DIONYSIUS trial

Does Increasing Oxygen Nurture Your Symptomatic Ischemic Ulcer Sufficiently?

Rationale

The treatment of ischemic diabetic foot ulcers (DFU) is an approved indication for hyperbaric oxygen therapy (HBOT), as acknowledged by the EUBS/SPUMS and UHMS. Therefore, HBOT is reimbursed in many countries by health insurance companies. However, substantial skepticism still exists among clinicians due to the limited and conflicting evidence for its effectiveness to promote wound healing and prevent amputations.

The $DAMO_2CLES$ trial (Santema et al, Diabetes care, 2018) showed some promising results for HBOT as an adjunctive treatment for patients with ischemic diabetic foot ulcers. However, the treatment effect was not convincing due to the limited number of patients available for inclusion in a single country. They found 10% less major amputations in patients treated with HBOT the intention-to-treat analysis, which was not statistically significant. In the per-protocol analysis the reduction of major amputations was 17%, which was statistically significant. The amputation-free survival (AFS) after HBOT was 13% higher in the intention-to-treat analysis, which was not statistically significant. In the per-protocol analysis the AFS was 26% higher as opposed to standard treatment, which was statistically significant. No significant effect was found on complete ulcer healing in neither the intention-to-treat nor the per-protocol analysis.

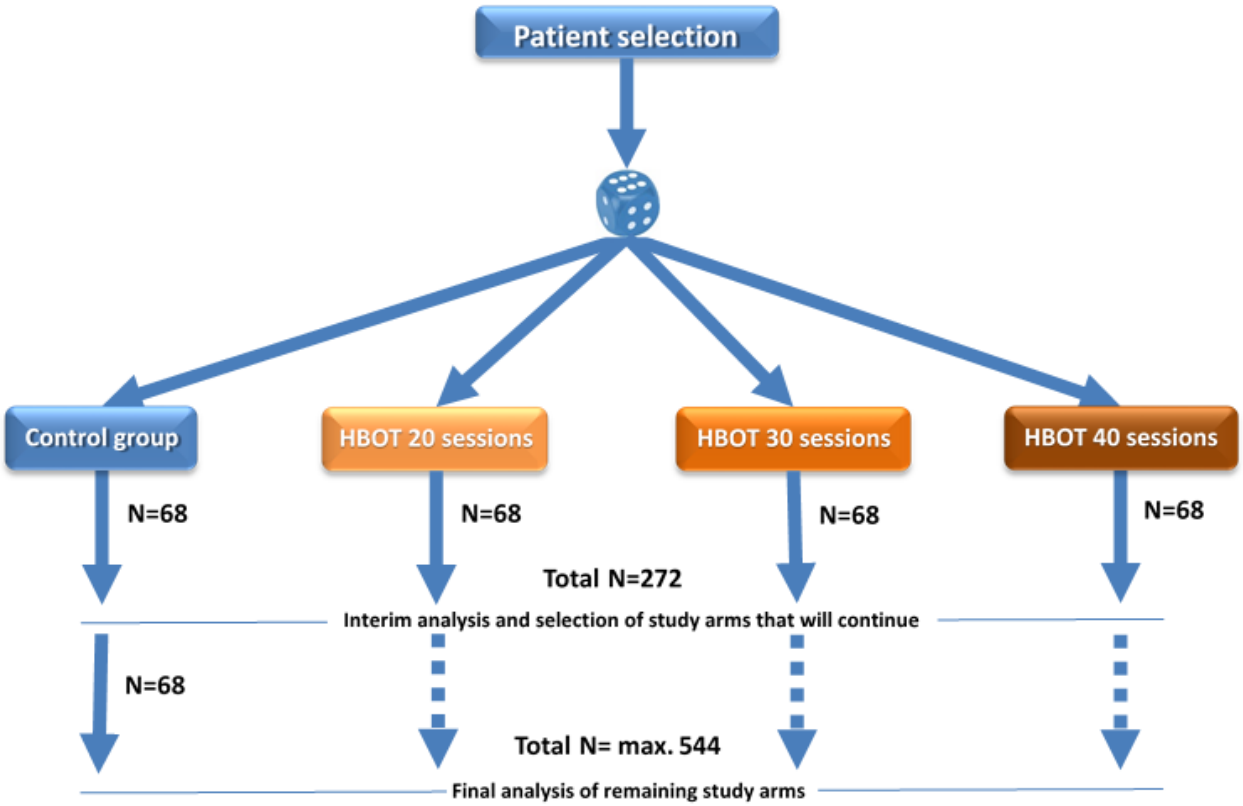
A recent meta-analysis from our group, accepted for publication in the journal of vascular surgery, and including four studies, shows that HBOT leads to a 15% reduction of major amputation rate, but shows no effect on minor amputation, complete ulcer healing or mortality with the currently available evidence.

Objective

To assess the costs and effects of HBOT on patients with an ischemic DFUs and the optimal number of HBOT-treatments to reach this effect.

Study design

International multicenter randomized clinical trial with an adaptive (multi-arm, multi-stage; MAMS) design, with a follow-up of 3 years, following the (extended) CONSORT-statement. Patients will be randomized to receive standard treatment or an additional total of 20, 30 or 40 HBOT treatments. When the first half of the included patients have reached 3 months of follow=up, an interim-analysis will be performed. Depending on the results, one or more arms can be stopped. If a significant effect is found during the interim-analysis, the study will be terminated. Up to 544 patients need to be included.



Study population

This multinational trial will be coordinated from the Netherlands. Ten Dutch HBOT-centers with a larger number of referring hospitals will participate and will include a substantial number of patients for the trial. Also centers from Australia, Germany, England, Spain and Italy will help to reach the total number of required patients. Both patients suitable and unsuitable for endovascular or open revascularization may be candidates for the study, and patients will be included prior to revascularization.

Inclusion criteria

1. Type I or II diabetes
2. Wagner 3 or 4 lower extremity ulcer(s), present for at least 4 weeks. In case more than one ulcer is present, the largest will be observed as target ulcer.
3. Leg ischemia, characterized by a highest ankle systolic blood pressure < 70 mmHg, or a toe systolic pressure < 50 mmHg or a TcpO2 < 40 mmHg
4. Complete assessment of peripheral arterial lesions from the aorta to the pedal arteries with duplex ultrasonography, magnetic resonance angiography, computed tomography angiography and/or intra-arterial digital subtraction angiography of the ipsilateral leg
5. Age ≥ 18 years
6. Written informed consent

Exclusion criteria

1. Chronic Obstructive Pulmonary Disease (COPD) GOLD IV
2. Treatment with chemotherapy, immunosuppressive drugs or systemic corticosteroids within last 3 months, as this interferes with normal wound healing

3. End stage renal disease requiring dialysis
4. Metastasized malignancy
5. Left ventricular failure with ejection fraction (EF) <20% or external pacemaker
6. Pregnancy
7. Insufficient proficiency of local language, or inability to complete the questionnaires

HBOT protocol

Patients allocated to the intervention group will receive 20, 30 or 40 sessions of HBOT adjunctive to standard care. HBOT will comprise a total of forty 90 to 120-minute treatment sessions at 2.2-2.5 ATA. Besides the 90 minutes of treatment, approximately 20 minutes are required for compression and decompression. During the treatment session the patients will breathe 100% FiO2 except for 3 blocks of 5 minutes during which atmospheric air will be administered to prevent oxygen intoxication.

Outcome measures

Primary Outcomes

Amputation rate (major and minor, i.e. above or below ankle), amputation-free survival,

Secondary Outcomes

Complete ulcer healing, cost-effectiveness and budget impact with costs per patient free of amputation, pain scores, need for additional vascular interventions, health-related quality of life scores (EQ-5D-5L and Vascuqol-6), functional status, time to complete wound healing and adverse effects of HBOT and mortality.