Editorial

Poorly designed research does not help clarify the role of hyperbaric oxygen in the treatment of chronic diabetic foot ulcers

Diabetic foot ulcers (DFUs) are one of the most common indications for hyperbaric oxygen treatment (HBOT). The role of HBOT in DFUs is often debated. Recent evidence-based guidelines, while recommending its use, urge further studies to identify the patient subgroups most likely to benefit from HBOT.[1] A recent study in *Diabetes Care* aimed to assess the efficacy of HBOT in reducing the need for major amputation and improving wound healing in patients with chronic DFUs.[2] In this study, patients with Wagner grade 2–4 diabetic foot lesions[3] were randomly assigned to have HBOT (30 sessions/90 min/244 kPa) or sham treatment (30 sessions/90 min/air/125 kPa). Six weeks after the completion of treatment (12 weeks after randomization) neither the fulfillment of major amputation criteria (11/49 vs. 13/54, odds ratio 0.91 [95% CI 0.37, 2.28], $P = 0.846$) nor wound-healing rates (20% vs. 22%, 0.90 [0.35, 2.31], $P = 0.823$) significantly differed between groups. The authors concluded that HBOT does not offer any additional advantage over comprehensive wound care.

Since this paper was published in *Diabetes Care*, one of the most prestigious diabetes journals, it is likely it will have a major impact on the clinical practice of many physicians dealing with diabetic foot problems. Although from a methodological standpoint the conduct of the study (prospective, double-blind, randomized, controlled) seems to be close to ideal, several significant flaws render the conclusions weak.

Firstly, there were some problems with the assessment of the primary outcome of "*meeting the criteria for amputation*". In their published protocol paper,[4] the triallists indicated that "*At the end of the 6-week follow-up phase……, the patient is sent to the participating vascular surgeon for an amputation evaluation*". However, in the published report in *Diabetes Care*, it is evident that patients were not assessed in a face-to-face consultation, but rather by the remote examination of wound photographs and clinical data "*Participant clinical data together with digital photographs of the study wound progress were presented to the vascular surgeon*". This departure from the original intent undermines the primary outcome of the study significantly. Fedorko et al claim this method of assessment has been validated, but neither of their supporting citations appear to substantiate this claim.[5,6]

Wirthlin et al assessed the level of agreement about a collection of wounds between surgeons who were present at the bedside and a remote group who assessed the wounds using a short clinical account and digital photography.[5] There was reasonable agreement between onsite and remote, although the specificity for particular signs ranged from just 27% (erythema) to 100% (ischaemia). Importantly, only a subset of eight of the 24 included patients had non-healing wounds and the proportion of those that were associated with diabetes mellitus is unknown. Further, the need for amputation was not among the management decisions examined. Wirthlin et al concluded "*a prospective trial of remote wound management …. is needed to further validate this technology.*"

The authors of the second supposedly supporting citation were mainly interested in the assessment of pressure ulcers by digital photography using the Photographic Wound Assessment Tool (PWAT) compared to the Pressure Sore Status Tool (PSST).[6] Of the 81 included lower leg ulcers, it is not clear how many were associated with diabetes mellitus. Indications for amputation were not considered. The authors concluded "*The PWAT may be valuable when a bedside assessment cannot be made. However, the size of circular wounds, wound depth, undermining/tunneling, and odor cannot be assessed using photographs.*"

In the Fedorko paper, the decision that there was an indication for amputation was made by the remote vascular surgeon by meeting any of the following criteria: "*persistent deep infection involving bone and tendons (antibiotics required, hospitalization required, pathogen involved); ongoing risk of severe systemic infection related to the wound; inability to bear weight on the affected limb; or pain causing significant disability*".[2] We are particularly concerned that the criteria, "*persistent deep infection involving bone and tendons*", is subjective. Recent studies have demonstrated that diabetic foot osteomyelitis may not necessarily require amputation and some cases may be cured with antibiotic therapy alone.[1] It is interesting to note that despite the high numbers of participants assessed as fitting the requirements for amputation (23% overall), no patient actually had a major amputation. The amputation outcome is inappropriately assessed, done at the wrong time, and the study is grossly underpowered to find any difference in the rate of true major amputation. Finally, whether the surgeon performed a baseline assessment of amputation prior to the randomised intervention is unknown. A comparison between the pre- and post-study estimates of amputation rates could have contributed to the interpretation of the results.

Secondly, the authors fail to provide a clear comparison of peripheral arterial disease (PAD) between the groups. Although patients were randomized and those who were possible candidates for major vessel revascularization were excluded from the study, microvascular status was not assessed. No transcutaneous oxygen measurements were made on any of the patients. Given that, firstly, the risk of microvascular vessel compromise increases with

diabetes duration, and secondly, transcutaneous oxygen measurements correlate with the possibility of good response to HBOT,[7] it is possible that clinically significant differences between groups were undetected. As an example, patients in the HBOT group had a markedly longer mean duration of diabetes (19.1 vs. 12.4 years) and would be likely to have more severe microvascular disease.

Thirdly, the follow-up period of six weeks after completion of treatment is very short. The study to which the authors refer to justify this follow-up period enrolled only patients with ulcers of Wagner grade 1 or 2 and specifically excluded patients with infection or ischaemia.[8] These are not representative of the patient population treated with HBOT.[7] The outcomes in patients with DFUs treated with HBOT should be assessed over a longer period. One such randomized controlled study demonstrated that patients receiving HBOT had significantly higher healing rates than placebo at one-year follow-up (25/48 (52%) versus 12/42 (29%); $P < 0.03$), but not at 12 weeks.[9]

Fourthly, the authors also failed to describe the experience of the vascular surgeon who adjudicated the wounds for amputation; how many years he was involved in the management of diabetic foot wounds or how specialized his practice was with these patients. Objective and universally recognized indications for amputation are yet to be established. Therefore, a multidisciplinary decision-making approach, rather than a single physician's decision, would have increased the credibility of the conclusion the authors reached. Notably, all previous studies of HBOT in this area have used actual amputation rates in order to have a clear clinical endpoint.

Careful patient selection is paramount for the cost-effective use of HBOT as an adjunct to normal wound care in diabetic wounds. As it is possible to identify wounds that have no potential to heal despite HBOT, all studies should incorporate transcutaneous oxygen measurements in their baseline evaluation. As the wounds in this study tended to be small (6.1cm² and 5.8cm² on average) and had persisted for (on average) one year despite state-of-the-art previous wound care, it is likely that at least some of these would not meet the predictive minimal criteria for healing potential with HBOT.[7]

The findings of this study do indeed show that the indiscriminate treatment of all diabetic wounds with HBOT is probably not (cost-) effective; however, the study conclusion that "*HBO has no benefit in the treatment of chronic diabetic foot wounds*" is erroneous.

References

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