



COMMENT ON SANTEMA ET AL.

Hyperbaric Oxygen Therapy in the Treatment of Ischemic Lower-Extremity Ulcers in Patients With Diabetes: Results of the DAMO₂CLES Multicenter Randomized Clinical Trial. *Diabetes Care* 2018;41:112–119

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I read with great interest the article by Santema et al. (1) published recently in *Diabetes Care*.

Two years ago, when I first read about the protocol of this study (2) that claimed to address one of the most controversial issues of hyperbaric oxygen therapy (HBOT), I was filled with the hope that it would help clarify the debate on the topic. While I applaud the authors' effort on conducting such a demanding study, the aberration from the initial protocol, particularly with regard to the sample size, unfortunately renders the results highly questionable.

In brief, a downward adjustment of the sample size, i.e., almost halving it from 226 patients to 120 patients, has most likely caused a type II error, i.e., although the results favor the use of HBOT in all outcome measures, none of the differences reached statistical significance. On closer look at the data in Table 2 in Santema et al. (1), readers will notice that the lower bound of the 95% CI in the risk difference column (particularly for limb salvage, amputation-free survival, freedom

from amputations index limb, and overall mortality) is very close to 0, meaning that should the study be completed with the initially calculated sample size ($n = 226$), the lower bound would probably be above the threshold of statistical significance, i.e., 0.

One other finding supporting the view that sample size matters is the per-protocol analysis A, which demonstrates significantly better outcomes in the HBOT arm with regard to two outcome measures (major amputation and amputation-free survival).

Finally, a serious matching error has probably added to the problem and caused bias. A closer look at Table 1 in Santema et al. (1) shows that patients in the standard care arm had significantly lower grade wounds (in total, 42% patients had Wagner grade III and IV wounds in the standard care arm vs. 55% in the HBOT arm). The fact that wounds with Wagner grade III and IV have a very high likelihood of osteomyelitis and that patients with osteomyelitis almost always suffer amputation (3)

causes a bias toward worse outcomes in the HBOT arm.

Taken together, the study by Santema et al. (1) showed that a more realistic treatment effect with a larger sample size, along with better matched groups, could have led to significant results in favor of HBOT.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

1. Santema KTB, Stoekenbroek RM, Koelemay MJW, et al.; DAMO₂CLES Study Group. Hyperbaric oxygen therapy in the treatment of ischemic lower-extremity ulcers in patients with diabetes: results of the DAMO₂CLES multicenter randomized clinical trial. *Diabetes Care* 2018;41:112–119
2. Stoekenbroek RM, Santema TB, Koelemay MJ, et al. Is additional hyperbaric oxygen therapy cost-effective for treating ischemic diabetic ulcers? Study protocol for the Dutch DAMOCLES multicenter randomized clinical trial. *J Diabetes* 2015; 7:125–132
3. Mutluoglu M, Sivrioglu AK, Eroglu M, et al. The implications of the presence of osteomyelitis on outcomes of infected diabetic foot wounds. *Scand J Infect Dis* 2013;45:497–503

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