ISRCTN12559751 https://doi.org/10.1186/ISRCTN12559751

Lymphocyte opioid receptors as innovative biomarkers for osteoarthritic chronic pain: study protocol for the assessment and risk management of opioid tailored therapy, before hip surgery, to prevent chronic pain and opioids tolerance/addiction development

Submission date 13/05/2017	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol
Registration date 23/05/2017	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 15/02/2018	**Condition category** Surgery	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims

Osteoarthritis is a condition that causes joints to become painful and stiff. When it affects the hip it can be treated with a hip replacement, where the damaged joint is replaced with an artificial one. Continued pain after surgery is a real health care problem. Excessive inflammation, the immune system, and the opioid receptors on the surface of the immune cells seem to have a central role. Although opioid drugs are usually used after surgery, the best treatment is not yet known. The aim of this study is to find out whether immune cells' opioid receptors could be used as markers to prevent chronic pain and opioid tolerance/addiction after hip replacement surgery.

Who can participate?

Patients aged 18 and over undergoing hip replacement surgery

What does the study involve?

Participants are randomly allocated to be treated with either tapentadol (an opioid drug) at one of two doses, or NonSteroidal Anti-Inflammatory Drugs (NSAIDs)/paracetamol. All groups follow the allocated plan for 30 days before surgery and 15 days after (if the patient feels pain). For each group, blood samples are collected before, during and up to 60 days after surgery in order to assess the immune cells' opioid receptor levels.

What are the possible benefits and risks of participating?

Patients may benefit from an easy and non-invasive diagnostic test. Patients won't be overloaded by clinical tests and will be enlisted during routine clinical visits, limiting anxiety,

stress, social problems and costs. The main risk could be the tolerance and/or addiction to opioids. The results of this study could be used to tailor treatment to prevent tolerance and/or addiction from occurring.

Where is the study run from?
Policlinico Tor Vergata (Italy)

When is study starting and how long is it expected to run for?
May 2016 to November 2017

Who is funding the study?
ISAL Foundation (Italy)

Who is the main contact?
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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
N/A

Study information

Scientific Title
An interventional, double-blind randomized parallel-group, phase IV study for the assessment of a tailored Opioid therapy and osteoarthritic chronic pain bioMarkers, to improve Arthoprosthesis patients rehabilitation (OpMarkArt)

Acronym
OpMarkArt (Opioids-Markers-Arthroprosthesis)

Study objectives
The trialists hypothesize that a pre-surgery opioid tailored therapy could modulate lymphocytes opioid receptors and the onset of postoperative osteoarthritic chronic pain. Thus, the trialists propose opioid receptors in the surface of lymphocytes as biological diagnostic markers in order to analyze chronic pain predisposition/evolution and opioids addiction/tolerance insurgence.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Institutional independent ethics committee of Policlinico Tor Vergata (Rome), 28/06/2016, ref: 110/16

Study design
Interventional multicentre double-blind randomized parallel-group phase IV study

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Total hip arthroplasty for osteoarthritis or aseptic necrosis of the femoral head

Interventions
60 patients undergoing hip surgery will be enrolled in a randomized phase IV study. Patients will be randomised in a double-blind manner into three medication arms administered in common practice. Randomisation will be performed using a computational approach, based on a single sequence of random assignments (simple randomization). Patients and their medical doctors will be blind to the assigned treatment. Each arm involves 20 patients:
1. Tapentadol 25mg x 2 die
2. Tapentadol 75mg x 2 die
3. NSAIDs/paracetamol in accordance with surgeon’s custom

All the arms will follow the specific pharmacological plan for 30 days before surgery and 15 days after (if the patient feels pain). Each patient will be subjected to five blood sample collections at precise time points: the day of enrolment and starting therapy (T0); the 30th day of therapy, coinciding with the moment of surgery (T2); the day after surgery (T3); 30 days after surgery (T4); 60 days after surgery, in correspondence with the final assessment and follow up (T5). T1 coincides with clinical examination, 15 days after the enrolment, without any blood collection.

On the day of surgery, patients will be monitored with standard practices, such as electrocardiogram, oxygen saturation, invasive and non-invasive blood pressure monitoring. They will attend a physical examination, concerning Harris Hip Score for evaluation of hip movement, stability, strength, presence of any deformities, joint and functional limitations; radiographs of the axial pelvis and in anteroposterior, to determine the extent of the degree of arthritis or necrosis; pain assessment will be done using the model inside the Harris Hip Score, by adding evaluations of pain intensity (NRI scale) during orthostatic and clinostat posture.

During the surgery, a bone marrow sample will be collected. Bone marrow biopsy will be fixed for 24h in buffered 4% formalin and included in paraffin. 3µm sections will be used for bone marrow morphological and morphometric evaluation through hematoxylin/eosin staining protocol and for cellular immune-phenotypic typization.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Tapentadol, NSAIDs/paracetamol

Primary outcome measure

1. Expression and functional characteristics of opioid receptors on the lymphocyte surface, measured using peripheral blood analysis (Immunophenotype analysis, Q-PCR, western blotting, ELISA) at T0, T2, T3, T4 and T5
2. Bone marrow morphological and morphometric evaluation, using bone marrow biopsy, hematoxylin/eosin staining protocol and cellular immune-phenotypic typization at T2

Secondary outcome measures
1. Hip movement, stability, strength, presence of any deformities, joint and functional limitations, evaluated using the Harris Hip Score at T0, T1, T2, T4, T5
2. Degree of arthritis/necrosis, measured using axial and anteroposterior pelvic radiographs at T0
3. Pain intensity, measured using the NRI scale at T0, T1,T2, T3, T4, T5
4. Electrocardiogram, oxygen saturation, invasive and non-invasive blood pressure monitoring at T2
5. Side effects evaluation (tolerance or addiction) at T2, T4, T5

Overall study start date
23/05/2016

Completion date
23/11/2017

Eligibility

Key inclusion criteria
1. Patients who started opioid analgesics category and will undergo total hip arthroplasty for osteoarthritis or aseptic necrosis of the femoral head
2. Patients who started NonSteroidal Anti-Inflammatory Drugs (NSAIDs) and will undergo total hip arthroplasty (THA) for osteoarthritis or aseptic necrosis of the femoral head
3. Males and female adults (from 18 years old)

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
60 patients

Key exclusion criteria
1. Unstable neurological pathologies
2. Uncompensated diabetes
3. Previous abdominal surgery with dynamic ileum risk

4. Viral infective pathologies
5. Patients unable to fill the informed consent form
6. Patients needing post-surgery mechanical ventilation
7. Patients attending a secondary surgery
8. Retreated patients

Date of first enrolment
02/12/2016

Date of final enrolment
02/08/2017

Locations

Countries of recruitment
Italy

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Sponsor type
Research organisation

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ROR
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Funder(s)

Funder type
Research organisation

Funder Name
ISAL Foundation

Results and Publications

Publication and dissemination plan
The trialists expect to publish the clinical and biological data in a high-impact peer reviewed journal.

Intention to publish date
23/11/2018

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository (IESSS - Ibis Enhanced Spontaneous Studies System).

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	19/12/2017		Yes	No