Lack of Effectiveness of Hyperbaric Oxygen Therapy for the Treatment of Diabetic Foot Ulcer and the Prevention of Amputation

A cohort study

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OBJECTIVE—Hyperbaric oxygen (HBO) is a device that is used to treat foot ulcers. The study goal was to compare the effectiveness of HBO with other conventional therapies administered in a wound care network for the treatment of a diabetic foot ulcer and prevention of lower-extremity amputation.

RESEARCH DESIGN AND METHODS—This was a longitudinal observational cohort study. To address treatment selection bias, we used propensity scores to determine the "propensity" that an individual was selected to receive HBO.

RESULTS—We studied 6,259 individuals with diabetes, adequate lower limb arterial perfusion, and foot ulcer extending through the dermis, representing 767,060 person-days of wound care. In the propensity score–adjusted models, individuals receiving HBO were less likely to have healing of their foot ulcer (hazard ratio 0.68 [95% CI 0.63–0.73]) and more likely to have an amputation (2.37 [1.84–3.04]). Additional analyses, including the use of an instrumental variable, were conducted to assess the robustness of our results to unmeasured confounding. HBO was not found to improve the likelihood that a wound might heal or to decrease the likelihood of amputation in any of these analyses.

CONCLUSIONS—Use of HBO neither improved the likelihood that a wound would heal nor prevented amputation in a cohort of patients defined by Centers for Medicare and Medicaid Services eligibility criteria. The usefulness of HBO in the treatment of diabetic foot ulcers needs to be reevaluated.

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Hyperbaric oxygen (HBO) therapy is used to treat foot ulcers that have not responded to initial care and thereby to prevent lower-extremity amputations (LEAs), both of which are complications of diabetes. HBO requires the exposure of a patient to 100% oxygen at a pressure two to three times greater than ambient atmospheric pressure (1). The efficacy of HBO as a treatment for lower-extremity ulcerations has been supported by several small randomized trials; its use also has been advocated by a number of review articles (2–7). However, a meta-analysis of these randomized trials did not find a long-term statistically significant improvement associated with HBO therapy and concluded that the overall quality of the reviewed studies was poor (8).

Randomized controlled studies are efficacy studies in that they estimate the likelihood that a drug or device, like HBO, will work in an ideal setting. Effectiveness studies estimate the likelihood that a drug or device will work in the "real world." Effectiveness studies can be difficult to conduct in that the design constraints of a randomized trial create a nonreal-world setting; therefore, frequently, effectiveness is assessed using cohort studies. The propensity score (PS) technique was first described ~30 years ago (9). The goal of this technique is to statistically control variables that might influence the selection of a therapy and thus to mimic the "even" distribution of variables seen in a randomized controlled study.

We compared the effectiveness of HBO with other therapies administered without HBO in a wound care network. We used PS approaches to compensate for the lack of randomized treatment assignment as well an instrumental variable analysis (Supplementary Data) to confirm our findings.

RESEARCH DESIGN AND METHODS

—Longitudinal observational data from the National Healing Corporation (NHC) were used. The study was reviewed and approved by the Institutional Review Board of the University of Pennsylvania. Our presentation is consistent with the STROBE statement for cohort studies.

Population

NHC is a company that provided comprehensive wound care management solutions to local wound care centers across the United States. NHC developed clinical pathways to guide treatment based on reviews of best practice and guidelines on

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proper diagnosis and medical care (e.g., debridement, good wound care, and offloading) that were taught to the local wound care providers. HBO was one of the therapies used in their centers. NHC maintained a database that included both administrative and clinical information.

Subjects were included in the study if they were treated at an NHC center between November 2005 and May 2011, and if the local wound care center had contractually agreed to provide data for research, resulting in 83 centers located in 31 states being available for study. All subjects in these centers were evaluated for eligibility. To be eligible, subjects must have had diabetes, adequate lower-extremity arterial flow (as determined by the clinician), and a wound on their plantar foot (hindfoot [heel], midfoot, or forefoot [toes]). All subjects must have experienced failure to heal during the first 4 weeks of wound center care and also to have experienced failure of decrease in their wound size by at least 40%. These inclusion criteria are consistent with the inclusion criteria of diabetic foot ulcer randomized clinical trials (RCTs) registered with the Food and Drug Administration and with the reimbursement guidelines from Centers for Medicare and Medicaid Services (CMS) (10–12). The CMS guidelines for HBO reimbursement suggest that patients should have type I or II diabetes, adequate lower limb arterial blood flow, a deep skin ulcer penetrating down to ligaments, muscle, or deeper with tissue infection (e.g., a Wagner wound grade of ~3), and a wound that has failed to heal despite a 30-day course of standard wound management. Similar criteria recently were approved by the National Health Insurance Program of Canada (13).

Validation

To validate our ability to properly access individuals with diabetes who had adequate lower-extremity arterial flow and foot ulcers, we received personal identifier redacted copies of the electronic medical chart with photographs for two groups of patients: one selected for having diabetic nonischemic foot ulcers (our target population, $n = 100$) and the other selected for having wounds of the lower extremity but not diabetic nonischemic foot ulcers ($n = 100$). The NHC codes for an individual having a diabetic foot ulcer were based on a diagnosis of diabetes, diagnosis of arterial and venous disease (exclusionary codes), and the location of the wound (e.g., foot). However, those in the other lower-extremity wound group could not have the codes listed for diabetic foot ulcers but could have the exclusionary codes. All materials were reviewed by a single investigator (D.J.M.) who was blinded to the database classification of the subject. An individual was thought to have a diabetic nonischemic foot ulcer if chart review revealed the following: diagnosis of diabetes; no mention of lower limb ischemia or venous disease; and wound location on the plantar aspect of the foot that could be confirmed by a photograph. To compare database ascertainment with actual chart assessment, we calculated the positive and negative predictive values, as well as the sensitivity and specificity of the ascertainment method.

Person-time

The study time began 28 days after an eligible individual was first examined and enrolled in an NHC clinic. This "pretrial" follow-up period is part of most clinical trials to ensure that a wound is chronic and not healing. Outcomes and person-time did not include this 28-day prestart time period. Person-time accrued until the subject had left the database, died, healed, had an amputation, or had been followed-up for 20 weeks since enrollment at the NHC center (i.e., 16 weeks after they were enrolled in our study population). We previously have used this definition of person-time in a similarly designed study (14).

Outcome

We studied two outcomes: healed wound (as determined by the local wound care provider based on a wound being fully epithelized and no longer requiring a bandage) and LEA. All outcomes were assessed 16 weeks after the subject became eligible for our study or 20 weeks after enrollment at an NHC center.

Covariates

Covariates included age, sex, wound duration at enrollment, wound size at enrollment, Wagner grade, number of wounds on the patient, wound location, history of neuropathy, history of wound recurrence, and history of osteomyelitis or abscess.

Statistical analysis

Descriptive statistics were generated for covariates and presented as percentages, means and standard deviations. Statistical tests for testing differences between groups or quintiles included χ^2 tests, *t* tests, and ANOVA.

In this study, treatment allocation was not random, but determined by a health care provider. Hence, selection bias could potentially affect our results if the choice of therapy depended on patient factors that were associated with the outcome (in this case LEA or impaired heal).

To minimize bias we used a PS approach. This approach allowed us to achieve balance on observed covariates between treatment groups so that the treatment groups were more comparable (9). The PS provides a summary value for the potential measured confounders. The PS represents a summary value of the potential covariates for each patient and are defined, regardless of the actual treatment choice, as the probability that each patient would receive the treatment of interest given the background covariates of that subject. Our PS model was used to balance a number of baseline covariates such as age, sex, wound age, wound size, Wagner wound grade ≥2, the number of wounds on the patient, history of neuropathy, history of wound recurrence, and history of osteomyelitis or abscess. Importantly, wound age, wound size, and Wagner wound grade ≥2 at first visit are highly predictive of the likelihood that a subject will heal and has been used in other PS studies of wound therapies (14–16).

We first used logistic regression to estimate the PS for each individual by regressing treatment assignment on relevant covariates. We used the estimated PS in several models based on matching and stratification (based on PS quintiles) as a weighting factor and as a continuous covariate for adjustment in proportional hazards analyses. In all proportional hazard models, the proportional hazards assumption was tested and confirmed using log-log plots and Schoenfeld residuals test.

We also conducted an instrumental variables analysis, which is an alternative statistical approach used to minimize selection bias from unmeasured and measured confounders (Supplementary Materials) (9,17). This approach is further described in the Supplementary Materials. All analyses were conducted using STATA version 12.1.

Sensitivity analyses

In nonrandomized studies, an observed association between treatment and outcome

may reflect the effects of unknown or unmeasured confounders that might not have been adjusted for using the PS approach. We conducted a sensitivity analyses to assess the effects of an unmeasured binary confounder on the estimated hazard ratio (HR) for amputation and healing obtained using the PS model (18,19). Sensitivity analyses were performed using R version 2.14 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Database validation

Of the 200 charts reviewed, in those categorized as diabetic nonischemic foot ulcer, the diagnosis was confirmed in 93 of 100; in those categorized in the other lower-extremity wound group, 98 of 100 were confirmed. Therefore, our database algorithm had a positive predictive value of 97.9% (95% CI 92.6–99.7), a negative predictive value of 93.3% (86.7–97.3), a sensitivity of 93% (86.1–97.1), and a specificity of 98.0% (93.0–99.8).

Effectiveness of HBO

There were 11,301 subjects with 32,021 wounds enrolled at eligible wound care centers with diabetic foot ulcers between November 2005 and May 2011. Per the enrollment criteria, these subjects had adequate lower-extremity arterial flow (as determined by the clinician) and a wound on their plantar foot (hindfoot [heel], midfoot, or forefoot [toes]). Finally, per our inclusion criteria, to more closely mimic Food and Drug Administration–approved RCTs, our study was limited to 6,259 subjects who did not experience healing or have an LEA or who experienced failure to decrease the wound size by at least 40% in the first 28 days of care. The majority (83%) of subjects were excluded because they had healed or had an amputation in the first 28 days of care. The average age of this cohort was 62.8 ± 24.6 years, 43.5% were women, 74.2% were white, and 4.5% had LEA (Table 1). The average wound was 1.5 ± 6.7 cm^2 and 1.1 ± 4.0 months old, with 19.3% of the wounds being Wagner grade ≥3, and 48.6% of the wounds healed by study week 16 (Table 1). In total, we analyzed 767,060 person-days of wound care therapy. HBO was administered to 12.7% of the subjects, most frequently to a depth of 2.0 atm (88.5% of treatments), 5 days per week (88%), and for 90-min sessions (99.5%).

Within PS strata, with the exception of wound grade, the distributions of all covariates were similar regardless of treatment. As an example, Table 2 shows the balance of the three variables most often used to predict that a wound will heal. Those in quintile 2 (a group less likely to receive HBO) and quintile 5 (most likely to receive HBO) were not well-balanced ($P < 0.002$ and $P = 0.05$, respectively) with respect to the percentage of individuals with wounds of Wagner grade ≥2.

Survival analyses with adjustment for the PS showed that individuals receiving HBO therapy were more likely to have a lower limb amputation (HR 2.37 [95% CI 1.84–3.04]) and were less likely to heal (0.68 [0.63–0.73]) when compared with those who did not receive this therapy (Table 3). These estimates were nearly identical for all analytic methods (PS adjustment, stratification, or nearest neighbor matching). However, because of our failure to fully balance Wagner wound

Table 1—*Basic characteristics of the study cohort*

	Full cohort	HBO not used	HBO used	*P*
N	6,259	5,466 (87.3)	793 (12.7)	
Male (%)	3,556 (56.8)	3,045 (55.7)	511 (64.4)	<0.0001
Age in years (SD)	62.1 (20.9)	63.0 (16.9)	61.6 (14.5)	0.0004
Wound duration at time of first visit, months (SD)	1.02 (4.0)	0.96 (3.9)	1.0 (4.0)	0.011
Wound size at time of first visit, cm^2 (SD)	1.6 (6.2)	1.6 (6.2)	1.9 (6.3)	<0.0001
Wagner grade ≥3 (%)	3,988 (22.8)	2,708 (18.4)	1,280 (45.7)	<0.0001
Amputations (person) week 16 (%)	168 (2.68)	115 (2.1)	53 (6.7)	<0.0001
Healed wounds week 16 (%)	8,521 (48.6)	7,311 (49.6)	1,210 (43.2)	<0.0001
Major amputation (person) week 16 (%)	96 (1.53)	70 (1.28)	26 (3.28)	<0.0001

Values are presented as mean (SD) or *n* (%). *P* values compare HBO users to nonusers and, as appropriate, are based on *t* test or χ^2 test.

Table 2—*A sample of the covariate balance based on PS quintiles is illustrated using three variables that are highly predictive of wound healing*

	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5	
	No HBO	HBO	No HBO	HBO	No HBO	HBO	No HBO	HBO	No HBO	HBO
Wound size (cm^2)	3.0	3.6	3.6	2.6	3.0	3.0	4.6	5.2	5.9	4.3
P	0.63		0.49		0.95		0.44		0.09	
Wound duration (weeks)	5.3	3.4	4.8	5.8	4.5	4.2	3.7	3.6	2.3	2.7
P	0.59		0.28		0.76		0.86		0.32	
% Grade ≥2	8.4	7.1	75.3	68.6	94.9	93.7	97.7	97.7	98.0	98.9
P	0.52		0.002		0.23		0.99		0.05	
Observed percent healed by week 16	37.7		47.2		49.2		49.0		45.4	
Modeled percentage healed by week 16	38.5		47.2		48.6		47.7		46.6	

P values from two-sample *t* tests (for variables mean wound size and wound duration) and Pearson χ^2 test (for the variable percentage of patients with a wound Wagner ulcer grade ≥2) comparing the two patient groups categorized according to their HBO treatment status (HBO and No HBO) are displayed. To demonstrate the ability of these three covariates to predict outcome, observed percentage of healed subjects by week 16 and the percentage predicted by a logistic regression model based on the three covariates are listed.

Table 3—*HRs for the effectiveness of HBO versus conventional care using PS approach*

	Unadjusted analysis	Fully adjusted	Mantel-Haenszel using quintiles	Nearest neighbor matched	Limited to new subjects	Outcome by week 6	Limited to those with Wagner grade ≥3	Outcome as major amputation
Amputation	2.37 (1.84–3.04)	2.41 (1.88–3.11)	2.11 (1.78–2.50)	2.30 (1.76–3.01)	2.44 (1.77–3.39)	2.18 (1.59–3.00)	1.41 (1.10–1.80)	2.10 (1.45–3.05)
Healed	0.68 (0.63–0.73)	0.68 (0.63–0.73)	0.61 (0.58–0.65)	0.68 (0.63–0.73)	0.58 (0.52–0.65)	0.67 (0.61–0.74)	0.66 (0.59–0.73)	NA

The primary, unadjusted analysis assumed a continuous PS and a proportional hazards model. Adjusted model included the covariates age, sex, wound age, wound size, Wagner wound grade ≥2, the number of wounds on the patient, history of neuropathy, history of wound recurrence, and history of osteomyelitis or abscess. NA, not applicable.

grade and also to be consistent with CMS criteria, we separately evaluated individuals with Wagner wound grade ≥3 (Table 3). These subjects also were less likely to heal and more likely to have an amputation with HBO therapy (Table 3). The wound center had no effect on the likelihood that a wound might heal after controlling for wound duration, wound size, and wound grade.

Among those who received HBO, a median of 29 (25–75%; 15–48) treatments were received. It is important to note that those who received HBO received their LEAs ~3 weeks later than those who did not ($P = 0.02$). On average, amputations occurred at 88.6 ± 90.1 days for those who did not receive HBO versus 106.1 days ± 113.2 for those who received HBO. To assure treatment acceptance, HBO exposure was altered to require at least eight treatments; HBO therapy still was associated with increased amputation, (HR 2.03 [95% CI 1.49–2.77]) and fewer healed wounds (0.73 [0.66–0.81]).

We conducted a regression-based sensitivity analysis to assess the effects of an unmeasured confounder on the estimated treatment effect HR resulting from the PS analysis. Analyses were conducted for both the estimated HRs for amputation (HR 2.37 [95% CI 1.84–3.04]) and healing (0.66 [0.63–0.73]). For the amputation outcome, the effect estimate was quite robust in the presence of an unmeasured confounder. For example, if there was an unmeasured confounder that was prevalent in 80% of those who received HBO and in only 10% of those in the comparison group, and if the HR for this unmeasured confounder was quite extreme with respect to amputation (i.e., HR 2.5), then after adjustment for the hypothetical unmeasured confounder we would have an HBO-based HR of 1.24 with 95% CI of 0.96–1.59, meaning that those who received HBO had a similar outcome as those who did not. For the healing outcome, similarly, the estimated HR after adjustment for measured confounders via the PS was 0.66 (0.63–0.70). In this case, if the unmeasured confounder was present only in 10% of the treated group and in 80% of the comparison group, and if the hazard associated with the unmeasured binary confounder was 2.0, then the new adjusted HR would be 1.08 with 95% CI of 1.03–1.19. In this situation, our HR would be <1 and no longer statistically significantly. However, it is important to realize that our a priori assumption was that HBO prevented amputations and healed more wounds. For this assumption to be true, the direction of the effect estimates would have to be reversed (e.g., the 2.37 we measured changed to 0.5 to show fewer amputations) and would have to be statistically significant. For this to occur, the magnitude of the unmeasured confounder presented would need to be even more extreme and therefore is even more unlikely to exist. Finally, we also conducted analyses using an instrumental variable that yielded similar results (Supplementary Data).

CONCLUSIONS—HBO therapy has been used to treat chronic wounds for >20 years. Unfortunately, the literature on the efficacy of HBO therapy is not clear. Perhaps more importantly, there have been no studies of the effectiveness of this therapy. The importance of effectiveness studies on therapies for the treatment of diabetic foot ulcer is critical, as evidenced by the poor utilization of efficacious therapies like skin substitutes, recombinant human platelet-derived growth factor, and total contact casting (20–22). These are therapies that have been extensively investigated with high-quality efficacy studies, although not all are consistently reimbursed and therefore are not used extensively in clinical practice. In our study, we were not able to show that HBO prevented amputation or improved the likelihood that a wound would heal. In fact, using multiple analytic approaches, it appeared that those who received HBO were 1.5 to 3 times more likely to have an amputation than those who did not receive HBO, and they were also 1.2 to 3 times less likely to heal their foot ulcer.

HBO has the potential to have many differing effects on a chronic wound and it may not be reasonable to assume that this therapy should be used to fully heal a wound. In fact, those who study wound care have been concerned that the requirement by regulators that a wound care product must heal a wound to receive approval may be naïve and not consistent with the biology of wound repair. HBO therapy may have a beneficial effect on microbial balance, soft tissue infection, and angiogenesis. HBO simply may be a part of the answer and not a therapy that should be used until a wound fully heals. Approximately one-third of the subjects in our study who received HBO received more than the recommended maximum

number of treatments (e.g., >40) (23). Most wound care guidelines explicitly mention the need to try other therapies if a therapy is not successful (24). It is conceivable that more attention needs to be given to the coordination between HBO usage and debridement or the use of other adjuvants like skin substitutes, recombinant human platelet-derived growth factor, total contact cast, and others (24). Further, this potentially improper usage may explain the conflicting reports in the literature about the efficacy of HBO (8). In this regard, there is precedence for differing outcomes with HBO. Osteoradionecrosis of the jaws is another condition treated with HBO and the timing of surgical intervention is an important variable with respect to success (25). A standard protocol shown to be effective is 20 preoperative HBO treatments before oral surgery. When HBO is used without surgical intervention it has no lasting benefit (26).

In 2012, an RCT-based meta-analysis was published on the efficacy of HBO (8). The authors found seven RCTs of 369 subjects that evaluated the efficacy of HBO as compared with conventional therapy (8). HBO therapy varied from 2 to 3 atm for 45 to 120 min, administered once or twice per day, 4 to 5 times per week (8). The case definition for diabetic foot ulcer varied across studies but mostly included wounds below the ankle in individuals with diabetes. The wound grade varied from Wagner grade 0 to 4, with most studies including individuals with wounds of grade ≥2 and allowing individuals with poor lower-extremity arterial blood flow (8). The conventional therapy arm also varied by trial but usually involved off-loading the foot. Not all trials reported all outcomes. Their meta-estimates did not show an advantage of HBO therapy as compared with standard therapy with respect to a healed wound at 6 months (two trials, $n = 112$) or 1 year (three trials, $n = 212$) (8). They also were not able to show fewer amputations, fewer minor amputations (four trials, $n = 242$), or fewer major amputations (five trials, $n = 309$) in those who received HBO as compared with standard therapy (8). Although they could not show a statistically significant advantage, in most circumstances HBO appeared to be superior to conventional therapy. Pooled data from three of the trials ($n = 140$) at 6 weeks did show that individuals who received HBO were more likely to heal (8). Interestingly, a recent randomized trial had demonstrated that another device was approximately two times more efficacious than HBO, but this same device was later shown not to be more efficacious than standard off-loading (27). It is important to realize that many of the subjects studied in the trials described would not have met CMS eligibility criteria for treatment.

We did not evaluate other therapies used by the wound care centers. HBO is used as an adjunctive with other therapies. Our goal was to compare those who received HBO with those who did not receive HBO. The NHC algorithm suggests that individuals with diabetic foot ulcers receive debridement, off-loading, good wound care, and the consideration of other therapies like recombinant human platelet-derived growth factor and skin substitutes. We did not investigate which other therapies were the most successful, but our results indicate that as a group they were more successful than HBO and these other strategies need to be considered.

Even though we used statistical methods such as PS or instrumental variable, to try to understand and adjust for treatment selection bias, it is still possible that our results are biased. However, we did include in our PS variables that have been shown to correctly predict whether a wound will heal and to explain >90% of variability between predicted and actual outcomes (16,28,29). The covariates that are most highly predictive of wound healing were either well-balanced (i.e., wound duration and wound size) or evaluated by exclusion (i.e., wound grade). These variables have been used in other PS assessments of the effectiveness of wound therapies (14,28). Finally, we conducted a sensitivity analysis to evaluate the effect of unmeasured confounders on our results. The results of the sensitivity analysis demonstrate the robustness of our results with any potential unknown confounders. However, until multiple, well-designed, large RCTs evaluate outcomes other than a fully healed wound, it may not be possible to truly understand if HBO provides a benefit. Also, because we conducted our study in wound care centers, our results might not be generalizable to all wound care providers. However, all wound care providers do not have HBO facilities; however, many wound care centers like NHC do have HBO on site, thereby improving the likelihood that our study generalizes to those that have HBO on site.

In conclusion, HBO did not appear to be useful for the prevention of amputation and did not improve the likelihood that a wound would heal in a cohort of patients defined by CMS eligibility criteria. To date, this is the largest study of HBO. We used several techniques to ensure that treatment selection bias was minimized. It is important to note that our findings may not be consistent with the Food and Drug Administration clearance for this device, which was based on the Undersea and Hyperbaric Medical Society–approved indications. Per these recommendations, HBO therapy is for the enhancement of healing in selected problem wounds. It is entirely likely that HBO therapy enhances a specific aspect of wound repair and should not be used as a single agent to completely heal a wound. This also was likely true for several scientifically valid compounds, which when tested in vitro and in animal studies had shown promise with respect to wound healing but when tested in humans were not shown to heal chronic wounds (11,30). The usefulness of HBO in the treatment of diabetic foot ulcers needs to be better-clarified, preferably using well-designed RCTs and perhaps using other healing-based end points other than a healed wound.

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D.J.M., J.G., O.H., M.P., and N.M. designed the study, conducted analyses, had access to the data, analyzed and interpreted the data, and wrote the manuscript. H.A.G. contributed to the design, contributed to the interpretation of the analyses, and reviewed and edited the manuscript. S.R.T. designed the study, interpreted the analyses, and reviewed and edited the manuscript. All authors approved the final version of the manuscript. D.J.M. is the

guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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