Obtaining healthy bone marrow and blood to put JUVENTAS in perspective

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Primary Objective: The primary goal of this study is to obtain BM and PB from healthy controls without overt cardiovascular diseases (ie patients that undergo orthopaedic or vascular surgery [atherosclerotic disease excluded]) in order to compare...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Observational invasive

Summary

ID

NL-OMON35539

Source
ToetsingOnline

Brief title
JUVENTAS in perspective

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Critical Limb Ischemia (CLI) / Peripheral Arterial Occlusive Disease (PAOD)

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Nederlandse Hartstichting & Stichting De Drie Lichten

Intervention

Keyword: Blood, Bone Marrow, Healthy controls, Stem Cells

Outcome measures

Primary outcome

The main study parameters tested in this study are the progenitor cell levels, of EPC in particular, in BM and blood of healthy controls and how they relate to levels in patients with CLI. Cells will be counted and characterized using fluorescence activated cell sorting (FACS). This will be performed using the same protocols as for patients suffering from CLI, which participate in the Juventas trial.

With this method the amount of EPCs can be assessed as well as certain other cell populations potentially involved in vascular health and neovascularization. Antibodies to CD34, CD31, KDR, CD133, CD45, CD184, CD140b, CD14 and CD26 will be used.

Secondary outcome

Secondary parameters in this study apply to mechanisms involved in EPC mobilization and function, such as BM and PB levels of growth factors (VEGF, EGF, bFGF, SDF-1a etc), cytokines (IL-6, IL-2 etc) and other mediators such as proteases (MMP*s) and nitric oxide related mechanisms (eNOS, NO, MAPK etc). Additionally, specific cell populations will be isolated (ie mononuclear cell fraction [MNC]) and cultured according to standardized pre-tested culture protocols to obtain mesenchymal stem cells (MSCs; from BM-MNC) and circulating angiogenic cells (CACs; obtained from PB-MNC). The former being involved in progenitor cell mobilization and angiogenic processes and the latter deemed to

be important for paracrine stimulation of angiogenesis.

Different BM derived subfractions (eg BM-MNCs, CD14+, CD34+, and MSCs) will be studied for there in vitro migratory function, using trans-well assays, and in vivo neovascularization stimulating potential in an animal model (hindlimb ischemia mouse model).

Studying levels and function of these cells from healthy donors compared to patients with CLI will provide detailed insights in whether and how the function of (endothelial) progenitor cells is impaired in patients with CLI.

This improved knowledge on disturbed mechanisms will be a foundation to elucidate how we can further improve cell-based therapies in patients with cardiovascular diseases, CLI in particular. These quantitive and functional assays will enable an as optimal as possible use of the materials obtained in the Juventas trial, as well.

Study description

Background summary

Progenitor cells and progenitor cell therapy have raised much interest in the past decade. A wide variety of diseases, mainly of cardiovascular origin, have been associated with reduced numbers and impaired function of (endothelial) progenitor cells (EPC). Much of the EPC research in cardiovascular diseases has focused on levels and function of blood-derived EPC, while the genuine EPC pool resides in its niche in the bone marrow (BM). To draw mechanistic conclusions on disturbance of mobilization from the BM to circulation and dysfunction of the progenitor cells residing in the BM cells harvested from patients (with critical limb ischemia [CLI]) should be placed in perspective to those derived from healthy controls.

Study objective

Primary Objective: The primary goal of this study is to obtain BM and PB from

healthy controls without overt cardiovascular diseases (ie patients that undergo orthopaedic or vascular surgery [atherosclerotic disease excluded]) in order to compare EPC levels (characterized and counted with flow cytometry) of CLI patients and healthy controls in both BM and PB.
The BM and PB-borne progenitor cell levels and several plasma and serum factors involved in neovascularization from controls without cardiovascular diseases will be compared to patients with CLI included in the Juventas trial. The ultimate goal is to provide conclusions on how mechanisms involved in EPC mobilization from the BM to circulation, and progenitor cell numbers and (dys)function in patients with CLI are changed compared to healthy controls and the role of the BM herein.
Secondary Objective(s): To provide a foundation for further improvement of cell- or cell-based therapies in patients with CLI (and cardiovascular diseases in general) based on the findings of this study.

Study design

Cross-sectional observational study

Healthy controls included in this study will not be followed in time, since we are not interested in the outcome of the controls. BM and PB are withdrawn and a short health related checklist will be obtained from the healthy controls (to exclude cardiovascular diseases and to be informed on medication use). Measurements performed in the patient materials are performed at baseline and will be compared to baseline measurements performed in the patients with CLI included in the Juventas trial.

Study burden and risks

The BM will be harvested peroperatively by cannulation of the bone with a needle in order to obtain approximately 20cc of BM by aspirating via a 50cc syringe. In short we will adhere to the following procedure, after the initiation of general or local anaesthesia, the BM puncture site is indicated by the surgeon performing the intervention. The BM puncture site is the location where active BM resides (iliac crest, caput femoris, acetabelum, distal part of the femur or the proximal tibia) and will always be in the area involved in the surgical procedure, thus no extra incisions have to be made. After cannulation of the BM cavity with a BM aspiration needle (15G x 10-68mm), regularly used for BM aspirations at the Department of Haematology and for the BM aspirations performed in the Juventas trial, a 50cc syringe will be applied at the tip of the BM needle and the proper amount (20cc) of BM will be aspired and collected in two sodium-heparin coated 10cc tubes. Afterwards the BM needle will be removed and the surgical procedure will be continued according to the normal surgical routine.
BM harvesting has been performed with low complication rates in general haemathology as well as in clinical trials (ie Juventas trial). In these cases

the bone is not directly visualized and hence chance for complicated procedures seems even more likely. Additionally, in this study we only require a rather small amount of BM when compared to the previously mentioned procedures (100-1000cc). Besides this, a similar procedure is yet performed during orthopaedic surgery in the UMC Utrecht without complications.
BM aspiration is generally considered to be safe and feasible. The majority of the complications are related to the large amount of BM harvested (up to 1000cc) and the anaesthesia applied. BM aspiration during general surgical procedures to obtain small amounts of BM has been reported previously by others to be safe and feasible.
The subjects in this study do neither directly nor indirectly benefit from participation. Nevertheless, the additional burden and risks are fairly small and seem well tolerable and the results serve potential future mechanistic insights and therapeutic developments for large amounts of patients suffering from peripheral arterial disease. Moreover, the availability of blood and BM from healthy controls would greatly enhance the information and strengthen the potential mechanistic conclusions obtained from the patient materials obtained in the Juventas trial (06/030).

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

- Age >18 years;
- Patients undergoing surgical procedures during which bony structures containing active bone marrow are encountered (eg pelvic girdle, caput femoris, acetabulum, distal femur or proximal tibia);
- Scheduled for surgical intervention;
- Approval of both the anaesthetist and the surgeon performing the surgical procedure;
- Written informed consent.

Exclusion criteria

- History of overt cardiovascular disease;
- Major trauma involving multiple bones or damaged internal organs;
- Known disease originating from the bone marrow (ie leukaemia, lymphoma, metastatic disease);
- Chronic autoimmune disease (ie SLE, rheumatic arthritis etc);
- Known infection with HIV, hepatitis B or C virus.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	52
Type:	Actual

Ethics review

Approved WMO Date:	03-10-2011
Application type:	First submission
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	NL37442.041.11