Study Protocol

VM_Compression

ClinicalTrials.gov Identifier: NCT04637997

Influence of flat-knitted compression stockings class I/II on the morphology of venous malformations

- Is there a therapeutic effect?

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1 Study title, version number, version date

1.1 Study title

Influence of flat-knitted compression stockings class I/II on the morphology of venous malformations

- Is there a therapeutic effect?

1.2 Version number

Version 1.0

1.3 Version date

18.10.2017

2 Project summary

Diseases with vascular malformations are rare and often congenital, affecting patients of all ages. Depending on their extent and localization, they can cause discomfort and, especially if activity is restricted, lead to loss of or reduced quality of life.

The therapy is usually reserved for a few specialized centers and includes interventional sclerotherapy as well as conservative therapy by compression with appropriate compression stockings. However, there are currently no study-based recommendations for this approach.

The aim of this study is to prove a therapeutic effect of compression therapy using flat-knitted compression stockings on venous malformations of the extremities and to derive from this a therapy recommendation in connection with an improvement in the health status and quality of life.

For this purpose, patients with a confirmed venous malformation of the upper or lower extremity independent of previous therapy will be included. We will investigate patients with epi- and/or subfascial localization of the venous malformation independent of the local extent (cross-articular or not).

3 Responsibilities

3.1 Study lead

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3.2 Sponsoring

Department of Vascular Surgery, University Hospital Erlangen.

The company *medi* from Bayreuth, Germany, finances the study, but does not function as a sponsor.

4 Scientific background

Vascular malformations are a rare disease with a prevalence of 1.5% in the whole population. 2/3 of peripheral vascular malformations are venous malformations, of which 40% are located at the extremities.

They develop congenitally and are characterized by growth proportional to body growth. Hormones (puberty, pregnancy), infections, operations, traumas stimulate growth. They do not show any regression tendencies.

Depending on their localization and extension, they can lead to considerable discomfort with limited physical activity and loss of quality of life.

In Germany, the therapy of venous malformations lies within the responsibility of a few specialized centers and depends on the physical impairment and subjective symptoms. In addition to interventional sclerotherapy, conservative therapy is performed in the form of compression therapy with appropriate compression stockings. To date, however, there are no study-based investigations and recommendations for this kind of therapy.

The study is intended to investigate the influence of flat-knitted compression stockings of different compression classes (class I and II) on the morphology (volume behavior) of venous malformations and to derive a therapeutic recommendation. The hypothesis is that a sufficient compression effect is already present in stockings of compression class I. We anticipate a relevant effect on the volume of the malformation under this kind of treatment. Furthermore, it is assumed that the effect of the compression therapy occurs immediately after the application of compression.

5 Study objectives

The aim of this study is to prove a therapeutic effect of compression therapy using flat-knitted compression stockings on venous malformations of the extremities and to derive from this a therapy recommendation in connection with an improvement in the health status and quality of life.

5.1 Primary/secondary objectives and hypotheses

Primary hypothesis:

The hypothesis is that a sufficient compression effect with volume relevance to the malformation is already present in compression class I.

Secondary hypotheses:

Furthermore, it is assumed that the effect of the compression therapy occurs immediately after the application of compression and has an effect on the patient's quality of life.

Primary objective:

- Determination of volume difference of the malformation by use of non-invasive measurements (Perometry, MRI)

Secondary objective:

- Determination of volume difference of the malformation immediately after the application of compression by use of non-invasive measurements (Perometry, MRI)
- Determination of the quality of life by the questionnaire SF-12
- Determination of handling and wearing comfort of compression stockings in everyday life by the questionnaire "*Tragekomfortbogen*" (*comfort of wearing questionnaire*)

5.2 Study type

This is a prospective, monocentric, double-blinded, non-invasive, interventional single group study.

6 Target parameters

6.1 Primary target:

- Volume of affected extremity(ml)
    - *This target is measured non-invasively by perometry and MRI*

6.2 Secondary targets:

- Volume of affected extremity immediately after application of compression (ml)
    - *This target is measured non-invasively by perometry and MRI*
- Quality of life by SF-12 (short form 12) questionnaire
- Handling and wearing comfort of compression stockings in everyday life by questionnaire "*Tragekomfortbogen*" (*comfort of wearing questionnaire*)

7 Study design

7.1 Monocentric / multicentric

This is a monocentric interventional comparative therapy study with prospective data acquisition.

7.2 Study arms: intervention/control

This is a single group study with crossover components. Participants receive randomly and double-blinded either class I compression stockings or class II compression stockings. After four weeks, an exchange of compression classes takes place, so that all participants wear both classes of compression stockings within eigth weeks.

7.3 Randomization

Randomization of patients is done with regard to the order of compression classes of the compression stockings. Patients are randomly assigned to compression class II or I for the first four weeks of compression therapy.

7.4 Blinding

This is a double-blind study. Neither investigator nor patient know the compression class (class I versus class II) of the compression stockings used in the different investigation periods in this patient.

8 Study population

8.1 Inclusion and exclusion criteria

Inclusion criteria:

- Patients with a confirmed venous malformation of the upper/lower extremity independent of previous therapy with epi- and/or subfascial localization of the venous malformation independent of the local extent (cross-articular or not)
- Compression stocking can be put on independently or by the parents
- Written declaration of consent present

Exclusion criteria:

- Lack of compliance, patient is not available for control appointments
- Additional drug therapy (anticoagulation) for extensive venous malformations with threatening thromboembolic complications
- Known allergic reaction/intolerance to components of flat-knitted compression stockings
- Pregnancy
- Rejection of the study participation by the patient
- Contraindications for the planned MRI examination (pacemakers, implants not suitable for MRI, claustrophobia)

- Occurrence of an emergency situation
- Severe heart failure as contraindication for compression therapy
- PAD as contraindication for compression therapy

8.2 Participant number

Approximately 25 patients with venous malformation of the upper/lower extremities, age 6-70 years are to be included. Compression in the form of individually fitted compression stockings will be applied by the patient himself or by his parents.

8.3 Recruitment routes and measures

Patients are informed about the possibility of participating in the study during a routine presentation of the vascular surgery consultation hours. If patients are willing to participate, they will be fully informed about objectives and methods, benefits and risks, and the revocability of their participation in the study.

9 Study plan

9.1 Procedure for informing about and obtaining consent

Participants can only be included in the study after a written declaration of consent has been given. The written declaration of consent requires that the patients are informed orally and in written form about the objectives and methods, benefits and risks as well as the revocability of their participation in the study.

It must be clearly communicated to the study participant that a withdrawal of consent is possible at any time and without any disadvantage for further treatments or therapy.

The original of the consent form is kept in the study folder at the study site. The participant receives a copy of the patient information and consent form.

9.2 Measurements

Investigation day 0

After informing of the subjects, gender, age and localization of the venous malformation are recorded for all study participants as basic data. The measurements for the individualized preparation of class I and II compression stockings are then taken.

Between investigation day 0 and 28 participants do not wear any compression stockings.

Investigation day 28

Participants fill out the SF-12 questionnaire. Then a measurement of the volume of the affected extremity is performed by perometry and MRI. First without any compression stocking and afterwards with both individualized compression stockings of class I and II.

This is followed by a four-week treatment with one of the two compression stockings, whereby the selection of compression class will be double-blinded.

Investigation day 56

After four weeks of compression therapy with the first compression stocking all subjects are examined at day 56 by SF-12 questionnaire and by the questionnaire "*Tragekomfortbogen* " (*comfort of wearing questionnaire*). Then the therapy is continued for four more weeks with the remaining compression stocking that has not yet been worn. Even during this compression therapy the compression class is unknown to the patient and investigator.

Investigation day 84

After the four weeks lasting therapy with the other compression class, participants are examined at day 84 in the two questionnaires (SF-12 and "*Tragekomfortbogen* " [*comfort of wearing questionnaire*]) again.

Figure 1 shows the graphical presentation of the planned measurements as well as their chronological sequence for each subject.

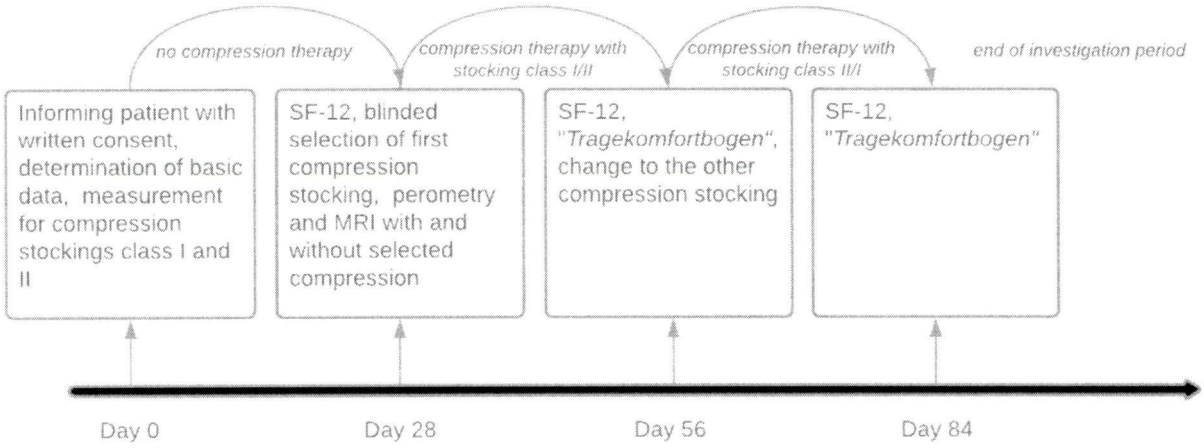


Figure 1: graphical presentation of all measurements with chronological sequence for each subject

9.3 Recording of target parameters

- Determination of volume of the malformation by perometry
- Determination of volume of the malformation by MRI
- Determination of quality of life by SF-12 (questionnaire)
- Determination of handling and wearing comfort of compression stockings in everyday life by "*Tragekomfortbogen*" (*comfort of wearing*) (questionnaire)

9.4 Total study duration

Corresponding to the number of patients, the expected total duration of the study until the inclusion of the last patient is approximately 12 months. Participation in the study overall takes approximately 4,5 hours per patient. For the investigation day 0 we assume an examination duration of approximately three hours. Each of the following investigation days (day 28, 56 and 84) will last approximately half an hour. There are four examination time points per patient needed.

10 Risk-benefit analysis

10.1 All study related risks

Time periods without compression therapy

While patients do not wear stockings (especially between investigation day 0 and 28), swelling and slight pain of the affected extremity may occur. However, there are no health risks.

Compression therapy

Incorrect measured compression stockings can cause skin damage, which can result in lacerations, blisters and pressure sores or necrosis. Nerve damage or deep vein thrombosis can also develop. Since the stockings are individually fitted by experts and only low compression classes are used, the risk of such damage is considered extremely low. Other risks associated with compression therapy will be avoided by exclusion of patients with contraindications for compression therapy.

MRI

Since it is a native MRI (1.5 or 3.0 Tesla) without contrast medium, hardly any risks are to be expected from the examination.

Damage caused by metal-containing implants etc. is avoided by excluding these patients from the examination.

Claustrophobia may occur, in which case the examination is aborted.

The noise exposure caused by the examination can lead to reduced hearing ability, therefore all patients wear hearing protection. Due to the relatively short duration of the examination of 20 minutes and the wearing of hearing protection, the risk of damage to the inner ear is considered extremely low.

The native MRI examination with field strengths of 1.5 or 3.0 Tesla is a routine routine method and no negative changes in the organism have been described so far.

Perometry

There are no known risks or side effects related to perometry.

10.2 Benefits associated with the study

The data obtained in the study can provide essential information about the behavior of venous malformations under compression therapy and the quality of life during this therapy. It is therefore possible that this therapeutic procedure can be used in the future to treat patients conservatively with an increased quality of life.

10.3 Termination criteria

Termination criteria for the individual participant:

Participation in the study is discontinued if any study related risks e.g. skin or nerve damage/deep vein thrombosis caused by compression stockings or contraindications for MRI occur.

Termination criteria for the whole study:

Termination of the entire study must be declared if significant and unobserved serious adverse health effects, which have not been known or observed so far, occur. Otherwise, a termination of the entire study is not planned.

10.4 Statement on medical justifiability

Based on previous experience with compression therapy and MRI the risk of occurrence of unwanted events is stratified as extremely low.

11 Biometrics

Continuous variables are given as means with standard deviation. Categorial variables are given as frequencies and percentage. Although making use of a crossover design, we do not expect any carryover or period effects due to the nature of the treatments. Therefore, differences between the treatments and baseline measurements are evaluated using Wilcoxon signed rank tests. Moreover, linear regression analysis is used to adjust for variations in

baseline measurements for the direct comparison of compression classes. A p-value below or equal to 0.05 is considered to indicate statistical significance.

All results will be calculated using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

12 Data management and data protection

12.1 Data acquisition and storage

All raw data, such as patient files, are source documents. Their availability is ensured for routine monitoring. The participation of the individual patients or test persons in the study is documented. The study leader maintains an independent list for the identification of the participating patients. This list contains the names and date of birth as well as the date of examination and pseudonymization codes of the patients and subjects. The study leader is responsible for the quality of data collection and storage. The data storage (complete data) takes place on computers or specially designed network drivers of the University Hospital Erlangen.

Digital data acquisition and storage on durable and secured carriers for 10 years in the facility (Institute of Radiology, University Hospital Erlangen) according to the guidelines of the Friedrich-Alexander-University Erlangen-Nuremberg for the protection of good scientific practice of May 13, 2002, among others in the PACS (Picture Archiving and Communication System) of the University Hospital Erlangen, which is also used for the image archiving of all radiological images in everyday clinical practice.

12.2 Pseudonymization

Prior to a scientific analysis of the materials and data of this study, all information will be pseudonymized according to the guidelines of the Federal Data Protection Act. Patient identification list is exclusively in the possession of the investigator.

Data will only be shared with the above-mentioned centers/persons involved in the direct evaluation of the study and treatment of the patient.

12.3 Data transfer

A transfer of the data or biological material is not intended in this study and will not take place. The study results can be published anonymously, whereby it will not be possible to draw conclusions about the identity of the participating persons. The data will be kept for ten years and will then be destroyed.

12.4 Revocation, data deletion

If the declaration of consent is revoked, data collection up to this point can be taken into account. The patient has the right to demand that the data be destroyed. The revocation and the request for data deletion is possible at any time. The participants will be explicitly informed about this orally and in writing.

13 Handling of biomaterials

No biomaterials are obtained.

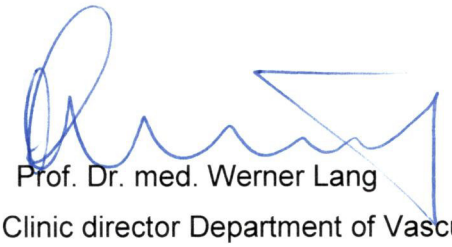
14 Insurance

No separate proband insurance will be concluded.

15 Signatures

Dr. med. Antje Mükke

Study director



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