Ischemic and diabetic wounds of the lower extremity

Advances in patient-centered surgical care

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CHAPTER 9

Hyperbaric oxygen therapy in the treatment of ischemic lower extremity ulcers in patients with diabetes: Results of the DAMOCLES multicenter randomized clinical trial

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Chapter 9

ABSTRACT

Background – Conflicting evidence exists on the effects of hyperbaric oxygen therapy (HBOT) in the treatment of chronic ischemic leg ulcers. The aim of this trial was to investigate whether additional HBOT would benefit patients with diabetes and ischemic leg ulcers.

Methods – 120 patients were randomized to standard care without (SC) or with HBOT (SC+HBOT). Eligible diabetic patients had a Wagner grade 2-4 ulcer present for at least 4 weeks and concomitant limb ischemia with or without revascularization options. Primary outcomes were limb salvage and complete wound healing after 12 months of follow-up, as well as time to wound healing. Other endpoints were amputation-free survival (AFS) and mortality.

Findings – Both groups contained 60 patients. Limb salvage was achieved in 47 patients (78%) in the SC group vs. 53 (88%) patients in the SC+HBOT group (risk difference [RD] 0.10, 95% CI -0.04 to 0.23). After 12 months, 28 index wounds were healed in the SC group vs. 30 in the SC+HBOT group (RD 0.03, 95% CI -0.14 to 0.21). AFS was achieved in 41 patients in the SC group and 49 patients in the SC+HBOT group (RD 0.13, 95% CI -0.02 to 0.28). In the SC+HBOT group 21 patients (35%) were unable to complete the HBOT-protocol as initially planned. Those who did had significantly less major amputations and higher AFS (RD 0.26, 95% CI 0.10 to 0.38).

Interpretation – Additional HBOT did not significantly improve complete wound healing and limb salvage in patients with diabetes and lower limb ischemia. However, a trend was seen towards a better amputation-free survival among HBOT-treated patients. The potential efficacy of HBOT may not be realized because a considerable number of patients is unable to complete a full HBOT-regimen.

Funding – This study received an unrestricted grant from the Netherlands Organization for Health Research and Development (Grant # 837002005).
INTRODUCTION

Chronic ulcers of the lower extremity pose a major healthcare problem, especially among diabetics. Diabetic patients have a 3-11% annual risk of developing lower extremity ulcers.\textsuperscript{1,2} Diabetic foot ulcers usually result from a combination of neuropathy, trauma and foot deformities. Many patients have concomitant peripheral arterial occlusive disease (PAOD), which is a particularly detrimental prognostic factor.\textsuperscript{3,4} Ischemic diabetic ulcers are notoriously difficult to treat and require complex and costly multimodal treatment, consisting of pressure offloading, optimizing glycemic control, revascularization and local wound treatment.\textsuperscript{5} The presence of ulcers has a significant adverse effect on patients’ quality of life (QoL).\textsuperscript{6-9} Despite optimal treatment, ulcers in patients with diabetes and concomitant limb ischemia are refractory to wound healing. Major amputation rates have been reported at 5 to 23\%, two years following revascularization.\textsuperscript{10} This has prompted the search for effective alternative or additive treatment options.

Hyperbaric oxygen therapy (HBOT) is used variably in clinical practice, based on the premise that improving the oxygenation of wounds may expedite their healing and could potentially prevent amputation.\textsuperscript{11-13} However, previous clinical trials and systematic reviews on the effectiveness of HBOT as an adjunct to standard wound care have provided conflicting evidence on the efficacy in both diabetic and non-diabetic patients.\textsuperscript{14,15} This was mainly due to clinical heterogeneity in terms of vascular status, HBOT regimen, wound characteristics and outcomes, limiting the ability to make practical recommendations as to the usefulness of HBOT.

To address these issues and provide relevant recommendations for clinical practice, the objective of the DAMOCLES trial ("Does Applying More Oxygen Cure Lower Extremity Sores?") was to investigate whether HBOT, as an adjunct to revascularization and standard wound care, can improve wound healing and reduce major amputation rates in patients with diabetes and ischemic lower extremity ulcers.

METHODS

Study design

The DAMOCLES study was designed as a multicenter, randomized, parallel-group, superiority trial and was conducted at twenty-four hospitals in the Netherlands and one in Belgium. Also, all nine public HBOT facilities in the Netherlands and one affiliated to the Antwerp University Hospital in Belgium participated in this trial. The study was completed and reported according to the revised CONSORT statement.\textsuperscript{16} The study protocol of this trial was registered (www.trialregister.nl; NTR 3944) and published previously.\textsuperscript{17} Here, we will reiterate the essentials.
The protocol was approved by the medical ethics review board of the Academic Medical Center (Amsterdam, the Netherlands) and by the local site investigators. The study was carried out in accordance with the Declaration of Helsinki and the Medical Research Involving Human Subjects Act. Written informed consent was provided by all participants.

Data Safety Monitoring board (DSMB)
A DSMB was composed of four members, independent of the trial investigators, i.e. a surgeon, an internist, a hyperbaric medicine specialist and a research methodologist. The DSMB advised the DAMOCLES study investigators regarding the safety of the study participants before the start of the study and after inclusion of 85 participants for an interim safety- and effectiveness analysis.

Patients
Participants were eligible for inclusion if they met all of the following criteria: (1) type 1 or 2 diabetes; (2) an ulcer of the lower extremities graded as Wagner grades 2-4, and present for at least 4 weeks; (3) limb ischemia, defined as an absolute ankle systolic blood pressure <70 mmHg, an absolute toe systolic blood pressure <50 mmHg or a forefoot transcutaneous oxygen pressure (TcpO₂) <40 mmHg; (4) indication for revascularization has been assessed before randomization and according to local practice standards (i.e., based on findings from duplex ultrasonography, magnetic resonance angiography or digital subtraction angiography of the lower limb arteries).

Patients were excluded if they met any of the following criteria: (1) previous ipsilateral major amputation (i.e., above the ankle); (2) an absolute contra-indication for HBOT (e.g., Chronic Obstructive Pulmonary Disease (COPD) GOLD IV, severe heart failure with a left ventricular ejection fraction <20% or an external pacemaker, metastasized malignancy, or pregnancy); (3) current renal replacement therapy; (4) current treatment with chemotherapy, immunosuppressive drugs, or high-dose systemic corticosteroids (>10 mg per day); (5) unable to complete questionnaires in Dutch.

Sample size
As stated in the published study protocol, the initial sample size calculation was based on an expected increase in limb salvage of 12%, which would require a total of 226 participants (113 in either group). During the course of the study it became clear this number could not be reached within the maximum inclusion period possible [i.e. 30 months] , given the available budget. Hence, the sample size was adjusted, based on an expected increase in complete wound healing and limb salvage, as derived from a subset of diabetic ischemic ulcer patients in a recent systematic review of previous clinical trials. To detect a 29.6% increase in complete wound healing and a 25% increase in limb salvage with 80% power at a 0.05 significance level with a one-sided log-rank test, 108 patients (54 in either group) were needed. Anticipating a 10% drop-out rate due to withdrawal or loss to follow-up, we planned to include 120 patients in the trial.
Randomization
Patients were randomly assigned in a 1:1 ratio to a standard care (SC) group or to standard care with additional HBOT (SC+HBOT) using a web-based dedicated computer randomization software program (ALEA v. 2.2, NKI-AVL Amsterdam, The Netherlands) in order to ensure allocation concealment. Stratification was performed for wound size of the index ulcer (less or more than 3 cm diameter) and for the amenability for a revascularization procedure.

Interventions
All patients enrolled in this trial had an open or endovascular revascularization if applicable and optimal conservative treatment (antibiotics, anticoagulants, glycemic control), as well as local wound treatment, according to the guideline produced by the International Working Group on the Diabetic Foot,5 and local best practice.

Patients who were allocated to SC+HBOT were referred to a HBOT facility for intake and medical screening. If applicable, revascularization was generally performed before the start of the HBOT to avoid interruption of HBOT. HBOT included sessions of 90 minutes in a multi-placed chamber, pressurized at 2.4 or 2.5 atmospheres absolute (ATA) during which patients were breathing 100% FIO2 except for 3 blocks of 5 minutes during which ambient air was administered to prevent oxygen intoxication. HBOT was scheduled for 5 days per week until a maximum of 40 sessions was reached or until complete wound healing was achieved.

Data collection and outcome measures
In patients with more than one ulcer, the one with the largest diameter at baseline was designated as the index ulcer. Follow-up took place during outpatient visits 3, 6 and 12 months after Recruitment. Local investigators provided baseline and follow-up data of all included patients using a pre-defined standard case report form (CRF). During follow-up, this CRF was used to collect data on wound healing, wound severity, revascularization procedures, amputations, hospital admissions and other adverse events. Patients were asked to complete questionnaires about functional status, quality of life and costs/expenses at baseline, and after 3, 6 and 12 months of study participation. Number of completed HBOT sessions, forefoot normobaric and hyperbaric TcpO2 measurements and hyperbaric adverse events were recorded in the CRFs in each HBOT center.

Primary endpoints were limb salvage and occurrence of, and time to, complete index wound healing after 12 months of follow-up. Limb salvage was defined as freedom from major amputation of the index limb (i.e. an amputation above the ankle). Complete wound healing was defined as complete re-epithelization. Wounds leading to a major amputation were classified as ‘not healed’. Wounds that healed after a minor amputation were classified as ‘healed’. Recurring ulcers after initial healing were classified as ‘healed’, but are reported under the secondary outcome ‘ulcer recurrence’.
Secondary endpoints were: freedom from minor amputation on the index limb (i.e. toe or transmetatarsal amputation); amputation-free survival (AFS; i.e. alive without major amputation of the index limb); need for additional revascularization on index limb that was not planned at the moment of randomization; new or recurrent ulcers; forefoot \( \text{TcpO}_2 \) during the first hyperbaric treatment; (serious) adverse events, defined as any untoward medical occurrence, including complications related to HBOT; major morbidity, and all-cause mortality. Quality of life and cost-effectiveness were assessed and analyzed separately. These results will be presented in another publication.

**Statistical analysis**

All statistical analyses were done with the Statistical Package for the Social Sciences version 22 (SPSS Inc., Armonk, NY, USA). Primary analyses were conducted using the intention-to-treat (ITT) and per-protocol principles on the primary endpoints to assess the maximum attainable benefit of HBOT. Missing data were handled by carrying the last observed outcome forward.

In ‘per-protocol analysis A’ we compared patients undergoing a ‘full’ HBO treatment course, i.e. if treatment was continued until complete closure of the wound or for at least 30 completed HBOT sessions, with those who did not complete this HBOT-regimen and those who received SC. This should show the maximum attainable effect of HBOT.

For ‘per-protocol analysis B’ we compared all patients who underwent any HBOT-treatment with those who did not receive any HBOT, to account for participants who were randomized to SC+HBOT but did not commence with HBOT. Patients who were allocated to SC but underwent HBOT at their own request were analyzed in the SC group because they were not treated according to our HBOT regimen and treatment was not always meant for the initial index wound.

Descriptive statistics were presented as means with standard deviations (SD) or medians with interquartile ranges (IQR) depending on the distribution of the data. For dichotomous outcome measures the risk difference (RD) was calculated with its 95% Confidence Interval (CI) and the corresponding Number Needed to Treat (NNT). Time to complete wound healing and major amputation-free survival were plotted as Kaplan-Meier curves, and differences between the groups were analyzed using the log-rank statistic. Patients who were lost to follow-up or could not develop the event were censored in the Kaplan-Meier survival analysis. The level of statistical significance was defined as a P-value less than 0.05.

**RESULTS**

Between June 2013 and December 2015, 120 patients were included in the DAMOCLES study. Sixty patients were allocated to SC only. However, four of them received HBOT upon their own
request. A substantial proportion of eligible patients was unwilling to participate in our trial because they either considered HBOT too burdensome or because they wanted to receive HBOT anyway as a last resort treatment option. Of the sixty patients who were allocated to the SC+HBOT group, 49 (82%) actually started HBOT. Of the 11 patients who did not receive HBOT, five patients decided for themselves not to undergo hyperbaric treatment, four were deemed unfit by the hyperbaric specialist, and in two their ulcer healed prior to starting HBOT. Five patients withdrew from the study during the follow-up period and were lost to follow-up; two of them were allocated to SC and three to SC+HBOT. See Figure 1 for the full study flow. Baseline characteristics of included patients are shown in Table 1 and were similar in both treatment arms.

Among the patients that were allocated to SC+HBOT, 39 (65%) completed HBOT according to our definition for the per-protocol analysis A (until complete wound closure or ≥ 30 completed HBOT sessions). At baseline, patients treated with HBOT had a higher hemoglobin (mean 8.1 vs 7.3 mmol/l; MD 0.76, 95% CI 0.20 to 1.31) and were slightly younger (mean age 66.4 vs 70.4, MD 3.98, 95% CI -0.10 to 8.04). The eleven patients that were allocated to HBOT but did not start HBOT were analyzed in the SC group in per-protocol analysis B.

Primary outcome measures

Limb salvage

During follow-up, 13 patients (22%) underwent a major amputation of the index limb in the SC group vs. 7 (12%) patients in the SC+HBOT group (Table 2). The RD for limb salvage was 0.10 (95% CI -0.04 to 0.23). Figure 2 shows the survival curve for limb salvage (log rank p = .148). Per-protocol analysis A showed a statistically significant difference in limb salvage in favor of HBOT: 18 patients (22%) in the SC group underwent a major amputation of the index limb vs. 2 (5%) in the SC+HBOT group.
### Table 1. Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>SC N=60</th>
<th>SC + HBOT N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>70.6 (11.2)</td>
<td>67.6 (10.0)</td>
</tr>
<tr>
<td>Gender, male (%)</td>
<td>46 (77)</td>
<td>51 (85)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>27.1 (4.8)</td>
<td>28.3 (6.0)</td>
</tr>
<tr>
<td>Wound diameter in centimeters, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound diameter &lt; 3 cm</td>
<td>3.5 (2.9)</td>
<td>3.2 (2.7)</td>
</tr>
<tr>
<td>Wound diameter ≥ 3 cm</td>
<td>33 (55)</td>
<td>34 (57)</td>
</tr>
<tr>
<td>Wound diameter &gt; 3 cm</td>
<td>27 (45)</td>
<td>26 (43)</td>
</tr>
<tr>
<td>Wound duration in months, mean (SD)</td>
<td>6.0 (6.8)</td>
<td>5.6 (6.4)</td>
</tr>
<tr>
<td>Wound classification (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wagner grade II</td>
<td>35 (58)</td>
<td>27 (45)</td>
</tr>
<tr>
<td>Wagner grade III</td>
<td>16 (27)</td>
<td>20 (33)</td>
</tr>
<tr>
<td>Wagner grade IV</td>
<td>9 (15)</td>
<td>13 (22)</td>
</tr>
<tr>
<td>Index wound location (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toe</td>
<td>31 (52)</td>
<td>30 (50)</td>
</tr>
<tr>
<td>Foot (below ankle)</td>
<td>19 (32)</td>
<td>23 (38)</td>
</tr>
<tr>
<td>Forefoot after amputation</td>
<td>9 (15)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Above ankle</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Diabetes type, (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td>52 (87)</td>
<td>54 (90)</td>
</tr>
<tr>
<td>Duration of diabetes in years, mean (SD)</td>
<td>18.8 (15.1)</td>
<td>16.6 (11.2)</td>
</tr>
<tr>
<td>Peripheral arterial circulation parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean absolute ankle systolic blood pressure, mmHg (SD)</td>
<td>102 (61)</td>
<td>110 (43)</td>
</tr>
<tr>
<td>Mean absolute toe systolic blood pressure, mmHg (SD)</td>
<td>41 (35)</td>
<td>45 (30)</td>
</tr>
<tr>
<td>Mean foot dorsum transcutaneous oxygen pressure, TcPO2 mmHg (SD)</td>
<td>23 (17)</td>
<td>23 (15)</td>
</tr>
<tr>
<td>Amenable for revascularization at inclusion, yes (%)</td>
<td>24 (40)</td>
<td>25 (42)</td>
</tr>
<tr>
<td>Endovascular</td>
<td>19 (79)</td>
<td>22 (88)</td>
</tr>
<tr>
<td>Bypass</td>
<td>4 (17)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Endarterectomy in combination with endovascular revascularization</td>
<td>1 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Previous procedures index limb, yes (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral arterial revascularization</td>
<td>33 (55)</td>
<td>38 (63)</td>
</tr>
<tr>
<td>Minor amputation</td>
<td>23 (40)</td>
<td>20 (33)</td>
</tr>
<tr>
<td>Mobility (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking</td>
<td>21 (35)</td>
<td>27 (45)</td>
</tr>
<tr>
<td>Moderately disabled</td>
<td>34 (57)</td>
<td>23 (38)</td>
</tr>
<tr>
<td>Wheelchair dependent</td>
<td>5 (8)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Bedridden</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>14 (23)</td>
<td>13 (22)</td>
</tr>
<tr>
<td>Former</td>
<td>33 (55)</td>
<td>34 (57)</td>
</tr>
<tr>
<td>Current</td>
<td>13 (22)</td>
<td>13 (22)</td>
</tr>
</tbody>
</table>
DAMOCLES trial results

Table 1. Continued.

<table>
<thead>
<tr>
<th>Comorbidity (%)</th>
<th>SC N=60</th>
<th>SC + HBOT N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>45 (75)</td>
<td>39 (65)</td>
</tr>
<tr>
<td>Cardiovascular heart disease*</td>
<td>28 (47)</td>
<td>20 (33)</td>
</tr>
<tr>
<td>Previous TIA or stroke</td>
<td>6 (10)</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Distal neuropathy</td>
<td>41 (68)</td>
<td>32 (53)</td>
</tr>
<tr>
<td>Nephropathy**</td>
<td>12 (20)</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>24 (40)</td>
<td>17 (28)</td>
</tr>
<tr>
<td>Medication (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>41 (68)</td>
<td>41 (68)</td>
</tr>
<tr>
<td>Oral antidiabetic medication</td>
<td>45 (75)</td>
<td>43 (72)</td>
</tr>
<tr>
<td>Statins</td>
<td>47 (78)</td>
<td>44 (73)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>24 (40)</td>
<td>22 (37)</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>41 (68)</td>
<td>44 (73)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>45 (75)</td>
<td>45 (75)</td>
</tr>
<tr>
<td>Hemoglobin level, mmol/l (SD)</td>
<td>7.4 (1.1)</td>
<td>7.8 (1.2)</td>
</tr>
</tbody>
</table>

ABI: ankle brachial index, BMI: body mass index in kg/m², HBOT: hyperbaric oxygen therapy, SD: standard deviation, SC: standard care, TIA: transient ischemic attack
*Including AP, myocardial infarction, or previous coronary intervention
** Not requiring dialysis

...group (RD 0.17, 95% CI 0.03 to 0.28; NNT 6, 95% CI 3 to 33). In per-protocol analysis B, 14 patients (20%) in the SC group underwent a major amputation and 6 (12%) in the SC+HBOT group (RD 0.07, 95% CI -0.07 to 0.20).

Complete wound healing
As shown in Table 2, there was no significant difference between the two groups in rates of complete wound healing at the end of follow-up period, nor in the time to healing. During the study, 29 index wounds healed in the SC group (48%) vs. 33 in the SC+HBOT group (55%). At the end of the follow-up period (i.e., taking recurrences into consideration), 28 (47%) index wounds had permanently healed in the SC group compared to 30 (50%) in the HBOT+SC group. No statistically significant difference was found in the time to complete ulcer healing of the index ulcer between the both groups. In Figure 3, the survival curve for time to complete wound healing is shown (log rank p = .917).

Per-protocol analysis A showed that wound healing was achieved in 36/81 patients (44%) in the SC group and 22/39 patients (57%) in the HBOT+SC group (RD 0.12, 95% CI -0.07 to 0.30). In per-protocol analysis B, 49% of the ulcers healed in the SC group (35/71) and 47% (23/49) of the wounds in the SC+HBOT group healed (RD -0.02, 95% CI -0.20 to 0.15).
Chapter 9

Secondary outcome measures

Freedom from any amputation of the index limb
At the end of the follow-up period, 31 patients (52%) in the SC group remained free of any amputation (i.e., including minor amputations), compared to 38 (63%) patients in the SC+HBOT group (RD 0.12, 95% CI -0.06 to 0.28).

Amputation-free survival
At the end of follow-up, 41 patients were alive and free from major amputation on the index limb in the SC group vs. 49 in SC+HBOT group (RD 0.13, 95% CI -0.02 to 0.28). In Figure 4, the survival curve for AFS is shown (log rank \( p = .105 \)).

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Table 2a. Summary of the results (Intention-to treat analysis).

<table>
<thead>
<tr>
<th></th>
<th>SC (n=60)</th>
<th>SC + HBOT (n=60)</th>
<th>RD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete wound healing (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete wound healing at end of follow-up</td>
<td>28 (47)</td>
<td>30 (50)</td>
<td>0.03 (-0.14 to 0.21)</td>
</tr>
<tr>
<td>Achieved complete wound healing during study*</td>
<td>29 (48)</td>
<td>33 (55)</td>
<td>0.07 (-0.11 to 0.24)</td>
</tr>
<tr>
<td>Median time to complete wound healing (SE)</td>
<td>217 days (53)</td>
<td>202 days (63)</td>
<td></td>
</tr>
<tr>
<td>Limb salvage (%)</td>
<td>47 (78)</td>
<td>53 (88)</td>
<td>0.10 (-0.04 to 0.23)</td>
</tr>
<tr>
<td>Amputation-free survival</td>
<td>41 (68)</td>
<td>49 (82)</td>
<td>0.13 (-0.02 to 0.28)</td>
</tr>
<tr>
<td>Freedom from amputations index limb** (%)</td>
<td>31 (52)</td>
<td>38 (63)</td>
<td>0.12 (-0.06 to 0.28)</td>
</tr>
<tr>
<td>Overall mortality (%)</td>
<td>9 (15)</td>
<td>5 (8)</td>
<td>0.07 (-0.05 to 0.19)</td>
</tr>
<tr>
<td>Additional revascularization index limb*** (%)</td>
<td>17 (28)</td>
<td>14 (23)</td>
<td>0.05 (-0.11 to 0.20)</td>
</tr>
</tbody>
</table>

RD: risk difference, 95% CI: 95% confidence interval
*Patients who achieved complete healing of the index wound including recurrent wounds and major amputations
** Major and minor amputations
*** Not planned at inclusion

Table 2b. Summary of the results (Per-protocol analyses).

<table>
<thead>
<tr>
<th></th>
<th>SC (n=81)</th>
<th>SC + HBOT (n=39)</th>
<th>RD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per-protocol analysis A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete wound healing end of follow-up</td>
<td>36 (44)</td>
<td>22 (57)</td>
<td>0.12 (-0.07 to 0.30)</td>
</tr>
<tr>
<td>Underwent major amputation index limb</td>
<td>18 (22)</td>
<td>2 (5)</td>
<td>0.17 (0.03 to 0.28)</td>
</tr>
<tr>
<td>Amputation-free survival</td>
<td>54 (67)</td>
<td>36 (92)</td>
<td>0.26 (0.10 to 0.38)</td>
</tr>
<tr>
<td>Per-protocol analysis B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete wound healing at end of follow-up</td>
<td>35 (49)</td>
<td>23 (47)</td>
<td>-0.02 (-0.20 to 0.15)</td>
</tr>
<tr>
<td>Underwent major amputation index limb</td>
<td>14 (20)</td>
<td>6 (12)</td>
<td>0.07 (-0.07 to 0.20)</td>
</tr>
<tr>
<td>Amputation-free survival</td>
<td>51 (72)</td>
<td>39 (80)</td>
<td>0.08 (-0.08 to 0.22)</td>
</tr>
</tbody>
</table>

Numbers in bold indicate significant differences
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Figure 2. Kaplan-Meier curve for limb salvage (freedom from major amputation).

Figure 3. Kaplan-Meier curve for complete wound healing.

Figure 4. Kaplan-Meier curve for major amputation-free survival.
Additional revascularizations
In the SC group, 24 (40%) patients underwent planned revascularization vs. 25 (42%) in the SC+HBOT group. During follow-up, 17 patients (28%) in the SC group vs. 14 patients (23%) in the SC+HBOT group underwent revascularization of the index limb that was not already planned at study inclusion (RD 0.05, 95% -0.11 to 0.20).

Ulcer recurrence and new ulcers
Of the healed index ulcers, 6 recurred during follow-up. In the SC group, 2 of the recurrent ulcers ultimately healed again within the follow-up period and one failed to heal. In the SC+HBOT group, one healed within the follow-up period and two failed to heal again.

During follow-up almost one third of the participants developed a new ulcer; 19 patients (32%) in the SC group vs. 19 patients (32%) in the SC+HBOT group.

Adverse events and mortality
A total of 14 participants died during the follow-up period (9 [15%] in the SC group vs. 5 [8%] in the HBOT+SC group; RD 0.07, 95% -0.05 to 0.19). One patient died after a hyperbaric session due to perforation of the gall bladder and subsequent sepsis, but this was not likely to be related to the HBOT. Two serious adverse events occurred that were attributable to HBOT: one participant experienced an oxygen-induced seizure and another participant endured a barotraumatic perforation of the tympanic membrane. Both participants recovered without lasting consequences. Another three patients required preventive myringotomy with tube placement due to the inability to equalize the pressure of the middle ear during a hyperbaric session.

DISCUSSION

Among individuals with diabetic foot ulcers and concomitant lower limb ischemia, adding HBOT to standard care did not result in statistically significant benefits in terms of limb salvage or wound healing. However, the full potential of HBOT may not have been utilized in these patients, as HBOT was able to increase limb salvage rate in those who completed the full 30-session HBOT regimen.

Currently available evidence
Nowadays, HBOT is variably used in the treatment of diabetic foot ulcers because of inconclusive evidence on its efficacy. Conclusions based on observational studies and clinical experience are often biased because HBOT is commonly used as a ‘last resort’ treatment. Consequently, HBOT may be postponed unto the point at which a limb should be considered unsalvageable. Known and unknown confounding factors limit the ability to account for between-group differences in observational studies.
A number of previous clinical trials have attempted to determine the efficacy of HBOT, but have provided conflicting results. Three trials showed beneficial effects of HBOT. The trial by Abidia et al. included 18 patients with nonrevascularizable PAOD and suggested that treatment with hyperbaric 100% oxygen improved wound healing compared to hyperbaric air (i.e., atmospheric oxygen levels at elevated pressure). Faglia et al. demonstrated fewer major amputations but more minor amputations among patients treated with HBOT. They primarily included patients with a compromised peripheral circulation although patients with adequate peripheral circulation were not excluded from participation. The trial by Londahl et al. included both patients with limb ischemia and patients with an adequate peripheral circulation, and showed a significant increase in ulcer healing after HBOT. On the other hand, a recently published trial by Fedorko et al. failed to confirm the benefit of HBOT in patients without PAOD or those who had a recent intervention for PAOD. However, the conclusions of these trials are of limited value in making clinical recommendations because of short follow-up periods, methodological weaknesses, or small numbers of participants. Of particular importance is the notion that most previous trials either did not include patients with PAOD or did not distinguish between patients with or without PAOD, although the effect of HBOT could differ substantially between these patients on theoretical grounds.

To address these issues, the DAMOCLES trial specifically included patients with concomitant limb ischemia. Previous studies hinted at the possibility that HBOT could be more effective in the treatment of these patients, which is plausible given its mechanism of action. In our study, individuals who successfully completed the entire HBOT regimen had significantly improved limb salvage. In this sense, the DAMOCLES trial supports the underlying concept of HBOT.

One potential explanation for the negative overall results of the study is that patients with diabetic ulcers and concomitant PAOD are generally characterized by a poor overall clinical condition. In our study, a substantial proportion of participants (35% of those allocated to SC+HBOT) did not complete the full HBOT regimen. In many cases interfering medical circumstances or poor overall condition precluded HBOT. For example, to some patients the daily travel to a more or less remote HBOT center was already too burdensome. As such, lack of ability to adhere to a strenuous HBOT regimen could mitigate the efficacy of HBOT in clinical practice, even if HBOT would improve clinical outcomes under optimal circumstances.

DAMOCLES included only individuals with ischemic ulcers, which included both large-vessel disease and microvascular dysfunction (as assessed using TcpO₂). Although the number of participants with isolated microvascular dysfunction was too small to draw meaningful conclusions, one could speculate that HBOT is more effective in such subgroups of patients.
Chapter 9

Strengths and limitations

One major strength of the DAMOCLES trial is the fact that it is as of yet the largest trial ever performed in the realm of HBOT for ischemic wounds in diabetics. In addition, this trial is unique in that it addresses patients with ischemic diabetic foot ulcers who may also receive vascular reconstructions.

However, this study also has some limitations. First, in contrast to some previous studies, DAMOCLES did not employ sham treatment (i.e., administration of air instead of oxygen at hyperbaric pressure). Although sham treatment enables blinding of participants and staff, we deliberately chose not to use sham treatment, because breathing air at hyperbaric pressure increases blood oxygen levels and therefore possibly dilutes treatment effects. We believe the risk of consequent observer bias is limited because 1) wound healing was usually confirmed by observers unaware of treatment allocation, and 2) amputation decisions were made in multidisciplinary teams. Nevertheless, surgeons might be more inclined to perform a major amputation in patients allocated to standard care than in those receiving additional HBOT, in whom there was still hope for a good outcome. This inference might be supported by the double-blinded study by Londahl et al., who did not find a significant effect on amputation rates, whereas the non-blinded studies by Faglia et al. and Duzgun et al. did report significantly less amputations in patients treated with HBOT. However, we did not find that patients underwent a postponed amputation after HBOT as should be expected when the effect is completely caused by the non-blinded fashion of our study.

Second, lagging inclusion rates necessitated a downward adjustment of the sample size. We found a trend towards better outcomes in the SC+HBOT group for both primary outcome measures, and it is quite possible that the difference would have reached statistical significance if the initially anticipated sample size would have been attained.

Third, per-protocol analyses per se are at risk of selection bias. The effect of HBOT we found in per protocol analysis A could merely be due to selection of a subset of patients with a better general condition who might have had a favorable outcome even without HBOT. We found that the patients treated with HBOT were slightly younger and had a higher baseline hemoglobin level.

Lastly, some vascular surgeons tended to include patients only if there were no other options left, like revascularization. This seems reflected by the relatively low percentage of patients amenable for revascularization at the time of study inclusion. Of course, this may have mitigated our results although we did not find statistically significant differences on outcomes between revascularized and non-revascularized patients.
CONCLUSION

The results of the DAMOCLES trial suggest that addition of HBOT to standard care does not improve clinical outcomes in the overall population of individuals with diabetic ulcers and concomitant limb ischemia. A substantial proportion of participants was not able to complete the HBOT regimen, which possibly reflects the bad overall medical condition of participants. The observation that HBOT significantly improved limb salvage among those participants who did complete the HBOT regimen supports the potential value of HBOT, which may not be fully realized in clinical practice.

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