. These include mechanical and inflammatory mechanisms, as well as non-nociceptive pain mechanisms, including sensitization (Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs, as per the International Association for the Study of Pain, (3)). (4-6) This is based both on presence of symptoms commonly attributed to neuropathic or nociplastic (defined by the IASP as pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain, (3)), as well as inadequate response to nociceptive pain therapy such as NSAIDs. (3-8) Previous studies have shown that these types of pain may need different treatments. (9)

Currently, most treatments employed for pain in hand OA target nociceptive pain. (10) These therapies often have low effect sizes in relieving hand OA pain. (11) Better results are found in highly selected subgroups, such as for prednisolone in inflammatory hand OA. (9) However, even in this selected population treated with prednisolone 28% of patients showed no response to treatment. (9) A possible explanation for the lack of effect is the presence of multiple types of pain in hand OA, as outlined above.

This was seen in patients in the prednisolone trial, who reported non-nociceptive pain symptoms that did not seem to react to prednisolone, indicating that they might require other treatment than anti-inflammatory treatment. (12) Neuropathic pain symptoms are not expected to decrease in response to interventions aimed primarily at nociceptive pain. Therapies used to treat neuropathic pain may thus be of help to patients with hand OA. Therapies to treat neuropathic pain include pharmacological agents (anti-epileptics and anti-depressants, known to cause many side effects) and non-pharmacological options such as exercise, cognitive behavioural therapy, and education. (13)

For neuropathic pain caused by a single nerve, pulsed radiofrequency (PRF) therapy is also widely used. Conditions treated this way include carpal tunnel syndrome and neuralgias, and studies found beneficial effects for joint pain including knee OA. (14-16) Originally, PRF was applied with a needle inserted near the dorsal root or peripheral nerve. However, a transcutaneous (transcuteanous pulsed radiofrequency or tPRF) has been developed since (17). Previous research using this transcutaneous system has shown beneficial effects in patients with shoulder and knee pain, with superior effects when compared to transcutaneous electrical nerve stimulation (TENS). (18-21) Few side effects have been observed. Coupled with the non-invasive nature, this might be a good treatment option for pain in hand OA as well.

In conclusion, with this protocol we aim to investigate the efficacy of transcutaneous pulsed radiofrequency therapy in reducing hand pain in patients with hand OA.

METHODS

Design and setting

The PROAP trial is a hospital-based, sham-controlled randomized clinical trial. Patients are invited to participate in the study upon completion of both visits of the SensOA study (see previous chapter in this thesis), which in turn recruits patients from the Leiden University Medical Center rheumatology outpatient clinic. The data gathered during the SensOA study serves as baseline data for the PROAP trial.

Patient population

The study population consists of adult men and women, aged 18-80 years, with hand osteoarthritis according to the American College of Rheumatology (ACR) criteria for clinical hand OA, pain during more than half of the days of the previous six weeks and a minimal pain score of 30 out of 100 on a Visual Analogue Scale.

Exclusion criteria are as follows: an inability to understand the Dutch language, presence of psoriasis or a chronic inflammatory rheumatic disease, or presence of rheumatoid factor of anti-CCP, presence of fibromyalgia (ACR 2011 criteria, (22)), neurologic disorders, carpal tunnel syndrome, history of chemo- or radiotherapy, spinal surgery or trauma with lasting damage, cognitive impairment, psychiatric conditions, pregnancy, breastfeeding, eye surgery for glaucoma or keratoconus or other corneal surgery in the preceding three months and presence of an implantable cardioverter-defibrillator (ICD), neurostimulator or pacemaker.

Finally, patients are excluded from the PROAP trial if they have metal implants in the hand, arm, shoulder or neck on the side that is to be treated.

Sample size

Sample size calculations are based on a previous publication on tPRF in shoulder pain. We estimated a minimal clinical important difference of 15 mm, as was found in the earlier trial investigating tPRF versus sham. (18) This tPRF study reports a standard deviation of 20 mm. (18) Using an alpha of 0.05 and a power of 0.80 a total of 28 patients need to be included in the interventional part of the trial, for a total of 56. To include for loss of patients during the study we aim to include 60 in the trial.

Primary Objective

To assess the efficacy of tPRF compared to sham on NRS hand pain in patients with hand OA over 6 weeks, as measured with a pain dairy.

Secondary Objectives

- Efficacy of tPRF compared to sham on hand pain measured as difference in pain intensity (11-point NRS, 0-10) over twelve weeks after tPRF or sham
- Efficacy of tPRF compared to sham measured as changes in number of hand joints with patient reported pain based on hand diagrams, after six weeks and twelve weeks
- Efficacy of tPRF compared to sham on pain of the hand, measured by the AUSCAN pain subscale, after six weeks and twelve weeks
- Efficacy of tPRF compared to sham on stiffness of the hand, measured by the AUSCAN stiffness subscale, after six weeks and twelve weeks
- Efficacy of tPRF compared to sham on function of the hand due to hand OA, measured by the AUSCAN function subscale, after six weeks and twelve weeks
- Efficacy of tPRF compared to sham on MHOQ scores, after six weeks and twelve weeks
- Efficacy of tPRF compared to sham on painDETECT outcomes after tPRF or sham, after six weeks and twelve weeks
- Efficacy of tPRF compared to sham on depression and anxiety, measured by the HADS, after six weeks and twelve weeks
- Efficacy of tPRF compared to sham on Global perceived effect in hand OA, after six weeks and twelve weeks
- Efficacy of tPRF compared to sham on quality of life, measured by the SF-36, after six weeks and twelve weeks.

Exploratory objectives

- Association of response to tPRF, after six weeks and twelve weeks, and QST profiles at baseline
- Association of response to tPRF, after six weeks and twelve weeks, with local inflammation at baseline as measured by ultrasonography.

Intervention

tPRF will be applied using the Spring2 device and its matching accessories (skin electrodes and extension cables) of the company Springlife Medical (Utrecht, the Netherlands). It is a therapeutic device generating radiofrequency in a pulsed manner, intended for pain relief.

Two skin electrodes will be applied: one on the back of the neck contralateral to the treated hand, the second on the hand palm of the treated hand. The duration of the treatment will be 15 minutes at a set Amperage of 800 mA, applying an alternating electrical current with high frequencies (420 kHz) with a pulsed time cycle. This electrical current is not felt by the participant.

For the sham, the electrodes will be applied similarly, but the device will be run in a demo mode. The same visual signs are visible on the device in this mode, but no electricity is delivered. The demo mode and intervention are thus indistinguishable for participants.

Blinding and randomization

Participants will randomly be assigned to one of the two study groups, using a varying block schedule of 2 and 4. The randomization numbers will be generated using CastorEDC, and are visible only to the research nurse applying the treatment and data managers. Research nurses are instructed not to inform the participants regarding the applied intervention. Participants, assessors and investigators are blinded to treatment allocation and remain blinded until the database is locked and primary statistical analysis has been done. Unblinding will occur if necessary for medical or other safety reasons.

Assessments

As stated, all data collected during the SensOA study (see previous chapter in this thesis) serves as baseline data for the PROAP trial. The measurements that are performed on the follow-up visits will be described here.

Physical examination

Participants will undergo physical examination at baseline by a study physician, consisting examination of the hands (tender joint count, soft swollen joint count, bony

enlarged joint count and deformity joint count), length, weight, blood pressure, middle circumference, and assessment of the elbows, shoulders, acromioclavicular joints, sternoclavicular joints, ankles, toes and vertebrae according to the Doyle index. Additionally, the knees and hips are investigated following the ACR criteria.

At 6 weeks, examinations of the hands are repeated.

Questionnaires

After the second PROAP visit at 6 weeks and at the end of the 12-week follow-up period, patients receive an automated email with a link to the electronic case report form (eCRF). If preferred, patients can also receive a paper version of the questionnaires. The content and schedule of questionnaires is summarized in table 1.

Pain dairy

During 12 weeks of trial participation, patients are asked to keep a digital pain dairy. They receive an email daily, providing a link to a short questionnaire. Before the intervention is applied, the first page of the diary is filled in to collect a baseline measurement. Average pain, maximum pain, pain upon movement and pain during rest over the past 24 hours are collected on a 0-10 NRS scale for each hand separately. Usage and dosage of pain medication is also collected.

Once per week, the global perceived effect is also collected, consisting of the following two questions: To what extent have you recovered from your symptoms? How satisfied are you with your treatment? Both questions are answered on a 7-point scale.

QST

The short QST set from the SensOA is repeated at 6 weeks at the rheumatology outpatient clinic, consisting of three elements:

Temporal summation, by applying a single pinprick with a 256 mN punctate probe, followed by 10 repetitive pinpricks at the same location. Intensity of the first and last pinprick will be asked of the patient, using a 11-point NRS. The process will be performed 5 times, after which the ratio of NRS between mean initial stimulus and mean last stimulus will be calculated. An increase >2 is considered wind-up.

Numbness, tested by applying a pinprick with a 256 mN punctate probe on the patient's skin with patient's eyes closed. Patient will be asked to rate the pinprick as sharp or

Table 1. Overview of questionnaires

Questionnaire	Content	Week		
		0	6	12
Demographics	Marital status; Education level; Smoking and alcohol usage; Working status; Physical activity; Intensive hand usage	X		
Disease characteristics	Symptom duration; Dominant hand; Most problematic hand; Chronicity of hand pain; Other hand symptoms; Morning stiffness hand; Previous injections in the hand joints; Previous physical therapy for hands; Use of tools for hand OA; Previous operation on the hands; Previous fractures in the hands	X		
Joint symptoms	0-10 NRS pain for past 48 hours; Patient reported painful and stiff joints; Other painful joints; Other stiff joints	X	X	X
Medication usage	Use of painkillers; Use of dietary supplements; Calcium intake; Vitamin D intake; Use of other medication	X		
SCQ	Presence of, impairment due to and treatment for various comorbidities	X		
Family history	Presence of signs of OA and other diseases in the first-degree family members	X		
AUSCAN	Pain, function and stiffness of the hands	X	X	X
MHOQ	Total function, general daily functioning, labor prestations, pain, aesthetics and general satisfaction of the hands	X	X	X
PainDETECT	Signs of neuropathic pain. Additionally, a PainDETECT adjusted to specifically report for the left and right hands separately is collected at baseline	X	X	X
SF-36	Mental and physical health-related quality of life, divided into domains physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health.	X	X	X
IPQ	Illness perceptions, consisting of symptoms associated with disease, expectation regarding duration and constancy of disease, control over disease from personal and treatment influence, understanding of disease and emotions and consequences attributed to disease	X		
HADS	Signs of anxiety and depression	X	X	X
CORS	Coping styles employed, divided into comforting cognitions, limiting activities, seeking distractions, optimism, adjusting activities, using creative solutions, accepting dependency and taking others into consideration	X		
CSI	Signs of and diagnoses associated with central sensitization	X	X	X
PCS	Signs of pain catastrophizing	X		

SCQ = Self-administered comorbidity questionnaire. AUSCAN = Australian/Canadian Hand Osteoarthritis Index. MHOQ = Michigan Hand Outcome Questionnaire. SF-36 = Short Form-36. IPQ = Illness Perception Questionnaire. HADS = Hospital Anxiety and Depression Scale. CORS = Coping with Rheumatic Stressors. CSI = Central Sensitization Inventory. PCS = Pain Catastrophizing Scale.

Table 2. Overview of examinations during in-person visit or follow-up by telephone

Investigations	Content	Week		
		0	6	12
General physical examination	Length, weight, middle circumference, blood pressure	X		
Doyle Index	Standardized examination of pain evoked through application of pressure (elbow, shoulder, acromioclavicular, sternoclavicular, MTP-I and MTP II-V joints) or movement (cervical spine, lumbar spine, ankle, talocalcaneal and midtarsal joints), scored 0-3.	X		
Standardized examination of hands	Assessment of pain, bony enlargement, soft swelling and deformity of the CMC-I, IP, PIP, DIP, MCP joints and the wrist.	X	X	
Grip strength	Assessment of grip strength, as the average of 3 measurements per hand, with VAS pain scores collected before and after the 6 measurements.	X		
Knee examination	Standardized knee examination, consisting of palpation, investigation of range of motion for extension and flexion, crepitation, soft swelling, bony swelling, warmth, morning stiffness and knee pain.	X		
Hip examination	Standardized hip examination, consisting of range of motion of flexion and endorotation, pain on movement and endorotation, crepitation, flexion contractures, morning stiffness and hip pain.	X		
Short QST	Wind-up ratio, numbness and dynamic mechanical allodynia on the backs of both hands, including feasibility questions. Pressure pain threshold collect for left distal radio-ulnar joint, trapezius muscle, tibialis anterior muscle and CMC-I, IP, PIP, DIP and MCP joints.	X	X	
Extensive QST	Standardized collection of the cold and warm detection thresholds, cold and heat pain thresholds, thermal sensory limen, paradoxical heat sensations, mechanical detection and pain thresholds, mechanical pain sensitivity, dynamic mechanical allodynia, wind-up ratio, vibration detection threshold and pressure pain threshold. Tested at the most painful hand and least painful foot.	X		
Ultrasonography	Assessment of STT, CMC-I, IP, MCP, PIP and DIP joints for grey scale synovitis, osteophytes, effusion and doppler signal (all scored 0-3 according to the OARSI system). Additional assessment of collateral ligaments of IP, PIP and DIP joints for structural damage (scored as normal, damaged, or absent) and doppler signal (scored as absent or present).	X		
WPI/SSS	Verbally collected questionnaire regarding areas with pain in the past week, as well as questions regarding fatigue, waking refreshed, cognitive symptoms and various somatic symptoms, used to establish the ACR criteria for fibromyalgia.	X		
Signs of nociplastic pain	Questions regarding pain on movement, hypersensitivity to light, scents or sounds, and frequent waking during sleep.	X		
CCM	Confocal Cornea Microscopy, collecting images of both eyes.	X		
Laboratory investigations	Serum glucose, cholesterol, HDL-cholesterol, HDL-cholesterol ratio and triglycerides collected from patient care if available from the past six months, otherwise collected at baseline.	X		
Biomarker material collection	Blood and urine samples collected and stored at -80 for determination of biomarkers at a later point in time.	X		

Table 2. Overview of examinations during in-person visit or follow-up by telephone (continued)

Investigations	Content	Week		
		0	6	12
X-ray of the hands	Collected from patient care or previous research if available from the past six months, otherwise collected at baseline.	X		
VAS pain hands	Hand pain over the past 48 hours.	X	X	
Adverse event recording	Information on adverse events (any undesirable experience occurring to a subject during the study) and serious adverse events (untoward medical occurrence or effect that results in death, is life threatening, requires or prolongs hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect or any other important event that did not results in any of the previous but Xcould have based on appropriate judgement by the investigator. Elective hospitalisation is not considered a serious adverse event.	X	X	X

MTP = Metatarsophalangeal. CMC-I = first carpometacarpal. IP = Interphalangeal. PIP = Proximal interphalangeal. DIP = Distal interphalangeal. MCP = Metacarpophalangeal. STT = Scaphotrapeziotrapezoidal. OARSI = Osteoarthritis Research Society International. HDL = High density lipoprotein.

numb. Test will be performed on 5 areas of the hand. Any of the pinpricks rated as numb is considered abnormal.

Dynamic mechanical allodynia, tested by applying a stroke with a standardized brush of approximately 2 cm over the skin, with patient's eyes closed. This will be repeated five times with an approximately 10s inter-stimulus interval to account for potential wind-up. Patient will be asked to score a pain rating on a 0-10 NRS. Ratings above 0 are considered allodynia.

Timeline

Inclusion of participants was started in April 2022 and was finished in December 2024. Data analysis will be performed during of 2025, after which results will be submitted.

Statistical analysis

Primary objective

Continuous outcomes will be summarized using mean (SD) or median (IQR) as appropriate. Categorical outcomes will be described using N (%).

The primary outcome will be the treatment effect after 6 weeks measured as hand pain on a 11-point (0-10) NRS in the pain dairy, analyzed using generalized estimating equations with robust standard errors and the correlation structure specified as exchangeable. The primary analysis will be adjusted for baseline pain level, with treatment as independent

variable and time from baseline in weeks as the time variable. A model including age and sex will also be run. The outcome will be presented as a point estimate of the difference between the treatment groups, with a 95% confidence interval (95% CI) and two-sided p-value. A p-value lower than 0.05 will be considered statistically significant.

This outcome will be analyzed using the modified intention-to-treat (ITT) population. The modified ITT population will consist of all patients who underwent randomization and finished the procedure they were randomized for (sham or treatment). This includes patients withdrawn at some point during the study.

Two per protocol (PP) populations are defined as the patients who completed the entire study with no major protocol violations, providing data at physical visits at baseline and week 6 timepoints (per protocol population 1) or finishing the entire study (per protocol population 2), provided they have completed at least 80% of diaries up to that point. The analysis will be run on these populations as well, as a sensitivity analysis.

Secondary objectives

The analysis above will be repeated for hand pain data (collected from the dairy, NRS 0-10) up to week 12. It will similarly be repeated for the following outcome measures: Australian Canadian osteoarthritis hand index (AUSCAN) pain function and stiffness subscales, Michigan Hand Outcome Questionnaire subscales, number of painful joints indicated by patients, PainDETECT scores, Short Form-36 physical and mental health related quality of life subscales, Hospital Anxiety and Depression Scale (HADS) depression and anxiety subscales.

The global perceived effect outcomes will be described by providing numbers and percentages of the answer options per treatment arm at the weekly intervals. At week 6, the distribution of the answer categories will be compared between the treatment arms using a Fisher's exact test, or a Chi^2 test if there are sufficient numbers per answer category per cell (>5). If very low numbers per stratum are found, the Global Perceived Effect answers may be combined.

Exploratory objectives

Exploratory analyses will be performed by incorporating the QST profiles derived during the SensOA study in the primary analysis model. Similarly, sum-scores of ultrasonography measures will be incorporated in the primary analysis model as covariates.

Ethics and dissemination

The projects received approval by the Leiden-Delft-Den Haag Medical Ethics Committee (registration number P21.101). The trial is prospectively registered on clinicaltrials.gov (NCT05217979).

Patients are invited to participate by their treating rheumatologist at the outpatient clinic. If they are interested, they receive the patient information folder. One week later the study-physician contacts them to discuss the folder and any potential questions, after which patients can decide to participate or not. It is made clear that study participation is voluntary and refusal does not have negative impact on the patient. Patients sign informed consent forms for both the SensOA and the PROAP prior to participation. All data is pseudonymized and stored safely at Leiden University Medical Center.

Study findings will be analyzed and submitted to peer-reviewed international journals and congresses. Data analysis will begin when all data has been collected and the database has been locked.

DISCUSSION

Treatment options for hand OA pain are still inadequately effective, in part because our understanding of the aetiology of hand OA pain remains incomplete. Therefore, more research is needed, both regarding pain mechanisms in hand OA and regarding potential new treatments. In the PROAP study, we will investigate a potential new therapy in a very well characterized patient sample, of whom highly detailed information regarding their pain is available.

This will allow us to investigate the effect of transcutaneous pulsed radiofrequency in a very well described sample. The generalizability of the sample we test the intervention in may be somewhat limited, due to the stringent exclusion criteria. This trial should thus be seen as a proof-of-concept trial for the use of transcutaneous pulsed radiofrequency in hand OA. Later trials may be needed to specify the patient group that may benefit most from this treatment.

The PROAP trial will provide valuable knowledge on a potential new treatment for pain in hand OA. This will be of importance for both patient care and future clinical trials.

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