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PROTOCOL PAPER

Combined Treatment With Hyperbaric Oxygen Therapy and Endovascular Therapy for Patients With Chronic Limb-Threatening Ischemia

— Study Protocol for the HOTFOOT Multicenter Randomized Controlled Trial —

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Background: Hyperbaric oxygen therapy (HBOT) is regarded as one of the therapeutic options added to standard care to improve lower-limb outcomes in patients with chronic limb-threatening ischemia (CLTI). However, the current guidelines specify that HBOT should not be offered instead of revascularization to prevent limb loss in CLTI patients. The aim of the HOTFOOT study is to examine the impact of HBOT on wound healing in CLTI patients after successful endovascular therapy (EVT).

Methods and Results: The HOTFOOT study is a multicenter prospective randomized open blinded-endpoint trial that is to be conducted at 10 trial centers in Japan between February 2021 and February 2022. This study will enroll 140 patients with CLTI receiving successful EVT. Eligible participants will be allocated 1:1 to either the EVT+HBOT or EVT group; participants in the EVT+HBOT group will receive 30 HBOT sessions. The primary outcome is the time to complete wound healing over the 6-month follow-up. Secondary outcomes during the 6-month follow-up are the proportion of patients who achieved complete wound healing, freedom from major lower-limb amputation, amputation-free survival, and freedom from target lesion reintervention.

Conclusions: This study is expects to assess whether HBOT, in combination with successful EVT, can improve lower-limb outcomes in CLTI patients.

Key Words: Chronic limb-threatening ischemia; Endovascular treatment; Hyperbaric oxygen therapy; Peripheral artery disease; Randomized controlled trial

In 2010, the number of patients living with peripheral artery disease (PAD) was estimated to exceed 200 million worldwide;[1] since then, the aging of the population, a diabetes pandemic, and the spread of chronic kidney disease have all led to an increase in the number of patients with PAD.[1,2] Chronic limb-threatening ischemia (CLTI) is the most serious stage of PAD and is associated with extremely poor prognoses for life and limbs. Recent global guidelines have emphasized the importance of evidence-based revascularization (i.e., bypass surgery or endovascular therapy [EVT]) to prevent of limb loss.[3] In particular, EVT is considered first-line therapy, with a minimally invasive approach, in high-risk patients with CLTI.[3]

Hyperbaric oxygen therapy (HBOT) is considered one of the therapeutic options that can be added to standard care to improve limb outcomes in CLTI patients, given its

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Table 1. Inclusion and Exclusion Criteria
Inclusion criteria
1. Age ≥20 years (no upper limit for age)
2. Ankle pressure <50 mmHg, toe pressure <30 mmHg, TcPO2 <30 mmHg, SPP <30 mmHg (in preprocedural assessment)
3. Foot ulcer/gangrene with significant peripheral artery disease: Fontaine stage IV, Rutherford category 5 or 6
4. Achieving primary success with EVT
Definition of primary success
1. Obtaining at ≥1 straight arterial flow from the groin to ankle
2. The presence of wound blush on the final angiograms
3. Postprocedural TcPO2 ≥30 mmHg or postprocedural SPP ≥30 mmHg
Exclusion criteria
1. Pregnancy or breastfeeding
2. Patients in whom HBOT is contraindicated
3. Patients scheduled to undergo LDL apheresis
4. Patients with severe infection: Grade 3 foot infection in the WIfI classification

EVT, endovascular therapy; HBOT, hyperbaric oxygen therapy; LDL, low-density lipoprotein; SPP, skin perfusion pressure; TcPO2, transcutaneous oxygen pressure; WIfI, Wound, Ischemia, and foot Infection.

ability to increase oxygen transport to hypoxic tissues. In addition, several studies have suggested that there are pleiotropic effects of HBOT, including increased levels of angiogenic and tissue growth factors, anti-inflammatory effects, and antibacterial effects.[4–6] Unfortunately, the current guidelines specify that CLTI patients with remaining severe ischemia should not be offered HBOT to prevent limb loss.[3] In addition, a recent randomized control trial (RCT) showed that the use of HBOT as adjunct therapy did not significantly improve limb outcomes in patients with diabetes and lower-limb ischemia.[7] Indeed, a Cochrane review of several trials testing the use of HBOT for the treatment of chronic wounds suggested that none of the trials evaluated the effects of HBOT on limb outcomes for arterial ulcers.[8] It has been postulated that the negative results of previous studies may be attributable to the wide variety of baseline characteristics (e.g., general condition and wound status) in CLTI patients, as well as heterogeneity in achieving the HBOT regimens and the completion of revascularization.[7,9] Thus, in some situations, under successful revascularization, we postulate that HBOT may actually be effective for the prevention of limb events in patients with CLTI.

To test our hypothesis, the aim of the HOTFOOT: Combined Treatment with Hyperbaric Oxygen Therapy and Endovascular Therapy for Patients with Chronic Limb-Threatening Ischemia study is to examine the effects of HBOT on wound healing in CLTI patients after successful EVT.

Methods

Study Design

The HOTFOOT study is designed as a multicenter prospective randomized open blinded-endpoint trial to investigate the efficacy of combined HBOT and EVT on limb outcomes in CLTI patients. The proposed trial is consistent with the CONSORT 2010 statement,[10] and is therefore designed to be correctly performed and reported. This study plan conforms to the principles outlined in the 1975 Declaration of Helsinki and later amendments. Ethics committee approval has been obtained for this study from the local institutional review board of each trial center, and informed consent will be obtained from all patients by local site investigators. This trial has been registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN 000042839).

Study Subjects and Eligibility

This study will recruit patients from 10 trial centers in Japan between February 2021 and February 2022. The inclusion and exclusion criteria, as well as the definition of primary success, are summarized in **Table 1**. In addition, detailed methods are provided in **Supplementary Material 1**.

Sample Size

The sample size has been determined on the basis of the primary outcome, namely the time to wound healing. The study has been powered to detect a 15-day relative reduction in the primary outcome (80% power and 95% confidence intervals), as estimated from the results of a recent RCT in patients with diabetes and PAD;[7] thus, a total of 126 participants (63 in each group) would be required. Anticipating a 10% dropout rate due to withdrawal or loss to follow-up, we plan to enroll 140 patients in this trial.

Randomization and Masking

The participants will be randomly allocated 1:1 to the intervention arm (EVT+HBOT group) or the control arm (EVT group) via an electronic data-capturing (EDC) system administered via the Internet using an automated web-based program implementing the method of block randomization. Patients and investigators will be not masked to treatment assignment. Conversely, the randomization will be masked to the independent reviewers at the core laboratory located in Fukui, Japan; therefore, these individuals will be able to provide independent imaging analysis of wound healing.

Interventions

All patients who are enrolled in the study will have already undergone endovascular revascularization and will be administered dual antiplatelet therapy (aspirin 100 mg/day and either clopidogrel 75 mg/day or cilostazol 200 mg/day) before their EVT procedures. Each EVT procedure will be performed by interventional cardiologists at the respective trial center. If patients have femoropopliteal lesions, these

Table 2. Outcome Measures
Primary outcome
1. Time to complete wound healing over the 6-month follow-up
Secondary outcomes
1. Proportion of patients who achieved complete wound healing at the 6-month follow-up
2. Freedom from 6-month major lower limb amputation
3. 6-month amputation-free survival
4. 6-month freedom from target lesion reintervention
Safety outcomes
1. Adverse events related to HBOT: middle ear barotrauma, paranasal barotrauma, dental barotrauma, pulmonary barotrauma, oxygen toxicity seizure, hypoglycemia
2. Endovascular procedure-related complications: vessel perforation, puncture site hematoma, distal embolism, slow flow, contrast-induced nephropathy
3. 30-day safety outcome: composite of all-cause death, major amputation, cardiovascular death, myocardial infarction, or stroke

HBOT, hyperbaric oxygen therapy.

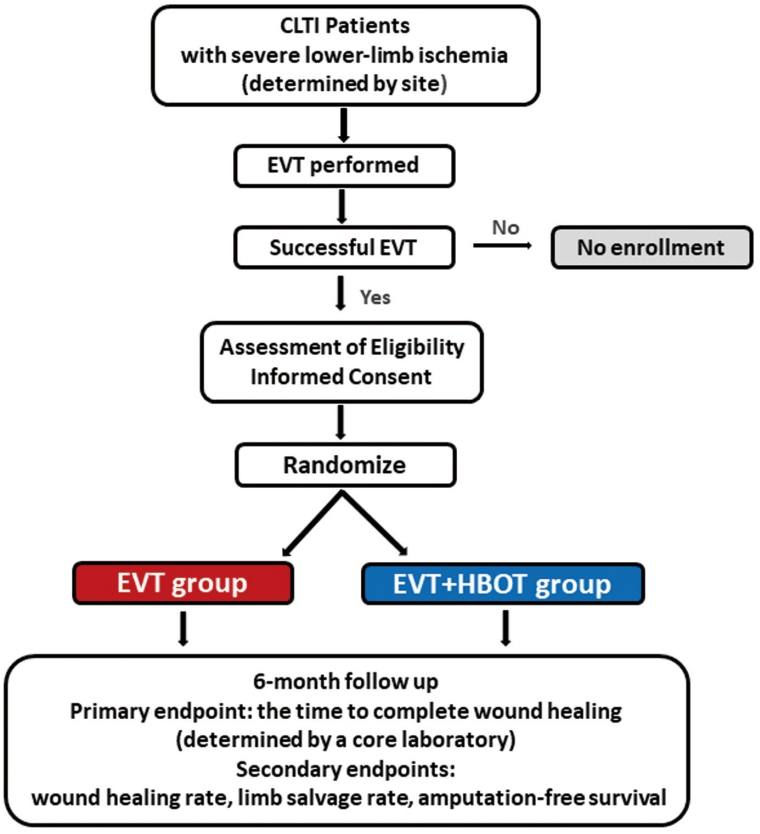

Figure. Study flowchart. CLTI, chronic limb-threatening ischemia; EVT, endovascular therapy; HBOT, hyperbaric oxygen therapy.

will be treated primarily with EVT. The operators will decide on the use of therapeutic devices based on their own judgment. In cases of infrapopliteal lesions, all EVT procedures will be performed according to the angiosome concept, if possible, including treatment with optimal balloon angioplasty. If revascularization of the angiosome-based target lesion fails, the study will instead treat a non-angiosome-based target lesion.[11] Adjunct therapeutic devices for infrapopliteal lesions (e.g., drug-coated balloons, stents, and atherectomy devices) are not available in Japan.

Patients assigned to the EVT+HBOT group will undergo medical screening before starting HBOT, and HBOT will be conducted at a hyperbaric unit in each hospital. Each session of HBOT will be performed for 90 min in a chamber pressurized at 2.0–2.5 atm absolute with 100% oxygen. HBOT sessions will be scheduled until wound healing has been achieved or up to a maximum of 30 sessions.

Outcome Measures and Data Collection

The primary outcome will be the time to complete wound healing over the 6-month follow-up. Complete wound healing is defined as completion re-epithelialization, inde-

Table 3. Schedule of Assessments

Assessment	Enrollment	Follow-up			
		1 month	2 months	3 months	6 months
Informed consent	○				
Baseline characteristics	○				
Adverse events	○	○	○	○	○
Wound assessment	○	○	○	○	○
Laboratory tests	○				
Rutherford classification	○	○	○	○	○
WIfI classification	○	○	○	○	○
Angiography	○				
SPP or TcPO2	○	○	○	○	○
Duplex ultrasound	○	○	○	○	○

SPP, skin perfusion pressure; TcPO2, transcutaneous oxygen pressure; WIfI, Wound, Ischemia, and foot Infection.

pendently determined by a core laboratory. The secondary outcomes consist of the proportion of patients who achieved complete wound healing at the 6-month follow-up, freedom from 6-month major amputation (MA), 6-month amputation-free survival (AFS), and 6-month freedom from target lesion reintervention (TLR). MA is defined as any above-ankle amputation,[12] AFS is defined as freedom from the composite of MA and all-cause mortality,[13] and TLR is defined as any repeat intervention of the target lesions or surgical bypass of the target vessel due to restenosis.[12] In cases of delayed wound healing, attending physicians and wound care teams in each hospital will determine reintervention strategies. The safety outcomes in this study are presented in **Table 2**. Detailed methods for adjudicating anticipated adverse events are provided in **Supplementary Material 2**.

The study flowchart is shown in the **Figure**. The investigators at each trial center will enter patient data and treatment characteristics using standard case report forms located on the trial website at the time of enrollment and 1, 2, 3, and 6 months after enrollment. The follow-up measurements to be recorded are presented in **Table 3**. The items recorded at baseline, including patient characteristics, laboratory data, and angiographic findings, are presented in the **Supplementary Table** and are described in detail in **Supplementary Material 3**. The outcomes data will be checked at the same time as the follow-up measurements are recorded. The methods of wound assessment and management in each institution, as well as evaluation of the primary endpoint by the independent core laboratory, are provided in detail in **Supplementary Material 4**.

Statistical Analysis

Data for the randomized patients will be analyzed using the intention-to-treat principle. Data will be presented as the median with interquartile range for non-normally distributed variables and as the mean±SD for normally distributed continuous variables. Comparisons of continuous measurements between ≥2 groups will be performed using 2-tailed unpaired Student's t-tests or the Mann-Whitney test. Categorical variables will be compared by Chi-squared or Fisher's exact tests. Event-free survival curves will be constructed using the Kaplan-Meier method and compared using the log-rank test. $P<0.05$ will be considered significant. All statistical analyses will be conducted using R (R Foundation for Statistical Computing, Vienna, Austria).

Discussion

For diabetic foot ulcers with lower limb ischemia, several studies and systematic reviews have shown that HBOT can improve the limb salvage rate and wound healing rate.[14–16] However, those results were obtained from small RCTs, and some of those studies included insufficient data. Those studies also concluded that larger trials and appropriate data are needed.[14–16] Therefore, we have designed the HOTFOOT study to overcome the problems of previous trials, such as the small number of participants, low revascularization rates, and low completion rates of HBOT regimens.

The HOTFOOT study will be the first trial performed only in CLTI patients receiving successful EVT. The current guidelines recommend not offering HBOT (and instead using revascularization) for CLTI patients who exhibit severe residual ischemia.[3] To address this ethical issue, the inclusion criteria of the HOTFOOT study include obtaining at least one straight arterial flow from the groin to ankle with the presence of wound blush and the improvement of foot ischemia, as determined by transcutaneous oxygen pressure (TcPO2) or skin perfusion pressure (SPP); the use of these criteria is expected to ensure that eligible participants obtain reasonable results in lower-limb events even if HBOT is not efficacious in this context.[17]

A relevant recent RCT consisted of a large trial conducted in patients with ischemic diabetic ulcers; that study included 120 participants, but did not detect any improvement in limb outcomes with HBOT.[7] That trial was unique in terms of the enrollment of patients who were eligible for revascularization, given that only 40% of those enrolled underwent revascularization.[7] In contrast, the proposed HOTFOOT study will enroll 140 patients with CLTI, all of whom will undergo revascularization using EVT. Another previous RCT showed that a higher completion rate of the HBOT regimen resulted in a better wound healing rate;[9] however, approximately 35% of participants were not able to complete the HBOT regimen in the ischemic diabetic ulcer RCT of Santema et al.[7] Therefore, the HOTFOOT study will seek completion of the HBOT regimen, up to a maximum of 30 sessions. If the proposed study is successful, this trial is expected to overcome major problems in previous relevant RCTs.

In the HOTFOOT study, the primary endpoint (the time to wound healing) is expected to be more readily attainable

than more complex endpoints, such as limb salvage. Previous studies have demonstrated that the effectiveness of HBOT in ischemic diabetic foot ulcers reflects improved oxygen supply, resulting in the healing of these wounds.[9] The poor wound healing rate in CLTI patients undergoing EVT is regarded as a major shortcoming compared with treatment by bypass surgery.[18] We hypothesize that HBOT may contribute to solving this important shortcoming of EVT.

Conclusions

The HOTFOOT study will be the first and largest RCT to investigate the impact of the combination of HBOT and EVT in patients with CLTI. This trial is expected to assess whether HBOT, in combination with successful EVT, improves the time to complete wound healing in patients with CLTI.

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Disclosures

None declared.

IRB Information

This study was approved by the Institutional Review Board of Tokeidai Memorial Hospital (Protocol ID: 20-23).

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
http://dx.doi.org/10.1253/circrep.CR-21-0097