Identification of inflammatory mediators in spinal liquor and the knee in relation to synovial nerve sprouting and pain in osteoarthritis

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Our key objective of this study is to elucidate potential peripheral and central mechanisms that determine chronic pain characteristics in humans with OA.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Joint disorders
Study type	Observational invasive

Summary

ID

NL-OMON49579

Source
ToetsingOnline

Brief title
OAPII

Condition

- Joint disorders

Synonym
Osteoarthritis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: ReumaNL en onderzoekssubsidie Pfizer

Intervention

Keyword: Cerebrospinal fluid, Nerve, Osteoarthritis, Pain

Outcome measures

Primary outcome

We will dichotomize the cohort on the following three outcome parameters to assess whether the the biological measurements/mediators are different between the dichotomised subgroups. Knee VAS and widespread pain are measured prior to TKR, and at 6 weeks, 6 months, and 1 year after TKR but only specific timepoints are used yo dichotomize the cohort.

1. Self-reported knee pain severity at the time of TKR: severe pain (VAS >=40/100 at rest) versus limited pain (knee VAS <40/100 at rest).
2. Pain persistence: persisting self-reported pain at 6 and 12 months after TKR (knee VAS at rest>10) versus no persisting pain (knee VAS at rest =< 10)
3. Widespread pain: presence or absence of widespread pain according to the American College of Rheumatology criteria (pain present in upper and lower quadrants and on both sides of the body) prior to TKR.

Independent continues variables:

Biological measurements

For precision proteomics to determine cytokines, chemokines, growth factors, and damage molecules in CSF, SF and homogenized ST, we will use proximity extension assay (PEA) technology based Proseek Multiplex panels (Olink

Proteomics).

Secondary outcome

Independent continues variables:

-Quantitative sensory testing (QST)

QST will be conducted at the index knee and 2 other body area*s (arm and lower leg) and includes.

1. cold pain thresholds (index knee, lower leg, arm);

2. heat pain thresholds (index knee, lower leg, arm);

3. pressure pain threshold to cutaneous blunt stimuli (index knee, lower leg, arm);

4. cuff pressure pain threshold (both lower legs);

5. Summation of Thermal (heat) (index knee; arm);

6. Summation of Mechanical cuff pressure pain (lower leg);

7. Conditioned pain modulation

- Pain assessment, questionnaires:

1. The Knee Injury and Osteoarthritis Outcome Score (KOOS)

2. Measure of intermittent and constant osteoarthritis pain (ICOAP).

3. Graded Chronic Pain Scale (GCPS)

4. Paindetect

Other biological measures

-Metabolomics:

-Innervation knee tissue

Study description

Background summary

Pain is the predominating clinical feature of osteoarthritis (OA), is often hard to manage effectively, and is a major reason for patients to undergo total knee replacement (TKR). Yet, OA pain is still understood poorly; it is highly variable, can be widespread, can only partly be explained by the extent of joint damage, and persists after TKR in considerable numbers of patients. This disconnect between joint pathology and the magnitude, persistence and widespreadness of pain could be explained by neuroplastic changes in the sensory nervous system, spinal cord neuro-inflammation and local inflammatory (synovitis) characteristics.

Study objective

Our key objective of this study is to elucidate potential peripheral and central mechanisms that determine chronic pain characteristics in humans with OA.

Study design

Design: An observational, longitudinal clinical study, with detailed pain phenotyping determined by pain questionnaires and QST, combined with sampling of CSF, SF and ST at the time of TJR in regular practice.

Setting: Collection of spinal cerebral fluid, synovial fluidand tissue, bone, and cartilage tissues will be performed at the St. Antonius Ziekenhuis. Questionnaires and QST will be performed within 1-6 weeks before TKR, and 6 weeks and 6 months post TKR. Questionaires will also be performed 1 years after TKR. Multiplex analyses and metabolomics of fluids and tissue homegenates and all statistical analyses, including coded patient data, will be performed at the University Medical Center Utrecht.

Duration: Inclusion is estimated to take 30 months (~50 inclusions/year, ~10% of total population undergoing TKR) with one year follow-up after the last inclusion.

After informed consent (see 9.1 for exact detail on recruitment and consent), patients are asked to fill out the ICOAP (intermittent and Constant Osteoarthritis Pain), KOOS (pain stiffness and physical function) and PAINDETECT (neuropathic pain components) questionnaires, and Graded Chronic Pain Scale (CPGS)

Data collection:
After consent, patients will be asked prior to (1-6 weeks) TKR, and6 weeks, 6 months, and 1 year after TKR to:
i) Provide a pain VAS (visual analogue scale) for the affected knee. The pain VAS is a validated, widely used unidimensional measure of pain intensity.
ii) Fill out 4 pain questionnaires (KOOS, PAINDETECT, ICOAP, GCPS). Details provided under 6.1.2.
iii) Report widespread pain by checking-off body areas where they experienced pain (head, neck, hands, arms, chest, shoulders, stomach, upper and lower back, legs, and feet). This will be used to determine if participants fulfill criteria for widespread pain, according to the American College of Rheumatology criteria (pain present in upper and lower quadrants and on both sides of the body).

i-iii) Estimated time: 15 minutes

iv) Undergo quantitative sensory testing (QST) and pressure cuff algometry to assess the nociceptive and non-nociceptive afferent systems in detail and identify loss-of-function and gain-of-function. QST of the affected knee will help reveal subgroups of sensitized OA patients by performing QST of the index knee. Specific elements of QST (pressure pain; thermal pain; windup) will also be measured at 2 distant body regions (arm, lower leg) to reveal subgroups of generalized pain phenotypes. Total duration of the assement is 60 minutes .
v) At the day of surgery, CSF (500 uL) will be collected prior to the spinal anesthesia that is part of the standard operation procedures for TKR. Knee tissues will be collected (waste material of TKR). More specific, synovial fluid (SF) and synovial tissue (ST), cartilage and bone will be collected and stored for further analysis.

Study burden and risks

Benefit: Patients have no direct benefit of participating in this study. Results will elucidate the underlying mechanisms of osteoarthritis pain and may provide insights for novel pain treatment strategies. Based on the pilot study the lack of a direct benefit for the participating patients is not considered to be a risk.

Burden: Patients will undergo 3 times QST procedures and have to fill out questionnaires. Prior to spinal anaesthesia, 500 ul cerebral spinal fluid will be obtained in a syringe. Since the aspiration can be performed with the same

needle as injection of the spinal anaesthesia requires no additional burden is introduced. The aspiration will take approximately maximum 5 minutes.
Risks: Postdural headache or infection is negligible

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet the following criteria:

• At least 18 years of age
• Be eligible for TKR under spinal anaesthesia, according to routine clinical practice.

• Able and willing to give written informed consent

Exclusion criteria

• Auto-immune disease or diabetes mellitus because they may also affect the sensory system.
• Use of (pain) medication other than acetaminophen/paracetamol, NSAIDs and/or opioids.
• Polyneuropathy or other neurologic disease that might affect outcome measures.
• Major cognitive or psychiatric disorders.
• Problems with communication (language, deafness, aphasia etc.)

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-06-2021
Enrollment:	125
Type:	Actual

Ethics review

Approved WMO

Date:	21-12-2020
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	29-04-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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
CCMO	NL73157.041.20