PRIMA trial

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON25940

Source
Nationaal Trial Register

Brief title
PRIMA

Health condition

Osteoarthritis of the Ankle (Ned: enkelartrose)

Sponsors and support

Primary sponsor: University Medical Center: Academic Medical Center Amsterdam
Source(s) of monetary or material Support: Dutch Arthritis foundation

Intervention

Outcome measures

Primary outcome

American Orthopaedic Foot and Ankle Society (AOFAS) score at 26 weeks follow-up,

Secondary outcome

1. Pain scores: (VAS 0-100) during activities of daily living and the pain sub-scale of AOFAS (0-40)

2. Ankle activity score (0-10)

3. Subjective patient satisfaction (4 categories)

4. Health related quality of life (SF-36 scale)

5. The Global Attainment Scaling (GAS)

6. EQ-5D-3L utility score

7. Ankle Osteoarthritis Score (AOS)

8. Foot and Ankle Outcome Score (FAOS)

Study description

Background summary

Summary

Pain is the cardinal symptom of ankle osteoarthritis (OA) and is a complex phenomenon with limited understanding of its pathomechanisms. The main objectives in the clinical management of OA are to reduce inflammation and cartilage degeneration processes as well as relieve pain. Platelet-rich plasma (PRP) is a high concentrate of platelets derived from patient's whole blood, centrifuged to remove red blood cells. PRP has been used to encourage a healing response across several specialties, in particular dentistry, orthopaedics and dermatology. Growth factors stored in the platelets are assumed to facilitate an anti-inflammatory and analgesic effect.

A recent review concluded that in animal models PRP can diminish multiple inflammatory IL-1 mediated effects, and can also positively influence the collagen network of the cartilage and subsequently reduce pain and improve function.

Our recent and other systematic reviews showed that compared to placebo injections, hyaluronic acid or corticosteroid injections, PRP injections significantly decrease pain and improve function in knee OA patients. Given the clinical effect on pain reduction in knee OA and safety, PRP might serve as a promising non-surgical therapy for ankle OA. PRP might potentially delay the irreversible surgical options like arthrodesis and joint replacement. No significant adverse advents have been reported for any PRP trials regarding acute hamstring injuries, Achilles tendinopathy, knee OA and specifically not ankle OA. Until present, there is no RCT conducted on the efficacy of PRP in the management of ankle OA.

Hypothesis

We hypothesize that:

PRP injections are efficacious for symptom reduction and functional improvement compared to placebo injections in the treatment of ankle (talocrural) OA.

Workplan

Study design

A multi-center, stratified, block-randomized, double-blind, placebo-controlled trial comparing two treatment groups.

Study population

Patients with ankle (talocrural) OA will be included if they meet the following 3 inclusion criteria:

1. Severity of Ankle OA pain on visual analogue scale (VAS) (0–100 mm) ≥ 40 during daily activities

2. X-rays (AP and lateral view) indicating ≥ grade 2 on the Van Dijk classification

3. Age ≥ 18 years

Intervention

Patients will be randomised into two treatment groups: PRP injection or placebo (saline) injection. Both groups will receive two injections of PRP or placebo at an interval of 6 weeks.

Main study parameter/endpoint

American Orthopaedic Foot and Ankle Society (AOFAS) score at 26 weeks follow-up, validated scale for ankle OA (0-100) measuring three subdomains (pain, function and alignment).

After 26 weeks, the principal investigator will be unblinded after the analysis of the primary outcome. The patients will remain blinded to the therapy until 52 weeks follow-up.

Power analysis Based on previous and ongoing studies, the study protocol of the randomised controlled trial is designed to detect a difference of 12 points (0-100) on the AOFAS score (minimal clinical relevant difference) between the groups. Based on a previous placebo

controlled RCT on injection therapy (hyaluronic acid) in ankle OA of DeGroot et al. a standard deviation of 16.3 can be expected. Taking into account a two-sided level of significance of 5%, a power of 90% and a dropout rate of 15%, approximately 50 (40 plus 15%) patients per group will be needed (N=100).

STATISTICAL ANALYSIS

Loss to follow-up

The coordinating researcher will attempt to limit loss to follow-up as much as possible by contacting every patient and being present at every patient visit. All digital questionnaires will be constantly monitored to ensure they are being filled in and otherwise followed up by the coordinating researcher. In the event of patient withdrawal, an analysis of demographic and prognostic characteristics will be done on these cases and the remaining patients. As previously described by Järvinen et al, we will document the patient eligible for and compliant with each follow-up.

Missing items

Missing items of a score will be handled according to the instructions of the specific scales. In the event of no instructions, we will calculate the percentage of missing items on a scale. Due to the potential impact on trial conclusions, multiple imputation (if >10% missing items on a scale) will be applied.

Sample size

Based on previous and ongoing studies, the study protocol of the RCT is designed to detect a difference of 12 points (0–100) on the AOFAS score. There is no official agreement on the minimal clinical important difference for the AOFAS score regarding ankle OA. However in relatable musculoskeletal literature, 10%–15% of the used scale was reported.13 25 26 Our predefined minimalclinical important difference of 12% is located within this range.13 25 26 Based on a previous placebo-controlled RCT on injection therapy (hyaluronic acid) in ankle OA by De Groot et al, an SD of 16.3 can be expected. Taking into account a two-sided level of significance of 5%, a power of 90% and a dropout rate of 10%, approximately 50 (45 plus 10% drop out) patients per group will be needed (n=100 in total).

Data management

After giving permission for participating in this study, patients will receive a link to fill in digital surveys. All data gained outside Castor EDC will be stored on the AMC secured hard drive. All data will be coded and stored in the Castor EDC online database, which meets the AMC safety criteria and GCP guidelines. The primary investigator and project leader will safeguard the coded data through password secured access. All patient’s data will be archived for at least 15 years and handled with in accordance with the Dutch Personal Data Protection Act
(Wbp). Data protection is provided through the safety protocol of Castor EDC with automated backups and Secure Sockets Layer (SSL) security.

Deviation of the protocol (submission date IRB 21-4-2020, approval date 6-5-2020)

To prevent potential immediate hazard to the patients and in compliance with the

institutional and national Covid-19 -related clinical research regulations, we deviated from the protocol and replaced patients following Institutional Review Board (IRB) (in Dutch: Medisch Ethische Toetsingscommissie) approval (submission date 21-4-2020; approval date 6-5-2020).(1,2)

During the COVID-19 pandemic, 12 received their first intervention (intra-articular injection), but these patients had no access to receiving their second injection at the pre-defined 6 week time-interval. Following consultation with the head of the department and/or local principal investigators, considering the risks and descaling of elective patient bound activities, we found the COVID-19 associated potential risks to outweigh the potential damage due to the disease for which they had no access to the intervention.In these extreme circumstances, we are confronted with a crisis and are forced to think of solutions in order to maintain the quality of the study. The European Committee for Human Medicinal Products, recommend collection of as much data as possible. In the current situation we find the trial load for patients no longer participating too heavy and thus unethical. Consequently, we will limit data collection in these patients to the primary outcome measure, AOFAS at 26 weeks (1x 10 min by videoconsult).
Following IRB approval on 6-5-2020, Deviations of the protocol include:
1. Post randomisation replacement during the Covid-19 related regulations: Participationof 12 patients who had no access to the intervention (second injection)will be discontinued
2. These 12 patients for which participation has been discontinued, will be replaced by 12 new inclusions.
3. Since trial patients may not be able to come to the investigational site for protocol-specified visits at 26 weeks (due to local regulations) due to the COVID-19 pandemic, video consultations will be implemented when necessary and feasible, and will be sufficient to assure the safety of trial patients.

General Covid related actions
The Sponsor and clinical investigators will document how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which and how trial patients will be impacted. We will capture specific information in the case report form that explains the basis of potential missing data, including the relationship to COVID-19 for missing protocol-specified information (e.g., from missed study visits or study discontinuations due to COVID-19). This information, will be summarized in the clinical study report.
The proposed IRB amendment (submitted on 21-4-2020) with changes in the protocol will be updated in the data management and/or statistical analysis plan amendments. Prior to locking the database, we will address in the statistical analysis plan how protocol deviations related to COVID-19 will be handled for the pre-specified analyses.

Statistical analysis
A standard operating procedure will be available to logically recode and clean the data. The data will be interpreted according to a blinded data interpretation scheme described by Järvinen et al. A statistical expert (SB) is present among the authors. The authors will interpret the statistical results until a consensus is reached. Once the authors are in agreement, the two groups will be unblinded and no changes will be made to the interpretation of the results. Baseline characteristics Baseline characteristics will be analysed

between groups
using descriptive statistics.

Primary outcome measure
Analysis will be performed using an intention-to-treat approach. To test for the effect of treatment on the between-group difference in primary outcome, we will use a repeated measurement general linear model. Changes from baseline to all follow-up time points will be included in the model. Adjustments will be made for those baseline variables that influenced the primary outcome with $p<0.10$.

Secondary outcome measures
To test for the effect of treatment on between-group differences in secondary outcomes, we will use the repeated measurement general linear model. Changes from baseline to all follow-up time points will be included in the model.

Economic analysis
In the event of a positive significant outcome, an economic analysis is needed to support a possible change of practice. An economic analysis (costs) will be performed in order to determine cost-effectiveness. We will assess the differences in mean quality-adjusted life years (QALYs), costs and net benefits between the PRP injection group and the placebo group using linear models. We express the cost-effectiveness by using cost-effectiveness acceptability curves from both a healthcare perspective and a societal perspective. With multiple
bootstrap replicates of the average difference in costs and effects in the incremental cost-effectiveness plane, we will express the uncertainty of our cost-effectiveness analysis.
The cost-effectivity analysis will be performed with a 1 year time horizon. We use the three-level EQ-5D questionnaire (Euroqol, Rotterdam, the Netherlands) to calculate QALYs as the area under the curve of the utility scores measured over 12 months, according to the Dutch pricing system. The analysis will be based on indirect costs and direct costs and will be determined using PRODISQ. PRODISQ is taken at baseline and every 3 months thereafter up until 1 year.

Expected results

We will provide evidence for the (potential) efficacy of PRP for symptom reduction and functional improvement in the treatment of ankle OA. A positive outcome will have an effect on the economical and disease burden. The relatively simple content and widespread availability of the PRP intervention and previously reported good safety will contribute to simple and optimal nationwide implementation.

Conclusion

Our project will provide conclusions on the efficacy of PRP in ankle OA.

Study objective

PRP injections are efficacious for symptom reduction and functional improvement compared to placebo injections in the treatment of ankle (talocrural) OA.

Study design

Inclusion: PRP or Saline injection, PROMs (AOFAS, VAS, AAS, Subjective patient satisfaction, SF-36, GAS, EQ-5D-3L, AOS en FAOS) PRODISQ and physical examination

6 weeks: PRP or Saline injection, PROMs (AOFAS, VAS, AAS, Subjective patient satisfaction, SF-36, GAS, EQ-5D-3L, AOS en FAOS) and physical examination

12 weeks: PROMs (AOFAS, VAS, AAS, Subjective patient satisfaction, SF-36, GAS, EQ-5D-3L, AOS and FAOS) and PRODISQ

26 weeks: PROMs (AOFAS, VAS, AAS, Subjective patient satisfaction, SF-36, GAS, EQ-5D-3L, AOS en FAOS) and physical examination. Since trial patients may not be able to come to the investigational site for protocol-specified visits (due to local regulations) due to the COVID-19 pandemic, video consultations will be implemented when necessary and feasible, and will be sufficient to assure the safety of trial patients.

39 weeks: PRODISQ questionnaire

52 weeks: PROMs (AOFAS, VAS, AAS, Subjective patient satisfaction, SF-36, GAS, EQ-5D-3L, AOS en FAOS)

5 years: PROMs (AOFAS, VAS, AAS, Subjective patient satisfaction, SF-36, GAS, EQ-5D-3L, AOS en FAOS)

Intervention

Intra-articular injections of the ankle:

Platelet rich plasma vs Placebo (saline)

Contacts

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Eligibility criteria

Inclusion criteria

1. Severity of Ankle OA pain on a visual analogue scale (VAS) (0–100 mm) ≥ 40 during daily activities

2. X-rays (AP and lateral view) indicating ≥ grade 2 on the Van Dijk classification[10]

3. Age ≥ 18 years

Exclusion criteria

1. Patient has received injection therapy for ankle OA in the previous 6 months

2. Patient does not want to receive one of the two therapies

3. Patient has clinical signs of concomitant OA of one or more other major joints of the lower extremities that negatively affects their daily activity level

4. Previous ankle surgery for OA or Osteochondral defects (OCD) < 1 year (not including surgery for an ankle fracture in the past)

Study design

Design

Study type:	Interventional
Intervention model:	Parallel

Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-08-2018
Enrollment:	100
Type:	Actual

IPD sharing statement

Plan to share IPD: Undecided

Plan description
Participant data that underline the results reported in this article following de-identification will be shared anonymously on request following publication. Data will be shared, wherever legally and ethically possible and in line with ICMJE guidelines, with researchers who provide a methodologically sound proposal.

Ethics review

Positive opinion

Date:	06-06-2018
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL7056
NTR-old	NTR7261
Other	Amsterdam UMC : ABR: NL64160.018.18

Study results

Summary results
Chronic achilles tendinopathy by de Vos et al. JAMA 2010 (PRICT-study, registration NTR1420, ABR NL 22805.098.08).

Acute hamstring injuries by Reurink et al. NEJM 2014 (HIT-study registration NTR2771, NL34660.098.10 / 10-163; ABR / METC Zuidwest Holland).[