ISRCTN87180032 https://doi.org/10.1186/ISRCTN87180032

Prevention of ischemia/reperfusion injury by C1 esterase inhibitor (C1 INH): Assessment of reperfusion injury in total knee arthroplasty

Submission date 24/10/2016	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 04/11/2016	**Overall study status** Completed	
Last Edited 12/01/2022	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims

Knee replacement surgery (arthroplasty) is a routine operation where a damaged, worn or diseased knee is replaced with a new, artificial one. The most common reason for knee replacement surgery is osteoarthritis, but there are others including rheumatoid arthritis, gout, haemophilia, death of bone in the knee following a problem with the blood supply, injury to the knee and diseases that result in unusual bone growth (bone dysplasias). A tourniquet is used for this purpose and leads to the During total knee arthroplasty (TKA – where the entire knee joint is replaced), the blood supply to the knee needs to be stopped (intentional ischemia) in order to do the surgery well and to reduce blood loss during the surgery. Tourniquets are used for this purpose and are applied to stop blood flow to the affected e knee and leg from between 30-120 minutes. It is known that reintroducing blood flow (reperfusion) to an organ or tissue after a prolonged period of ischemia can lead to something called ischemia/reperfusion (I/R) injury. I/R injury is an inflammatory (swelling) reaction of the tissue, probably caused by the presence of 'danger' signals on the ischemic endothelium (the inner surface of blood vessels) , which triggers a number of reactions such as the plasma cascades (which causes, for example, blood clots) and also immune system responses. So far, however, the use of a tourniquet in orthopaedic surgery (such as TKA) and how this may lead to I/R injury has not been investigated in detail. In clinical practice, postoperative edema formation (swelling caused by fluid building up in the tissues) in the lower limb (knee and leg) after TKA is often thought to be caused by surgical trauma rather than I/R injury. However, a longer ischemia time in TKA leads to more severe postoperative pain and edema formation, and the link to I/R injury has been made in this study. Previous studies have shown that I/R injury can be reduced if activation of the plasma cascade systems and/or the endothelium is prevented. I/R injury is rats have been prevented by injecting them with a protein called C1-inhibitor before application of the tourniquet. If this could be used for patients, they may benefit from reduced inflammation, including pain and edema formation.

With this in mind, this study is looking at how activation of the endothelium and the plasma cascades in I/R injury after TKA occurs in order to help design a possible study testing C1-inhibitor in the future.

Who can participate?
Adults that are about to have a total knee replacement

What does the study involve?
All patients have total knee replacement surgery. In line with standard practice, some patients have the procedure done with a short period of intentional ischemia using a tourniquet (less than 30 minutes). Other patients will have the procedure done with a longer period of intentional ischemia using a tourniquet (90-120 minutes). All patients are followed up for 48 hours after their surgery to check for evidence of edema and how much morphine is required to relieve pain. Blood sample are taken to look for evidence of coagulation (blood clotting), inflammation and immune system responses.

What are the possible benefits and risks of participating?
There is no direct benefit or risk for the patient because it is an observational study.

Where is the study run from?
Orthopaedic department, University Hospital Bern (Switzerland))

When is the study starting and how long is it expected to run for?
December 2016 to December 2018

Who is funding the study?
CSL Behring AG(Switzerland)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
201609_DCR_UNIBE_Rieben

Study information

Scientific Title
Prevention of ischemia/reperfusion injury by C1 INH. Assessment of reperfusion injury in total knee arthroplasty: pilot study

Study objectives
Total knee arthroplasty can be associated post operatively with edema formation and pain due to ischemia reperfusion (I/R) injury. I/R injury usually develops due to the use of a tourniquet to provide a bloodless surgical field. The exact mechanisms are still not known but the activation of the complement system leads to the development of an inflammatory response that ends with edema and pain. The current study is a pilot study to diagnose the occurrence of reperfusion injury after both short and long tourniquet time.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Kantonale Ethikkommisson for die Forschung (KEK Bern), 27/07/2017, ref: 2017-00217

Study design
Single centre observational case-control study

Primary study design
Observational

Secondary study design
Case-control study

Study setting(s)
Hospital

Study type(s)
Diagnostic

Participant information sheet

Health condition(s) or problem(s) studied
Ischemia reperfusion injury after total knee arthroplasty

Interventions

Total knee arthroplasty is an elective surgical procedure that takes place when medication and /or walking support instruments can no longer relieve severe knee pain. Using a tourniquet is important to produce a bloodless surgical field but in the same time it causes ischemia to the leg. Both modalities (ischemia less than 30 minutes or ischemia up to 120 minutes) are a standard surgical procedure.

The procedure can be done either with a short (less than 30 minutes) or long (90-120 minutes) period of ischemia using a tourniquet - both are standard clinical procedures. This study will compare these two procedures.

The patients will be followed up for 48 hours after the surgery as followed (0, 4, 24 and 48 hours postoperative). Following up criteria are:
1. Calf circumference 15 cm below knee joint to assess 'edema', important clinical outcome to assess ischemia reperfusion injury
2. Amount of morphine intake to assess postoperative pain level
3. Blood samples to measure different complement, coagulation and inflammatory markers

Intervention Type
Procedure/Surgery

Primary outcome measure
Shorter tourniquet time – less expected edema of the calf muscle: Measurement of calf circumference 15 cm below knee joint before operation, immediately post OP, 4h, 24h and 48h post operative.

Secondary outcome measures
1. Plasma levels of CK-MM for muscle damage using an ELISA Kit
2. Plasma levels of pro-inflammatory cytokines and markers of the activation of the plasma cascade systems as well as the endothelium using different commercial available kits for each marker
3. Postoperative pain levels as assessed by postoperative use of analgesic (morphine). Assessment of the amount of morphine needed

All outcomes assessed at 0, 4, 24 and 48 hours after surgery

Overall study start date
01/12/2016

Completion date
31/12/2020

Eligibility

Key inclusion criteria
1. Adults aged 18-90
2. Scheduled for elective total knee arthroplasty

Participant type(s)
Patient

Age group

Adult

Lower age limit
18 Years

Upper age limit
90 Years

Sex
Both

Target number of participants
60 patients

Total final enrolment
40

Key exclusion criteria
1. Conditions which are known to influence edema formation
2. Trauma
3. Infections

Date of first enrolment
01/01/2017

Date of final enrolment
31/08/2020

Locations

Countries of recruitment
Switzerland

Study participating centre
University Hospital Bern (Inselspital)
Orthopaedic department
Freiburgstrasse 8
Bern
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Sponsor information

Organisation
Bern University

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Sponsor type
University/education

ROR
https://ror.org/02k7v4d05

Funder(s)

Funder type
Industry

Funder Name
CSL Behring AG

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal.

Intention to publish date
31/12/2022

Individual participant data (IPD) sharing plan
The current data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date