Interpretation of the study "Lack of effectiveness of hyperbaric oxygen therapy for the treatment of diabetic foot ulcer and the prevention of amputation"

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The publication in February 2013 of the epidemiological study "Lack of Effectiveness of Hyperbaric Oxygen Therapy for the Treatment of Diabetic Foot Ulcer and the Prevention of Amputation" by D.J. Margolis *et al*. [1] appears to contradict previous studies that had established the efficacy of hyperbaric oxygen (HBO_2) in healing recalcitrant diabetic foot ulcers (DFUs). In actuality, this retrospective longitudinal observational cohort study does not dispute prior prospective blinded, randomized placebo-controlled trials [2,3] that already evidenced the capacity of adjunctive HBO_2 for treating DFU, nor is this study intended to determine whether HBO_2 works as a form of treatment.

The authors observed for a trend in real-world outcomes (completely epithelialized wound and lower extremity amputation) of HBO_2 treatments compared to conventional therapy for DFU using culled data from a database of past treatments of 6,259 subjects who met study inclusion criteria. Statistical analysis, augmented by propensity score-adjusted models to adjust for treatment allocation bias and by additional analyses for confounders, found that HBO_2 did not improve the likelihood of a wound to heal and did not decrease the likelihood of amputation.

Unfortunately, their valid effectiveness study has been misconstrued as an efficacy study and their conclusion of lack of effectiveness erroneously equated as lack of efficacy. The evidence and results put forth by their investigation should be viewed in the correct context and should not be perceived nor exploited as an opponent against the utility of HBO_2. This review of the Margolis paper discusses that context and the many issues presented by the study.

I. Effectiveness study *vs.* efficacy study

The Margolis paper is an effectiveness study and not an efficacy study. This means that the authors used a retrospective analysis of existing data to evaluate how effectively HBO_2 has been applied toward producing expected outcomes in real-world practice. In contrast, efficacy trials, such as the Londahl [2] study published in 2010, looked for efficacy of HBO_2 through prospective data in an ideal, rigidly controlled experimental environment to determine whether HBO_2 actually worked as adjunctive treatment for non-healing diabetic foot ulcers.

The purpose of an effectiveness study is not the same as that of an efficacy trial and the two are not equatable. They signify two different objectives: One tries to determine if something actually works (efficacy) and the other tries to discern if that something has been beneficially employed (effectiveness). Though the terms are often used synonymously in the lexicon, and sometimes even incorrectly in the scientific literature, there is distinction between the two in research. Both types of studies are valuable and useful for validating new forms of treatments and for improving already existing ones.

The Margolis effectiveness study is directing attention to an important aspect of medical treatments: Has the efficacy of HBO_2 for DFU demonstrated in experimental studies translated into actual effectiveness when put into clinical practice? This study does not deny that hyperbaric oxygen therapy (HBO_2T) is efficacious as adjunctive treatment in the healing of diabetic foot ulcers and for prevention of major amputation, but it does conclude that HBO_2 has not displayed the same beneficial outcomes in an existing clinical practice setting as it has in several clinical trials.

II. Interpretation of the findings

A. Study outcomes reflective of and limited solely to one entity source

Though hyperbaric oxygen is often utilized as part of a wound care plan, HBO_2 is not a type of wound care. While there are hundreds of wound care centers in the United States that have procured hyperbaric oxygen chambers for their facilities, wound care is not the practice of hyperbaric medicine, nor is hyperbaric

medicine the practice of wound care. Non-healing diabetic foot ulcer represents only one indication among the 14 for which HBO_2 therapy has proven efficacy. However, due to the unprecedented increase of diabetes and its complications, DFUs constitute a major portion of patients treated at and of hyperbaric oxygen treatments performed in most wound care centers.

The data obtained in the study came from a wound management company that maintains an extensive database, which serves a variety of purposes. It is not a complete electronic health record, and thus certain potentially important patient metrics were unavailable for analysis. Keeping in mind that vagaries in data entry exist when mining data for a study, due to the large number of centers the available database represented a logical source for data on the effectiveness of HBO_2 in clinical practice. However, for the same reason that there is ease in studying such a volume of data obtained through one source, the outcomes data from the study can be attributed only to its one source.

It is presumed that all facilities contracted under a uniform practice management platform would follow a homogenous treatment algorithm for diabetic foot ulcer patients. However, the study provided no information regarding the treatment algorithm, the frequency with which interventions such as vascular screening or off-loading were employed, or with what uniformity patients were selected for HBO_2. Therefore, the conclusion of this study cannot be applied globally. The reported outcomes in this study are indicative of the effectiveness of the protocols and practices in utilizing HBO_2 under this management platform (insofar as they may be enforced) and ought not to be regarded as a broad indictment of hyperbaric oxygen therapy as practiced nationally. Variables such as quality of physician training, stringent documentation and adherence to evidence-based hyperbaric oxygen criteria and wound management protocols were not addressed in this study, yet have a profound effect on outcomes. The effectiveness of a treatment directly results from how it is employed by practitioners.

B. Mechanism, criteria and selection

The selection process for HBO_2T at this wound management company was not reported by the study, thus it is not known how the patients were selected for treatment. HBO_2 is adjunctive to proper diabetic foot ulcer care. Specific points of concern include:

1. HBO_2 works mechanistically by inducing angiogenesis and vasculogenesis [5,6] within the microangiopathic wound (diseased small-vessel wound), but neovascularization of the wound cannot be achieved if large-vessel ischemia has not been assessed and optimally repaired prior to initiating HBO_2. The study reports that subjects were noted as having "adequate lower extremity arterial flow as determined by the clinician." How this was done is unclear. The lack of documentation of the diagnostic test used to verify and quantify the vascular status of treated patients leads to the question of appropriate patient selection, which would skew outcomes.
2. As remarked by the lead author, the inclusion of Wagner Grade 2 DFUs in the study was necessitated by a preponderance of patients with Wagner 2 diabetic foot ulcers who were treated with HBO_2 at these centers. This is in contrast to Medicare coverage policy that limits coverage of HBO_2 for DFUs to Wagner Grade 3 or higher, reflecting accepted UHMS and evidence-based HBO_2 criteria for DFU. Among randomized controlled trials (RCT) performed for various forms of treatment for diabetic foot ulcers, only HBO_2 trials have included Wagner 3 or higher DFUs [8], giving it a unique place in the armamentarium of the wound care clinician. Conversely, since numerous therapies have shown to be of benefit in Wagner 2 ulcers, including aggressive off-loading, there is not likely to be a significant difference in outcome when the HBO_2-treated Wagner Grade 2 ulcer patients are compared to their cohort. Thus, HBO_2 would not show effectiveness if patients who are likely to "get well anyway" are selected for treatment.
3. HBO_2 is also not effective if it is not part of a multidisciplinary approach to therapy with the concomitant use of treatments directed at all the impediments to healing [4]. If optimally revascularized peripheral arterial disease, appropriate debridement, infection management, glycemic control and off-loading the wound are not maintained while HBO_2T is undertaken, the wound will not heal despite any success of HBO_2 in inducing good granulation tissue with neovascularization. It does not appear from the data presented that a multimodality team approach was in place as part of the methodology of these centers. It appears instead that, despite the propensity score adjustment in the study, the patients with the most advanced disease were directed to HBO_2T as the main mode of treatment rather than as adjuvant therapy. In this situation, it is not surprising that a beneficial effect of HBO_2 was not observed.

III. Analysis method of study

A. Lack of consensus as to successful outcome

Opinions vary in range as to the successful endpoint for a non-healing diabetic foot ulcer. Some physicians consider complete wound closure to be the objective. If the goal is bipedal ambulation, minor amputations (*e.g.*, toes) would be considered a successful outcome as long as a major amputation (below the knee or higher) is avoided. HBO_2 has previously been shown to increase the likelihood of minor amputation in exchange for a decrease in major amputation [12], an exchange generally agreed to represent an improvement in quality of life years. According to the Margolis study, any lower extremity amputation was classified as a negative outcome, so the beneficial effect of minor amputations could not be identified. The Margolis study underscores the need for consensus on the way in which DFU outcomes are reported.

B. Propensity score and sensitivity analysis

It is not the intent of this review to dismantle the epidemiological and statistical design of this study, which is a valid study of treatment effectiveness; however, two concerns must be noted. While the propensity score (PS) is used to adjust for the severity of wounds and for patient comorbidities, if done inappropriately PS can actually lead to increased rather than decreased bias [7]. There are confounders that can directly affect outcomes (infection severity, lack of off-loading, poor diabetes management, immunosuppression, smoking, renal failure, chronic heart failure and degree of tissue exposed) [8]. While sensitivity analysis of an individual potential confounder may be done, it is insufficient to account for all the potential effects of such a considerable list of known confounders. Further, sensitivity analysis cannot make allowances for any unknown confounding factors [8]. As discussed above, the database used did not contain adequate patient detail to allow for more detailed patient stratification.

IV. Summary

It is agreed with the authors of this study that HBO_2 should be utilized as a part of the overall strategy in healing recalcitrant diabetic foot ulcers rather than as a single agent to completely heal these wounds. It is also agreed that HBO_2 serves a specific purpose in the overall wound repair process, *i.e.*, its mechanism is to induce neovascularization and granulation tissue, establishing the foundation for the anticipated healing process to go to completion. The most appropriate endpoint in the application of hyperbaric oxygen for DFU has yet to reach consensus, though. Prior efficacy studies have shown that, conducted under specific indications, defined criteria and appropriate selection, beneficial outcomes can be achieved with HBO_2. The Margolis effectiveness study suggests that applied outside its parameters, HBO_2 does not provide further benefit beyond conventional wound care. The study reveals the need to evaluate clinical practice algorithms, to reassess how HBO_2 is utilized and to standardize endpoints in the treatment of DFU. The following points are reiterated and emphasized:

- HBO_2 has already been demonstrated with highest AHA Level 1A evidence to be of benefit as adjunctive therapy for the healing of diabetic foot ulcers [2,3,9,10,11].
- The lack of *effectiveness* of HBO_2T for DFU in this retrospective observational cohort study does not dispute the *efficacy* of HBO_2T for DFU shown in prospective RCTs.
- As there is variability in practitioner utilization, the parsed outcomes data are not generalizable to wound care or hyperbaric medicine practices globally.
- Adherence to appropriate patient selection and treatment criteria is essential to the effectiveness of HBO_2.
- The benefit of an exchange of a major amputation for a minor amputation was not identified in the classifying of any lower extremity amputation as a negative outcome of HBO_2. ■

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From the editors

GETTING BURNED . . .

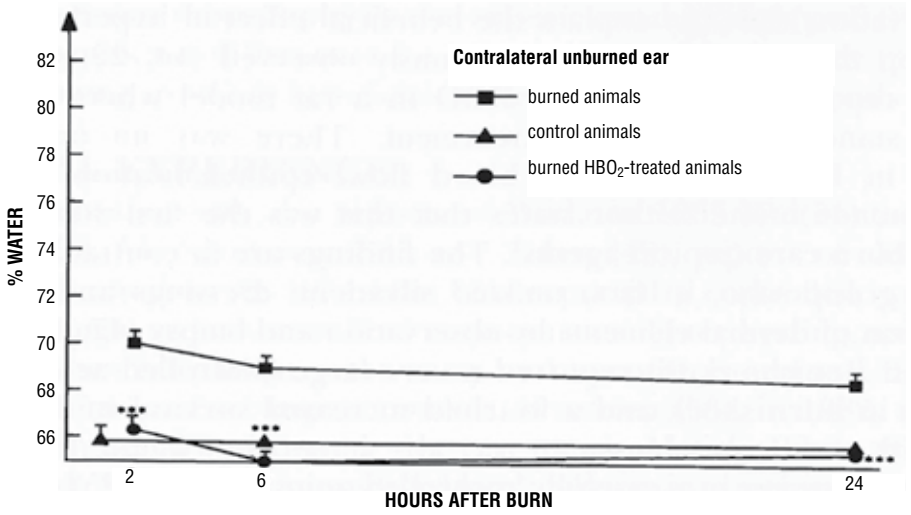
Adjunctive hyperbaric oxygen therapy in the treatment of thermal burns

The paper "Adjunctive hyperbaric oxygen therapy in the treatment of thermal burns," by Paul Cianci M.D., FACS, FUHM, John B. Slade Jr. M.D., Ronald M. Sato M.D. and Julia Faulkner, which appeared in the January-February 2013 issue (vol. 40-1), inadvertently switched two illustrations on Page 93: the current Figure 4 by Dr. Nylander, published incorrectly as Figure 5 in the original issue; and the current Figure 5 by Dr. Kaiser, published incorrectly as Figure 4 in the original issue. The corrected paper is available in the UHM archives at *www.uhms.org/?page=Journal*.

We sincerely regret the error.

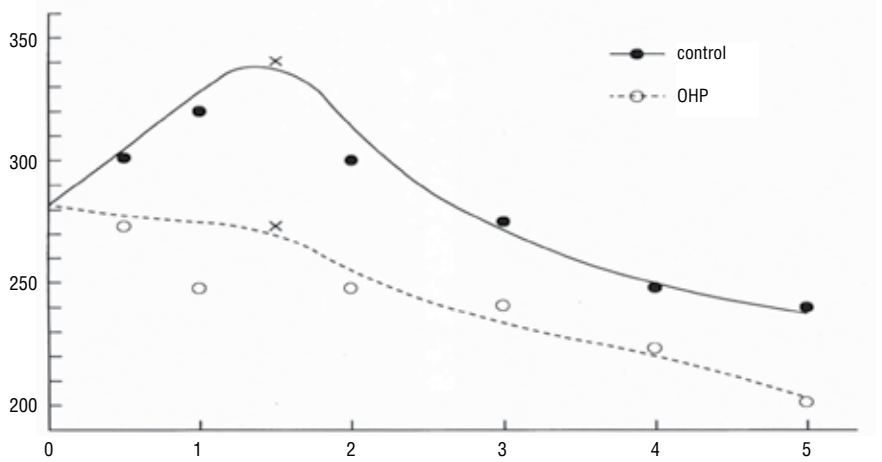
Corrected figures 4 and 5

Figure 4. Water content of the contralateral burned ear



Water content (± SEM) of the contralateral unburned ear in burned animals with and without HBO_2 treatment.

Figure 5. Tissue oxygen tension



Kaiser demonstrated in a full-thickness animal model a significant reduction of wound size in the hyperbaric-treated animals (open circles) *vs.* an increase in the control group, which remained larger at all times measured.