Human cell-sources for heart valve tissue engineering.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac valve disorders
Study type	Observational non invasive

Summary

ID

NL-OMON33239

Source
ToetsingOnline

Brief title
The HVTE Cell-source study

Condition

- Cardiac valve disorders

Synonym
not applicable

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: cellsource, heart valve, human, tissue engineering

Outcome measures

Primary outcome

The output of this study is composed of several components:

- Determination of expansion rate: which celltype can be expanded in the shortest period of time to reach clinically relevant numbers.

- Determination of cell phenotype: are the isolated cells still progenitors after in vitro expansion, or did they differentiate into a more specialized celltype? Known markers for the cells of interest are:

o MFs: vimentin and α-smooth muscle actin.

o Cardiac auricle: c-kit, Sca1, GATA4

o Bone marrow: CD73, CD90, CD105

o Blood: CD14

For this, we will use PCR, immunocytochemistry and FACS-analysis.

- Determination of ability to produce matrix. To be suitable for heart valve tissue engineering, cells need to be able to produce sufficient amounts of collagen. In our investigation, we will analyze this on mRNA and protein levels by investigating expression of marker protein Hsp47 and expression of collagen type 1 and 3. This will be done by PCR, immunocytochemistry and western blotting.

- Determine ability to produce proteins involved in matrix remodeling. Although the aortic valve should be able to resists high blood pressure, excessive

production of matrix can lead to stiff (fibrotic or stenotic) valves. The cells therefore need to be able to produce proteins that can degrade matrix and proteins that inhibit matrix degradation. This way, excessive matrix can be removed to prevent fibrosis, while it can be maintained at locations that bear the heaviest loads. To evaluate ability to remodel matrix, we will look at expression of proteases (MMP1 and 2) and their tissue inhibitors (TIMP1 and 2) on both mRNA and protein level, using PCR, zymography and western blotting.
- Finally, we aim to seed expanded cells on a small strip of a degradable carrier, to test the ability of the cells to make a strong tissue strip.
Strength of the tissue will be tested using straining-assays and several histochemical analyses to evaluate production and deposition of collagen, crosslinks between collagen fibers and deposition of other matrix proteins like glycosaminoglycans (GAGs).

Secondary outcome

not applicable

Study description

Background summary

Approximately 3000 heart valve replacements are performed in the Netherlands annually. The majority involves the aortic valve which (in comparison to the mitral valve) is almost impossible to repair. Stenosis and regurgitation (back flow through the valve) are the most important indications for aortic valve replacement. Currently available prostheses used for valve replacement have several disadvantages. Mechanical valves need life-long anti-coagulation therapy and biological prosthese have a limited durability. These valves also lack the ability to grow and remodel. The ideal prosthesis would be a living (growing) valve that does not cause thrombotic effects and does not evoke immune responses.

Tissue engineering is a technique in which autologous cells are seeded on an (artificial) carrier, or scaffold, to create a specified tissue. For heart valve tissue engineering, this would mean that cells derived from a patient that suffers from a valvular disease could be used to form a healthy living, functional heart valve. Proof of principle for this application has been provided by successful implantation of tissue engineered valves in pulmonary position in sheep.

Study objective

Our investigation aims at the translation of heart valve tissue engineering from the laboratory
bench to clinical application. In the present study, we compare different cell sources in their ability to form heart valve tissue. Furthermore, as we focus on translational medicine, it is necessary to use Good Tissue Practice (GTP) protocols.

Study design

in vitro

Study burden and risks

There is only very minor burden for these patients and no extra risk.
Requested samples:
- Great Saphenous Vein: ± 2 cm (For CABG usually a total of 25-35 cm of the GSV is required, for the study we will take out 2 cm extra). The scar on the leg will be 2 cm longer.
- Bone marrow: ± 2 cc (Following median sternotomy, bone marrow leaks out of the sternum, but perhaps some extra bone marrow needs to be scraped out of the sternum to obtain this volume). We expect no aaditional risk for the patient.
- Cardiac auricle: 2 g (In patient undergoing on pump CABG, a small piece of the cardiac auricle is removed for venous canulation and normally thrown away. The total weight of the heart is approximately 350 g).
- Blood: ± 20 mL (total volume of blood is approximately 5000 mL).
No other visits, questionnaires or examinations are required what so ever. No additional discomfort will occur. There will be no benefit either.

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

Patients that must undergo on pump coronary artery bypass-grafting including a venous graft.

Exclusion criteria

None

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-10-2009
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO

Date:	22-09-2009
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	NL27353.041.09