Systemic Hyperbaric Oxygen Therapy

Lower-extremity wound healing and the diabetic foot

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OBJECTIVE — To document peer-reviewed medical publications that have reported on hyperbaric oxygen (HBO) therapy as an adjunct to standard lower-extremity wound care, focusing on publications dealing with the diabetic foot.

RESEARCH DESIGN AND METHODS — A review of the medical literature was conducted using MEDLINE. Research articles involving HBO treatment and the diabetic foot were critiqued to identify factors that may have been a source of bias.

RESULTS — Of the published reports on human studies, seven involved diabetes-related foot pathology. Five of these studies, two of which were randomized, included a control group that did not receive HBO therapy. The controlled diabetic foot studies included an average of 28 subjects in the HBO therapy group (range 10–62) and an average of 16.2 subjects in the non-HBO control group (range 5–33). Most of the published reports have several potential sources of bias, including, but not limited to, inadequate evaluation of comorbid conditions relevant to wound healing, small sample size, and poor documentation of wound size or severity. Four of the seven reports involving the diabetic foot were published by a group of researchers at the University of Milan between 1987 and 1996.

CONCLUSIONS — Additional randomized placebo-controlled clinical trials in large diabetic populations would further lend credence to the presumption that HBO therapy improves clinical outcomes. Given the relatively high cost of this treatment modality, perhaps a more acute awareness of the medical literature would reduce the economic burden that HBO therapy imposes on care providers that are financially at risk.

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Although the clinical history of hyperbaric medicine dates back to the 17th century, reports of the beneficial effects of increased oxygen pressure on wound healing and infection did not appear in the medical literature until the 1960s. The most recent report by the Hyperbaric Oxygen Therapy Committee of the Undersea and Hyperbaric Medical Society (1) lists several indications for hyperbaric oxygen (HBO) therapy that are directly applicable to lower-extremity pathology. These include clostridial myonecrosis, acute traumatic ischemia, enhancement of healing in problem wounds, necrotizing soft tissue infections, refractory osteomyelitis, compromised skin grafts and flaps, and thermal burns. Interestingly, there are relatively few controlled clinical trials in human subjects involving HBO for the treatment of these conditions. In fact, the majority of published reports on this topic consists of review articles, case reports, uncontrolled studies, and animal or in vitro studies.

Based on our experiences, we believe that many clinicians routinely incorporate HBO sessions into their treatment protocols without full knowledge of the evidence-based data that support this therapy. Anecdotally, we have observed a tendency among physicians to view HBO therapy as a panacea for all types of nonhealing wounds, particularly diabetic foot wounds. This practice has been further complicated by patient-oriented television and print media campaigns that laud the benefits of HBO therapy for nonhealing wounds. Therefore, the purpose of this article is to document peer-reviewed medical publications that have reported on HBO therapy as an adjunct to standard lower-extremity wound care regimens in diabetic patients.

RESEARCH DESIGN AND METHODS

— A review of the medical literature was conducted using PubMed, the National Library of Medicine's World Wide Web–based MEDLINE search engine. The following key phrases were entered in the search engine to identify relevant articles: "hyperbaric oxygen," "wound healing," "diabetic foot," "gas gangrene," "chronic osteomyelitis," "necrotizing fasciitis," and "thermal burns." In addition, the references cited in the articles collected through the MEDLINE search were reviewed to identify other relevant publications.

Inclusion criteria for articles were as follows: articles published in English, articles from journals listed in *Index Medicus*, articles describing scientific research of systemic HBO as adjuvant therapy for either wound healing or infection, review articles describing the use of systemic HBO as adjuvant therapy for either wound healing or infection, and case reports describing the use of systemic HBO for either wound healing or infection. Articles were excluded if they were not published in English or if they were not directly applicable to lower-extremity pathology.

Articles meeting the inclusion and exclusion criteria were reviewed and placed into one of three categories: reviews and case reports, experimental animal or in vitro studies, or human studies. A table was constructed for the latter category to list relevant data from each article. Furthermore, research articles involving HBO treatment and the diabetic foot were cri-

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Abbreviations: HBO, hyperbaric oxygen; T_cPO_2, transcutaneous partial pressure of oxygen.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

tiqued to identify factors that may have been a source of bias. These factors included, but were not limited to, lack of a control group, inadequate sample size, insufficient evaluation of comorbid conditions, and poorly defined methods of retrospective analysis.

RESULTS — A total of 76 articles were identified that met the inclusion and exclusion criteria. There were 21 studies involving human subjects (2–22) (Table 1), 27 animal or in vitro studies (23–49), and 28 reviews and/or case reports (50–77). Of the studies involving human subjects, 62% (13 of 21 articles) included a control group. Of the published reports of human studies, seven involved diabetes-related foot pathology. Five of these studies, two of which were randomized, included a control group that did not receive HBO therapy. The controlled diabetic foot studies included an average of 28 subjects in the HBO therapy group (range 10–62) and 16.2 subjects in the non-HBO control group (range 5–33). Interestingly, four of the seven reports involving the diabetic foot were published by the same group of researchers at the University of Milan between 1987 and 1996 (8,9,13,14).

CONCLUSIONS — Although HBO therapy has gained popularity as an adjunctive treatment for diabetic foot wounds, there are surprisingly few published reports that support its efficacy. Furthermore, there seem to be no objective measures to assist clinicians in appropriately selecting patients for HBO therapy. Our literature search revealed only two reports of randomized controlled clinical trials that evaluated HBO therapy in the diabetic foot. Given the substantial cost associated with these treatments, a more thorough analysis of human studies dealing with HBO therapy for the diabetic foot is not only justified but necessary.

As previously indicated, more than half of the published research reports dealing with HBO therapy for diabetic foot disease originated from a group of researchers at the Center of Diabetology and Metabolic Diseases, Niguarda Hospital, and the Department of Anesthesia and Hyperbaric Medicine, Galeassi Institute, Milan, Italy (8,9,13,14). The first report published by this group appeared in *Diabetes Care* in 1987 (9). This nonrandomized study included 18 hospitalized diabetic subjects and 10 diabetic control subjects. Of the 28 study subjects, 23 had gangrene of the foot and 5 had neuropathic ulcers. Both groups were treated with strict metabolic control and daily wound debridement. The HBO group had an average of 34 ± 21.8 HBO treatments of 90 min/day at a pressure of 2.5–2.8 atm. At the conclusion of the study, 16 patients in the HBO group had healed compared with only 1 patient in the control group. Additionally, 2 patients in the HBO group required an amputation compared with 4 patients in the control group (P = 0.001). The report does not discuss any differences in outcomes relative to potentially confounding variables, such as vascular disease, ulcer size and depth, or the presence of infection.

The same group of researchers from Milan published a second and identically titled report in the *Journal of Hyperbaric Medicine* in 1990 (13). The period of time during which the study patients were recruited (1982–1990) overlaps with the period of their first report (1982–1984), but the authors do not discuss whether any study subjects were included in both reports. Therefore, although the HBO group consisted of 62 diabetic subjects and the control group had 18 diabetic subjects, it is unclear whether this larger sample size does in fact represent a separate and distinct study population. The report indicates that there were no significant differences in major diabetic complications, such as peripheral vascular disease and peripheral neuropathy. The authors did not discuss the criteria for the operational definition of peripheral vascular disease and did not provide data on wound severity or the presence of infection among the study subjects. The patients in the HBO group underwent an average of 72 ± 29 sessions. The authors indicated that a pressure of 2.5 atm was used "as a reparative stimulus" and that 2.8 atm was used "as antibacterial support," but there is no information on how many treatments were given at each pressure. Of the 62 patients in the HBO group, 59 recovered without the need for an amputation (compared with 18 and 12, respectively, for the control group; $P <$ 0.001). Again, the authors do not discuss the effects of wound size, wound depth, infection, or peripheral vascular disease on clinical outcomes. Additionally, the study would have benefited from having a larger control group for comparison.

Oriani et al. (14) published a third report on HBO therapy and the diabetic foot in 1992. Again, the retrospective study period overlaps with that of both previously published reports, and, therefore, it is likely that data from nearly half of the patients included in this report had been published previously. The report gives no information on comorbid conditions, such as peripheral vascular disease, hyperglycemia, or other conditions that could adversely affect wound healing. Additionally, they provide no information regarding the average size and depth of the wounds or the presence of infection. There is no control group presented for comparison. During the study period, 151 diabetic patients with "major ulceronecrotic lesions of the lower extremities" underwent an average of 40 HBO treatments; the conditions of 130 patients healed, whereas the conditions of 21 patients deteriorated. The authors did not report any statistical analysis of their outcomes. Clearly, this report leaves many questions unanswered.

The most recent published report from the group of researchers at the University of Milan appeared in *Diabetes Care* in 1996 (8). In this report, the authors presented the results of a prospective randomized clinical trial, which included 35 subjects in the HBO group and 33 subjects in the control group. The control group did not receive placebo sessions in a hyperbaric chamber at normal atmospheric pressure, so it is unknown whether a placebo effect exists for this treatment modality. The authors report significantly fewer major amputations (below the knee or above the knee) for the HBO group, but only among patients with Wagner grade IV ulcers. There was no statistical difference in minor amputations between the HBO and control groups. Likewise, no intergroup variation in major amputations existed among patients with Wagner grade II or III wounds. The results of this well-designed study suggest that HBO therapy may be helpful in reducing major amputations among diabetic patients with Wagner grade IV foot ulcers.

In 1991, Wattel et al. (10) published the results of a noncontrolled study of HBO therapy for diabetic foot lesions. Their study consisted of 59 diabetic patients with neuropathic or ischemic wounds who underwent an average of 29 ± 19 HBO sessions at 2.5 atm. Although the abstract of the report indicated that 52 patients healed and 7 patients underwent an amputation, the report itself stated that 48 patients healed and 11 eventually required an amputation. The authors did not discuss this apparent discrepancy in outcomes. Additionally, there is no mention of differ-

Table 1—*Studies involving human subjects that met the inclusion criteria*

Reference	Type of study	Randomized	Controlled	*n*	HBO: control	Condition	Average number of dives	atm	Dive duration (min)	% Healed in HBO group	Better than control
2	Retrospective	NA	No	38	NA	Osteomyelitis*	48	2.4	90	89.5	NA
3	Retrospective	NA	No	44	NA	Osteomyelitis†	50	2	120	68.0	NA
5	Prospective	No	Yes	28	1:1	Osteomyelitis‡	NR	2	120	86.0	No
4	Retrospective	NA	No	198	NA	Necrotizing ST infection	31.7	2.4	90	76.8	NA
6	Retrospective	NA	No	24	NA	Necrotizing ST infection§	3	2.8	120	NR‖	NA
7	Retrospective	No	Yes	43	0.2:1	Clostridial myositis	NR	NR	NR	NR	No¶
16	Prospective	Yes	Yes	16	1:1	Chronic leg ulcers#	30	2.5	90	NR	Yes**
18	Prospective	No	No	19	NA	Varicose leg ulcers	30.35	2	120	89.5	NA
19	Retrospective	No	No	20	NA	Chronic wounds††	46	2.5	90	75.0	NA
17	Prospective	Yes	Yes	36	1:1	Crush injury	12	2.5	90	94.4	Yes
15	Prospective	Yes	Yes	48	1:1	STSG	3	2	120	84.2	Yes
22	Retrospective	NA	Yes	72	1:1	Severe burns‡‡	NR	NR	NR	38.9§§	No
21	Retrospective	NA	Yes	49	1:1	Severe burns‖‖	NR	2.5	90	NR¶¶	Yes
20	Prospective	Yes	Yes	16	1:1	Severe burns##	NR	2	90	NR***	Yes
8	Prospective	Yes	Yes	68	0.9:1	Diabetic foot ulcers	38	2.5	90	NR	Yes†††
11	Prospective	Yes	Yes	30	1:1	Diabetic foot ulcers	4	3	45	NR	Yes‡‡‡
13	Retrospective	No	Yes	80	3.4:1	Diabetic foot ulcers	72	2.5–2.8	NR	95.2	Yes§§§
14	Retrospective	NA	No	151	NA	Diabetic foot ulcers	40	2.5–2.8	90	86.1	NA
12	Prospective	No	Yes	10	1:1	Diabetic foot ulcers	30	2	120	80.0	No
9	Prospective	No	Yes	28	1.8:1	Diabetic ulcers/gangrene	34	2.5–2.8	90	88.9	Yes
10	Retrospective	NA	No	59	NA	Diabetic ulcers/gangrene	29	2.5	90	81.4	NA

NA, not applicable; NR, not reported; ST, soft tissue; STSG, split-thickness skin graft. *Chronic and nonhematogenous; †spinal cord injury patients; ‡chronic and refractory; §clostridial myonecrosis or necrotizing fasciitis; ‖overall mortality 25%; ¶fewer deaths in HBO group; #nondiabetic and nonischemic; **mean decrease in wound area at week 6; ††diabetic foot ulcers and ischemic ulcers; ‡‡mean total burn area 54.6%; §§survival % in HBO group; ‖‖50% or more body surface burned; ¶¶41.7% mortality HBO group and 68.0% mortality in control group; ##10–50% body surface area burned; ***mean healing time less for HBO group; †††significantly less major amputations among patients with Wagner Grade IV ulcers only; ‡‡‡significantly less major amputations and quicker control of infection; §§§significantly less amputations.

ences in many important variables, including the level of glucose control, wound size and depth, infection, or local wound care. The authors did note, however, that the group of patients who healed had significantly higher transcutaneous oxygen (T_cPO_2) measurements at the level of the wound than the group of patients who did not heal (taken at 2.5 atm O_2). Therefore, the authors conclude that T_cPO_2 measurements may be useful in selecting patients for adjunctive HBO therapy. However, one must consider the numerous key variables that were not mentioned in this report as a potential source of bias.

In 1992, Doctor et al. (11) published the results of a prospective randomized controlled study of HBO therapy for diabetic subjects with chronic foot lesions. Thirty patients were randomized into either a study group, which received conventional treatment plus HBO sessions, or a control group, which received conventional treatment alone. There were no significant differences in age, sex, duration of diabetes, neuropathy, or the presence of distal pulses. The report does not indicate whether a more extensive examination was performed to rule out peripheral vascular disease. Additionally, there is no mention of wound size or depth in either the study or the control group. The study group received four sessions of HBO therapy at a pressure of 3 atm for 45 min per session. Clearly, the number of HBO sessions is significantly fewer than those reported by others in the medical literature, and the benefit of such a small number of treatments is questionable. The authors reported significantly fewer major amputations in the HBO group than the standard treatment group. However, the report also indicated that "uncontrolled diabetes" indicated the need of a major amputation in five of the seven patients who required the procedure. There was no difference in the length of hospital stay or the number of minor amputations between the groups.

The most recently published prospective study of HBO for diabetic foot wounds appeared in 1997. Zamboni et al. (12) evaluated HBO therapy for a group of 10 consecutive insulin-dependent diabetic patients with lower-extremity wounds. Five of these patients refused HBO therapy and thus served as a control group. The authors did not record several variables that may have affected wound healing, such as wound depth, serum albumin, degree of glycemic control, and the presence of anemia or other general medical conditions detrimental to wound healing. The HBO group underwent five sessions per week of HBO therapy at 2.0 atm for a total of 30 treatments. The authors did not mention whether measures were taken to off-load ulcers located on the plantar aspect of the foot. The results of this small study indicate a greater reduction in wound surface area in the HBO group over the entire 7-week study. Additionally, none of the patients in either the HBO group or the control group underwent an amputation. These results are encouraging; however, a much larger study population is needed to make any meaningful conclusions.

After critiquing the medical literature that supports HBO therapy as an adjunctive treatment for diabetic foot wounds, we

conclude that additional research is needed to define the specific indications and benefits of this treatment modality. Specifically, randomized placebo-controlled clinical trials in large diabetic populations would further lend credence to the presumption that HBO therapy improves clinical outcomes. Clearly, it would be difficult to conduct a perfectly controlled HBO study because of the numerous clinical variables that affect wound healing. The most convincing work in the medical literature to date demonstrates that HBO therapy can reduce the number of major amputations in patients with Wagner grade IV wounds (8). Even these results should be reevaluated in a larger multicenter trial that would allow many of the potential confounding factors to be controlled or evaluated in the model. Interestingly, wound care centers often use the T_cPO_2 response to 100% oxygen challenge as a criterion to determine if the wound would benefit from HBO therapy. However, after reviewing the literature, we found only one very small human study that may support this practice (19).

The authors' anecdotal experience is that HBO therapy is commonly used as an adjunct to standard wound care in many types of wounds, both deep and superficial, infected and noninfected, ischemic, and well-perfused. It is reasonable to predict that, in many cases, aggressive local wound care and adequate off-loading would obviate any need for HBO therapy. There does not seem to be any evidence-based criteria to select patients for HBO therapy or to predict who will benefit and who will not. Given the relatively high cost of this treatment modality, perhaps a more acute awareness of the medical literature would reduce the economic burden that HBO therapy places on care providers that are financially at risk.

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