This study will clarify the effect of a prehabilitation program on delirium incidence in chronic limb threatening ischemia patients. This protocol describes the design of the study and the content of this specific prehabilitation program. The objective is to evaluate the effect of a multicomponent, multidisciplinary prehabilitation program focusing on optimizing the patient’s overall health and includes delirium risk assessment, nutritional optimization, home-based physical therapy, iron infusion in case of anaemia and a comprehensive geriatric assessment in case of frailty. The primary outcome is the incidence of delirium. Secondary outcomes include quality of life, amputation-free survival, length of hospital stay and mortality. Exclusion criteria are the requirement of acute treatment or patients who are mentally incompetent to understand the procedures of the study or to complete questionnaires. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group. A historical cohort from the same hospital is used as a control group.
• Delirium risk assessment
• Nutritional optimization,
• Home-based physical therapy,
• Iron infusion in case of anaemia
• Comprehensive geriatric assessment in case of frailty.
• Involvement of informal caregivers

This study will clarify the effect of prehabilitation on delirium prevention in patients with chronic limb threatening ischemia (CLTI). New insights will be obtained on optimizing a patient’s preoperative mental and physical condition to prevent postoperative complications, including delirium.

Introduction

Chronic Limb Threatening Ischemia (CLTI) is the final stage of Peripheral Arterial Disease (PAD).\(^1\)–\(^3\) It is defined by the presence of chronic ischemic rest pain, non-healing ulcers, tissue loss or gangrene.\(^1\) Annually, 500–1000 new cases of CLTI occur per 1 million people in Europe.\(^4\) Treatment is mainly aimed at limb salvage and consists of endovascular or surgical revascularization. Recently, in a small population, mostly consisting of fragile patients, conservative treatment was added as a treatment strategy.\(^5\)–\(^7\) Conservative treatment consists of wound care, antibiotics and minor amputations and is not associated with a higher mortality rate than the revascularization treatment options.\(^6\)–\(^8\) Recent studies report 1-year mortality rates of CLTI varying from 29% to 51% for patients aged 65 and older.\(^1,5,7\) Additionally, none of the invasive treatment strategies guarantees limb salvage; up to a quarter of the CLTI patients is at risk for major amputation despite revascularization attempts.\(^7\)–\(^9\) Furthermore, CLTI is both more prevalent and more severe in older people.\(^1,5,7,10\)

With the rapidly ageing population, the incidence of CLTI is expected to increase. This will have an impact on the functional and cognitive outcome and the Quality of Life (QoL) of the older vascular surgical population and will contribute to the rise of healthcare costs.

A frequent and severe complication in the older, hospitalized patient is delirium. This serious neuropsychiatric disorder is characterized by an acute and fluctuating change in cognition and a disturbance of consciousness, and is associated with prolonged hospital stay, worsening of functional and cognitive performance, decreased QoL, death and a significant increase in healthcare costs.\(^11\)–\(^13\) The incidence of postoperative delirium in older CLTI patients is high (5 to 39%), and may vary with treatment strategies for CLTI.\(^14,15\) There is an urgent need for delirium prevention. Currently no specific guidelines to prevent delirium in chronic limb threatening ischemia patients exist.\(^16\)

Prehabilitation is defined as preoperative optimization of the patient’s functional capacity and may be accomplished by offering a multicomponent, multidisciplinary program.\(^17\)–\(^21\) Prehabilitation is associated with a lower incidence of several postoperative complications, including delirium.\(^18,22,23\) This beneficial effect of prehabilitation is reported in patients undergoing elective abdominal aortic aneurysm (AAA) repair and patients undergoing surgery for colorectal carcinoma (CRC).\(^17\)–\(^19\) However, this potential positive effect has not yet been investigated in CLTI patients, possibly due to the assumption that these patients require immediate revascularization and have no time for a prolonged preoperative trajectory. From various studies it is nowadays known that immediate revascularization is not always required since conservative therapy could fit certain CLTI patients.\(^6\)–\(^8\) Therefore, we assume that a selected group of CLTI patients can be considered for a prehabilitation program prior to revascularization.

In our hospital we developed a specific, three-week multicomponent prehabilitation program for older CLTI patients based on our results of prehabilitation in older patients undergoing surgery for an AAA or for CRC.\(^18,19,24\) The primary aim of the program is to diminish the delirium rate. We designed a prospective observational cohort study to investigate the effects of the program on the incidence of delirium, functional outcome and quality of life in older CLTI patients that require surgical or endovascular revascularization. This paper describes the design of the cohort study and the background of the prehabilitation program.
Methods
Design and Setting
A prospective observational cohort study will be performed in a non-university, large teaching hospital in the Netherlands during the period 2013 to 2023. The abbreviation of the study is PETRI, which stands for Prehabilitation in the Elderly with chronic limb Threatening Ischemia.

The prehabilitation program for CLTI is implemented since November 2020. The evaluation period covers November 2020 to May 2023. Table 1 shows an overview of the study.

A historical group of patients, treated for CLTI between December 2013 and December 2019 and meeting the same inclusion criteria, will be used as a control group to evaluate the effects of the prehabilitation program. This data was collected retrospectively and most of this database was reported by Roijers et al.4 The specific inclusion period of 2013 to 2019 instead of 2013 to 2020 was chosen because of the COVID-19 pandemic, which possibly affected the normal course of healthcare in the Netherlands in 2020. We considered to make a comparison to CLTI patients < 65 years as a control group. We refrained from doing this, since the incidence of a delirium is significantly lower in younger patients, impairing statistical power.11,22,25–27 The method for delirium screening and the method of managing CLTI patients has not changed over time.

Recruitment and Participants
We aim to evaluate patients aged ≥ 65 years, visiting the vascular surgeon with CLTI. From November 2020 these patients were all referred to the “Multidisciplinary Vascular surgical outpatient clinic for the Elderly” (MVE) for screening and commencing the prehabilitation program. Patients will be included after written informed consent.

In- and Exclusion Criteria
Eligibility is considered when CLTI patients are planned for surgical or endovascular revascularization. Exclusion criteria for this study are: patients receiving conservative therapy; the requirement of acute hospitalization or acute treatment on the same day as the initial visit to the outpatient clinic; or if patients were judged to be mentally incompetent by the physician (not involved in the study) to understand the purpose and procedures of the study, to complete questionnaires or to give consent to participate.

Primary and Secondary Outcomes
The primary outcome is the incidence of delirium. Our daily screening method for delirium is described in earlier reports.12,24 Summarizing, it is based on the 13-item Delirium Observation Screening (DOS) score in combination with the DSM-V criteria and the Confusion Assessment Method (CAM).28,29 The geriatrician will be consulted in case of DOS-scores ≥ 3 to confirm the diagnosis of delirium. The DOS score will be routinely registered for all patients in both the control and the intervention groups. The duration of delirium in days will be noted.

Secondary outcomes are postoperative complications, rate of major amputations, amputation-free survival (AFS), length of hospital stay (LoS), in-hospital mortality, 30 day mortality, 6 month mortality and 12 month mortality. Complications will be categorized according to the Clavien–Dindo classification.30

The QoL will be assessed using the WHOQOL-BREF questionnaire.31 Functional outcome and health status will be measured by the SF-1232 and VascuQoL-6-NL33,34 questionnaires. The patient’s informal caregiver will be asked to complete the “Caregiver Strain Index Questionnaires”.35 The questionnaires will only be used in the prehabilitation group.

Sample Size Calculation
Based on previous studies, we assume that the rate of delirium in patients with CLTI is approximately 18%.4,14,25,36 Our hypothesis is that the implementation of the prehabilitation program will decrease the rate of delirium from 18% to 9%.

With an estimated power of 80%, a predefined p-value of 5% and an intervention to control ratio of 1:2, the study requires a total sample size of 504 patients of which 168 patients in the intervention group and 336 patients in the control group. This calculation was carried out using the online statistical power analysis program “Statulator”.37
| Care Worker               | Population                      | Action/test                      | Time Point, Study Period |
|--------------------------|---------------------------------|----------------------------------|--------------------------|
| Vascular surgeon         | All patients                    | Diagnosis                        | T0                       |
|                          |                                 | Request additional imaging       | T1                       |
|                          | All CLTI patients ≥ 65 years    | Referral to MVE                  | T2                       |
|                          |                                 | Definitive treatment plan        | T3                       |
|                          |                                 |                                  | T4                       |
|                          |                                 | Start PETRI-study                |                          |
| Biochemistry tests<sup>a</sup> |                                 |                                  |                          |
| VNP                      | All patients                    | Written informed consent         | T0                       |
|                          |                                 | Baseline characteristics         | T1                       |
|                          |                                 | Vital functions                  | T2                       |
|                          |                                 | Fall screening                   | T3                       |
|                          |                                 | KATZ-ADL                         | T4                       |
|                          |                                 | ISAR-HP                          |                          |
|                          |                                 | SNAQ-RC                          |                          |
|                          |                                 | MMSE                             |                          |
|                          |                                 | G8                               |                          |
|                          |                                 | V-possum                         |                          |
|                          |                                 | ASA-score                        |                          |
|                          |                                 | Charlson comorbidity index       |                          |
|                          |                                 | Check for delirium               | T0                       |
|                          |                                 |                                  | T1                       |
|                          |                                 |                                  | T2                       |
|                          |                                 |                                  | T3                       |
|                          |                                 |                                  | T4                       |
| Physiotherapist          | All patients                    | MIP                              | T0                       |
|                          |                                 | DEMMI                            | T1                       |
|                          |                                 | Grip strength                    | T2                       |
|                          |                                 | TUG                              | T3                       |
|                          |                                 | TCS                              | T4                       |
|                          |                                 | 10MWT                            |                          |
|                          |                                 | Home exercises<sup>b</sup>        |                          |

(Continued)
Table 1 (Continued).

| Time Point, Study Period | Outpatient Clinic | MVE | MM | During Admission | Discharge | 6m | 12m |
|--------------------------|-------------------|-----|----|------------------|-----------|-----|-----|
| 6m, 6 months; 12m, 12 months | MVE, Multidisciplinary Vascular surgical outpatient clinic for the Elderly; MM, Multidisciplinary meeting; CLTI, Chronic Limb Threatening Ischemia; VNP, Vascular Nurse Practitioner; KATZ-ADL, Katz index of Independence in Activities of Daily Living; ISAR-HP, Identification of Seniors at Risk – Hospitalized Patients; SNAQ-RC, Short Nutritional Assessment Questionnaire for Residential Care; MMSE, Mini-mental state examination; G8, Geriatric 8 (frailty score); V-possum, Vascular-Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity; ASA, American Society of Anaesthesiology Score; MIP, Maximal Inspiratory Pressure; DEMMI, The de Morton Mobility Index; TUG, Time Up and Go; TCS, Time Chair Stand; 10MWT, 10 meter Walking Test; MNA-SF, Mini Nutritional Assessment Short-Form; BMI, Body Mass Index; CGA, Comprehensive Geriatric Assessment; WHOQOL-BREF, World Health Organization Quality of Life Brief Version; SF-12, Short Form Health Survey; VascuQoL-6-NL, Vascular Quality of Life-6-NL. |

Outpatient Clinic

Patients with suspected CLTI will be examined by the vascular surgeon at the first outpatient clinic visit. Diagnosis of CLTI is based on the anamnesis with complaints of ischemic rest pain or night pain, (minor) tissue loss, non-healing ulcers and/or focal gangrene with diffuse pedal ischemia or impaired perfusion, quantified by a flat or barely pulsatile
ankle or metatarsal pulse volume recording (PVR), a low resting ankle pressure, a low ankle brachial index and/or a low toe pressure. Additional examination may include an Ankle-Brachial Index (ABI) or toe pressure (TP) in case of non-compressible vessels. Vascular imaging is performed by duplex, Magnetic Resonance Angiography (MRA) or Computed Tomography Angiography (CTA). The location and extent of the vascular pathology are scored by using the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease II (TASC-II) and description of the crural outflow in 1, 2 or 3 arteries.

**Standard Pre-Operative Workup**

In the period prior to the implementation of the prehabilitation program and the start of the MVE, CLTI patients received the work-up as described in the “outpatient clinic”-section above. Patients were screened by the cardiologist and anaesthetist prior to surgery. The schedule of this pre-operative workup remained unchanged for patients in the prehabilitation program. The components of the novel prehabilitation program are described below.

**Multidisciplinary Vascular Surgical Outpatient Clinic for the Elderly (MVE)**

CLTI patients ≥ 65 years are referred to the MVE. Patients are required to bring an informal caregiver. Involvement of an informal caregiver will be helpful in understanding and remembering information and may increase the compliance of the intervention. If required, home care for after discharge will already be arranged. Blood samples are drawn and several tests will be performed to obtain an impression of the patient’s condition and to start relevant or required interventions (Table 1). All components of the program are performed on one morning or afternoon.

The outcomes of all tests are reported in a weekly multidisciplinary meeting involving vascular surgeons and intervention radiologists. This information is used in addition to the anatomical lesion and complaints of the patient in the decision-making on treatment modality, which results in the advice for surgical revascularization, endovascular revascularization or conservative therapy.

The different components of the MVE are briefly described below.

**MVE: Vascular Nurse Practitioner (VNP)/Researcher**

The first MVE screening is performed by a “VNP” or researcher and focusses on baseline characteristics, signs of frailty, comorbidities, cognitive function and the presence of risk factors for delirium. Patients might subsequently be referred to the geriatrician, dietician and a “quit smoking coach” if indicated. Indications for referral are described in Table 1.

**MVE: Physiotherapist**

The second screening is performed by a physiotherapist. The physical state, muscle strength and cardiopulmonary condition of the patient are examined by performing functional tests, as described in Table 1.

Patients will receive instructions for tailor-made, unsupervised, home-based exercises, according to the “prehabilitation-peripheral arterial disease-protocol” (Supplemental Table 1). It is expected that home-based training lowers the burden for patients, increases compliance and decreases healthcare costs when compared to supervised in-hospital training. Exercises are aimed at gaining strength, training of transfers, training of respiratory muscles and increasing cardiopulmonary condition. Patients must keep track of their activities using a daily diary.

**MVE: Geriatrician**

If indicated (see Table 1), patients will undergo a comprehensive geriatric assessment (CGA) performed by a geriatrician to assess frailty and the risk of developing a delirium. Previous studies showed that performing a preoperative CGA in patients ≥ 65 years undergoing vascular surgery is associated with a shorter LoS and a lower incidence of postoperative complications. Based on the CGA, the geriatrician will, among other things, provide information to patient and family and define preventive measures for delirium and functional decline.
MVE: Dietician
If indicated (see Table 1), a dietician will evaluate the nutritional status of the patient. Patients may receive high protein nutrient drinks and recommendations on a high protein diet. All patients are informed on preoperative optimization of their diet.

MVE: Quit Smoking Coach
Active smokers are referred to a “quit smoking coach” to receive guidance in reducing nicotine abuse. The guidance is offered by “ZoHealthy lifestyle coach”, on an individual basis or in group therapy and will be commenced within 3 days after referral.

MVE: Ferinject Infusion
In case of anaemia, defined as a level of haemoglobin <8.1 mmol/L for male patients and <7.4 mmol/L for female patients, patients will receive iron infusion using Ferinject (ferric carboxymaltose) during a day-care admission. Patients will receive an intravenous dose of 1000mg Ferinject in 15 minutes.

Clinical Admission
At hospital admission, biochemistry tests will be repeated to check whether the haemoglobin level is improved and screening for delirium is performed as described in “study objectives”.

Process Evaluation
The patient’s compliance and experience with the program will be scored by completing the process evaluation form. This will be discussed by phone if it was not already completed by the patient during hospital admission. Patients register their activities during prehabilitation in a diary and complete the “process evaluation form” during their hospital stay. Within this form they score whether they followed the advices of the dietician, physiotherapist, geriatrician, “quit smoking coach” and how they experienced the prehabilitation program.

Follow-Up
All patients will receive the standard local follow-up schedule after revascularization. All QoL questionnaires will be completed again after 6 and 12 months of follow-up.

Interim Analysis
An interim analysis will be performed 12 months after start of this study. This analysis will be focused on the incidence of delirium, amputation free survival and 30-day mortality in the prehabilitation group compared to our control group. If these outcomes are worse than the historical cohort, we believe it would be unethical to continue the prehabilitation program.

Statistical Analysis
Statistical analyses will be performed using IBM SPSS statistical software (SPSS Inc., Chicago, Illinois, USA). A two-sided p-value <0.05 will be considered statistically significant. Results of categorical data variables will be described in frequencies with percentages and differences will be tested using the Chi-square test. Continuous data will be described as median (interquartile range) and Student’s t-tests or Mann–Whitney U-tests will be performed to test for group differences, depending on distribution of the data. Ordinal variables will be tested using the Mann–Whitney U-test. Adjusted analysis with prognostic baseline characteristics (eg gender, age) will be performed using regression analysis. Logistic regression analysis, using the “enter” method, is the primary analysis for the incidence of delirium, with adjustment for key prognostic factors found in earlier research (age, history of delirium and diabetes mellitus).\textsuperscript{4,43} This analysis corrects for baseline differences, optimizes statistical power, and provides better individualized treatment effect estimates.\textsuperscript{44} Missing data will be studied for specific patterns of occurrence, and multiply imputed using the Multiple Imputation by Chained Equations (MICE) algorithm.\textsuperscript{45}

Data analysis will be done according to the intention-to-treat concept, which implies that all patients are included in the analysis irrespective of whether they completed the prehabilitation program.
Ethics Committee Approval and Registration Number

Ethical approval for this study is obtained from Medical research Ethics Committees United (MEC-U), registration number W21.061. This study complies with the Declaration of Helsinki.

Discussion

To the best of our knowledge, this is the first study that will investigate whether prehabilitation reduces the incidence of delirium in patients with CLTI. Earlier studies already showed that prehabilitation successfully reduces the incidence of postoperative complications - including delirium - after major elective abdominal surgery. This intervention has not yet been explored in patients with CLTI. The typical CLTI patient is old, has several comorbidities and has at least a history of tobacco use and is therefore at greater risk for developing postoperative delirium. Investigation of the effect of prehabilitation on the incidence of delirium in CLTI patients is urgently needed.

Under the assumption that all patients with CLTI require acute revascularization, prehabilitation was not yet considered for this specific population. A prehabilitation trajectory should last just long enough to ensure its desired effect, but this should be without delay in treatment to prevent adverse outcomes to occur. Recent studies showed conservative treatment to be an appropriate option for certain CLTI patients. Stavroulakis et al and Santema et al reported no statistically significant differences in 1-year overall survival between CLTI patients receiving endovascular, open or conservative treatment. These novel findings suggest that revascularization does not always need to be performed immediately and gives an opportunity to optimize the CLTI patient’s preoperative condition using a prehabilitation program.

Since the primary interest lays in the prevention of delirium after revascularization, patients treated conservatively are excluded from this study. Conservatively treated patients are treated at the outpatient clinic and do not suffer from postoperative complications, such as delirium.

The goal of the MVE is not only to optimize patients, but also to identify patients who would not benefit from revascularization due to a greater risk for postoperative complications. Therefore, these patients will be treated conservatively. This is in line with the “do no further harm”-principle.

Severe cognitive impairment, eg dementia, to the extent that questionnaires cannot be completed, is an exclusion criterion. We are aware that our study population – older vascular surgical patients – may have a high incidence of cognitive impairment. We learnt from previous research in our centre that the incidence of CLTI patients suffering from dementia is low and that they are mostly treated conservatively. Therefore, we believe that this potential risk of selection bias will be low.

Another exclusion criterion is the need for immediate revascularization or hospitalization, since there will not be time to attend the full prehabilitation program. This lack of time for prehabilitation may lead to a suboptimal effect of the program. Preferably, the prehabilitation program will have a total duration of 3 weeks. This cut-off point is chosen based on both the time wherein revascularization should take place and the time that we expect to get optimal results from the program. For example, optimization of physical status, nutritional status or correction of anaemia can probably not be achieved in a shorter period of time. For the acutely admitted patients, as the normal course of care, a geriatrician is consulted directly upon admission to perform a comprehensive geriatric assessment and to provide subsequent advises.

A limitation is that this study is designed as a prospective observational cohort study and not as a randomized controlled trial. Previous studies already showed a decrease in postoperative complications, including delirium, by implementing a prehabilitation program. We believe that prehabilitation not only decreases the risk of postoperative complications, but also increases the postoperative functional outcome and QoL. Due to these clear advantages, the prehabilitation program was implemented as standard care for older CLTI patients in our clinic and it would be unethical to randomly assign patients for prehabilitation or a less beneficial health care course. Thus, to set up a study including contemporary controls, it would be necessary to expand to a multicentre study. While comparing our clinic with other clinics may be useful, comparing centres that approach vascular surgical patients in different ways may also lead to bias. Since delirium is not common in patients <65 years old, we decided not to compare our group with this younger population but to use an historical cohort that received the same management as current CLTI patients, except for the prehabilitation program.
Nevertheless, we aim for an evaluation of effectiveness. Hereo, we plan a systematic comparison with a similar group of patients in the same hospital, fulfilling the same objective inclusion criteria, and being evaluated according to the same outcomes. The primary outcome is the occurrence of delirium, which is an event that is systematically screened for in our hospital since many years.12

In conclusion, this study will offer new insights in whether a relatively novel strategy for optimizing a patient’s preoperative mental and physical condition is effective to prevent postoperative delirium.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. All authors declare that they have no conflicts of interest in this work.

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