Effects of smoking on cost and duration of hyperbaric oxygen therapy for diabetic patients with non-healing wounds

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Otto GH, Buyukcakir C, Fife CE. Effects of smoking on cost and duration of hyperbaric oxygen therapy for diabetic patients with non-healing wounds. Undersea Hyper Med 2000; 27(2):83–89.—During this study to determine the effects of smoking on diabetic patients undergoing hyperbaric oxygen therapy (HBO₂T) for nonhealing wounds, one physician visited five hyperbaric facilities and reviewed records on 1,006 patients who had received HBO₂T for diabetic wounds. Smoking history was documented on 469 patients, while 180 patients had complete information on number of HBO₂Ts, outcome, age, duration of diabetes, transcutaneous oxygen baseline in air at ambient conditions, Wagner score of the worst wound, smoking history, and intensity of treatment. These factors were statistically significant predictors of treatment outcome using multiple regression modeling. No difference was found between smokers with less than 10 pack-years of cumulative history and nonsmokers. After that point there was a significant increase in the number of HBO₂Ts needed to produce at least some healing in smokers vs. patients who had never smoked. The average patient with a greater than 10 pack-year smoking history who benefited from treatment was estimated to need between 8 and 14 more HBO₂Ts. This translates into an added treatment cost of $4,000 to $7,000 for the average patient who has smoked, and an estimated $22–37 million annually for the United States.

diabetes mellitus, transcutaneous oxygen, Wagner score, multiple regression modeling, chronic wounds

The negative effects of persistent smoking on wound healing are well known (1–3). A variety of mechanisms are postulated, including the potential vasoconstrictive effects of nicotine. The relationship between long-term smoking and the development of vascular disease is also well recognized (4,5). Diabetics may be especially vulnerable to both acute and long-term effects of smoking on wound healing (2,6). In a recent study (7), the outcome of diabetic patients undergoing hyperbaric oxygen treatment (HBO₂T) for non-healing lower extremity wounds was found to be significantly related to smoking history. The purpose of this paper is to further delineate the effects of smoking history on HBO₂T programs and the attendant cost of care. The costs associated with rehabilitation and loss of functionality borne by the patient are not addressed.

METHODS

This study is a subset of a larger outcome study designed to assess the effectiveness of HBO₂T for nonhealing wounds in patients with diabetes. Between November 1995 and June 1996, 1,006 patient records from five multiplace hyperbaric facilities in Texas were reviewed for details of medical history, treatment, and outcome. The data recording comprised 137 fields of information on a Lotus/Excel spreadsheet. Permission was obtained from the Committee for the Protection of Human Subjects at The University of Texas Health Science Center (Houston) and from the participating units. Since this was a retrospective analysis of chart information, no informed consent was required. Patient identifiers were encoded before data analysis to preserve confidentiality.

One physician reviewed records of patients with diabetes at all facilities so that uniformity of evaluation could be maintained. The following fields of information have particular importance:

1. The severity of the lower extremity wound measured by the modified Wagner grading scale.
2. The transcutaneous oxygen measurement (PwO₂) near the wound in air at sea level.
3. The age of the patient.
4. The known duration of diabetes, in years.
5. Smoking status (never, former, current).
6. If a smoker, how many pack-years? (Pack-years is the product of the average number of packs per day and the number of years smoked.)

7. Whether the treatment program was “interrupted”.
   This was defined as missing 5 consecutive days of treatment or receiving fewer than three treatments per week for 2 consecutive weeks.

The database consists only of patients having diabetes who did not have renal failure or receive autologous growth factors. The few patients who died before therapy was completed were also deleted because the termination of treatment was not directly related to wound outcome.

A multiple regression model was fitted to these data to predict outcome from these factors and was validated by predicting outcomes for 72 patients from a sixth clinic. The comparison of the calibration set of 180 patients and the validation set of 72 patients using percent correct, percent false positives, and percent false negatives in a chi-square test of homogeneity showed no difference in model performance ($P = 0.60$). The calibration set had 74.4% correct and the validation set had 68.1% correct assessments. The model allowed risk assessments to be made as a function of predicted score. The higher the score for any particular patient, the lower the risk of failure (no healing or amputation) and the higher the potential for benefit (some or complete healing). For any patient, the number of HBO2Ts required to drive the risk of failure down to 50% (an arbitrary selection) was defined as the minimal number of HBO2Ts needed, and the number of treatments needed to drive the probability of at least some benefit up to 90% was defined as the planned or expected number of treatments. Because smoking was a negative effect, the smoking effect on treatment was defined as the extra number of HBO2Ts needed to offset the effects of smoking (so that the two target scores could be made equal to those of a non-smoker).

Statistical analyses were made using SPSS version 8 and statistical routines programmed by the lead author on LOTUS 1-2-3 spreadsheets. The $P$ values cited for the regression studies relate to the partial t tests of the coefficients of the variables described and the others relate to Pearson’s chi-square test of homogeneity between tabulated groups.

RESULTS

Smoking patterns: The initial population was composed of 469 standard care patients with diabetes who responded to the question, “Have you ever smoked?” Standard care patients did not have renal failure or receive growth factor therapy. Fifty percent (233) had never smoked. Of the 236 smokers, only 139 had the number of pack-years of smoking recorded. This may have been due to lack of memory or uncertainty on the part of the respondent, or failure on the part of the clinic personnel to pursue the question. This reduced the effective database to 372 patients. As the model was developed, missing information further reduced the final database to 180 patients in which all five clinics were still represented. Fortunately, the smoking patterns of the 180 patients in the final database did not differ from the initial set of 372 (Table 1), or in the outcome pattern in a chi-square test of homogeneity ($P = 0.42$). Thus the model may be considered to be representative of the larger population. The low participation of current smokers (14/372 = 3.8%) is partially due to the requirement by many physicians that patients discontinue smoking before undergoing a course of HBO2T. Even so, their baseline transcutaneous oxygen in air at ambient conditions (15.9 mmHg) is significantly lower than that of former smokers (25.5 mmHg) or those who never smoked (20.9 mmHg) with $P < 0.05$ using the least significant difference test. This is consistent with the results reported by Lovich and Arnold (3). The average smoker smoked for 38.2 pack-years. The minimum was 1 pack-year and the maximum was 180 pack-years. Figure 1 displays the smoking intensity of the 139 smokers with pack-year histories recorded.

Modeling outcome response to smoking: A statistical model to predict outcome was developed using $P_{O_{2}}$ in air, and several other risk factors in a multiple regression analysis to explain treatment outcome, which was coded as: 1 = amputation, 2 = no healing, 3 = partial healing, and 4 = complete healing. The outcome categories coded 1–4 can be considered to be an outcome score on a continuous scale for categories 2–4 (no healing through complete healing). The natural logarithm of the treatment score was used as the treatment response variable rather than the raw score for the following reasons: a) the effects of outlier values were reduced; b) all explanatory variables were significant at the 3% level or less while in the raw score model the significance levels were 6% or lower; and c) the transformation spaces the outcomes in a way that may better conform to the value of the outcome to the patient. The original codes generate the following new codes: (1 → 0, 2 → 0.69, 3 → 1.10, and 4 → 1.39). Thus there is a larger gap between amputation and no healing than between some healing and complete healing. In any event, this type of transformation is commonly used by biostatisticians modeling non-linear relationships.

The effects of smoking have been widely modeled using pack-years as the most sensitive way to represent the intensity and duration of smoking. Lovich and Arnold (3)
Table 1: Smoking in the Population vs. the Model Database

<table>
<thead>
<tr>
<th>Reference Set</th>
<th>Smoking Status</th>
<th>Pack-years of Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>never</td>
<td>former</td>
</tr>
<tr>
<td>Population</td>
<td>233</td>
<td>125</td>
</tr>
<tr>
<td>Model</td>
<td>107</td>
<td>66</td>
</tr>
</tbody>
</table>

No difference in status, $P = 0.77$

No difference in pack-yr, $P = 0.63$

classified former smokers who smoked for 10 pack-years or less (and had quit for at least one year) as non-smokers, and the Wisconsin Study (9) found that the incidence of amputations in the younger-onset diabetic group was related to pack-years of smoking ($P = 0.0005$). Our study had similar results. It was found that 10 pack-years or less were equivalent to not smoking. After that point there was a significant increase in HBO$_2$Ts required to produce at least some healing in patients with a smoking history vs. patients who had never smoked. Between 10 and 100 pack-years there was a systematic, log-linear decrease in outcome score, and beyond 100 pack-years the effects seemed to be flat (no more damage was seen in the sample). We refer to this as a "ramp" function because it is zero for the first 10 pack-years and then "ramps up". The model $R^2$ was used to select the best ramp function. The Ramp 10 function simply sets any pack-year value of 10 or less to zero, subtracts 10 pack-years from the observed numbers above 10, and flattens the ends (Fig. 2). Increasing pack-years decreases the outcome score so that additional HBO$_2$T is required to compensate for the loss.

The multivariate model that best fitted the data was calibrated on 180 standard care patients (smokers and nonsmokers) who had complete medical data recorded on the variables in the model. Non-significant variables in partial $t$ tests ($P$ value $> 0.05$) were deleted from the model. The final model was:

$$
\text{Ln(outcome)} = 0.98061 + 0.2087\ln(\text{HBO}_2\text{T} + 1) + 0.0040\times \text{PtCO}_2(\text{in air}) - 0.0035\times \text{Ramp 10} - 0.1527\times \text{WG}_{\text{max}} - 0.0041\times \text{DurAge} - 0.1907\times \text{Interrupted}; \text{ model } R^2 = 22.8%$$

where:

- HBO$_2$T = number of hyperbaric treatments given,
- $P_{\text{tCO}_2}(\text{air})$ = transcutaneous oxygen value at the wound in air, mmHg,
- Ramp 10 = the value of the ramp function described above,
- WG$_{\text{max}}$ = the highest modified Wagner grade over the worst three wounds,
- DurAge = the sum of the patient's age and the known duration of diabetes, and
- Interrupted is an indicator variable (0,1) to show if the treatment regimen was interrupted.

If the score computed by this equation is greater than 0.69, it is predictive of healing. A score of 0.69 or lower is predictive of failure.
This model indicates that $P_{O_2}$ and the effects of smoking (as measured by pack-years) can be statistically separated. In other words, the effects of smoking manifest themselves in more ways than by simply reducing the $P_{O_2}$ at the wound site. A further examination of the correlation between the 117 smokers and their $P_{O_2}$ readings showed no relationship (only 117 of the 139 smokers had $P_{O_2}$ recorded). The simple regression model $R^2$ was 0.017, the $P$ value was 0.17, and the sign was reversed (higher pack-years implied better oxygen readings, not worse). After adjusting for the Wagner score, age, and duration of diabetes, the $P$ value of pack-years increased to 0.60 and the reversed sign persisted (in drops to 74 from 117). This surprising result further suggests that smoking does not impact healing through the $P_{O_2}$ mechanism.

Current smokers vs. former smokers: The next question investigated was whether being a current smoker represents an increased risk of nonhealing or amputation over former smokers. The ability to resolve this issue was limited in this retrospective study for two reasons: a) the policy at some facilities to screen out current smokers, making it more likely that only the best risks among them were admitted to treatment, and b) data were not collected to measure how many years ago the former smokers had stopped smoking. In the regression model reported above, only 7 of the 180 patients used to calibrate the model were current smokers. When an indicator variable was introduced to separate out their effects, it was not statistically significant ($P = 0.798$). When an interaction with pack-year terms was added, that was not significant either ($P = 0.276$). Thus, there is no evidence at this time that current smokers respond differently from former smokers with the same characteristics (number of pack-years, $P_{O_2}$, etc.). This differs from the lung cancer studies in which the risk of contracting cancer begins to drop when smoking is discontinued. Clearly, a larger sample size is needed to validate these preliminary findings.

Risk analysis: The model was also used to produce two types of risk analyses. The first was a risk of failure analysis (no healing or amputation) in which the proportion of treatment failures was computed as the number of HBO$_2$Ts increased. This was a decreasing function, meaning that the more HBO$_2$Ts administered, the lower the probability of failure. The other model looked at potential success and computed the success ratio of patients who had more than a specified number of treatments. This allowed a treatment plan to be tailored to each patient that would estimate the number of treatments needed to drive the risk of failure down to 50% (a suggested minimal number of treatments), and a higher number that would drive the success threshold up to 90%. We consider the latter number of treatments to be the “expected” number to be planned for at the beginning of the treatment regimen. These two concepts are used in the remainder of this paper. The effects of smoking are computed for each of these two measures. The expected number (required for a 90% likelihood of success) is 1.61 times greater than the number of treatments required for a 50% chance of failure.

Evaluating smoking effects: The remaining figures illustrate the results of different smoking intensities as modeled on 180 patients from five treatment centers. The effects of HBO$_2$T are a complex mixture of patient characteristics and the number of treatments administered. The figures presented to illustrate the effects of smoking

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Benefited</th>
<th>No Healing</th>
<th>Amputation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>61.84 (474)</td>
<td>65.17 (43)</td>
<td>64.00 (118)</td>
</tr>
<tr>
<td>Duration of diabetes, yr</td>
<td>16.62 (237)</td>
<td>18.92 (25)</td>
<td>19.41 (61)</td>
</tr>
<tr>
<td>Interrupted treatment, %</td>
<td>9.28 (474)</td>
<td>16.28 (43)</td>
<td>20.34 (118)</td>
</tr>
<tr>
<td>Ever smoked, %</td>
<td>50.45 (337)</td>
<td>46.88 (32)</td>
<td>56.96 (79)</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>7.12 (337)</td>
<td>9.37 (32)</td>
<td>6.32 (79)</td>
</tr>
<tr>
<td>Total wounds</td>
<td>1.31 (474)</td>
<td>1.35 (43)</td>
<td>1.34 (118)</td>
</tr>
<tr>
<td>The worst wounds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wagner score</td>
<td>3.02 (474)</td>
<td>3.23 (43)</td>
<td>3.53 (118)</td>
</tr>
<tr>
<td>Length, cm</td>
<td>5.18 (364)</td>
<td>4.15 (32)</td>
<td>4.67 (850)</td>
</tr>
<tr>
<td>Width, cm</td>
<td>2.49 (364)</td>
<td>2.09 (32)</td>
<td>2.56 (850)</td>
</tr>
<tr>
<td>Depth, cm</td>
<td>0.82 (363)</td>
<td>0.75 (32)</td>
<td>0.74 (85)</td>
</tr>
<tr>
<td>$P_{O_2}$ in air, mmHg</td>
<td>23.52 (356)</td>
<td>18.72 (36)</td>
<td>16.24 (101)</td>
</tr>
<tr>
<td>$P_{O_2}$ in oxygen, mmHg</td>
<td>95.04 (299)</td>
<td>99.06 (25)</td>
<td>49.45 (74)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses indicate the sample size.*
are calibrated for a patient who benefited from HBO₂T in our study and possessed the average characteristics noted in Table 2.

The effects of smoking were evaluated by inserting the characteristics of the average patient who benefited into the model and then altering the number of pack-years smoked and the number of HBO₂Ts needed to maintain the outcome score at the levels required in the risk models. Because smoking reduces the outcome score, the effect of smoking is measured by the added number of HBO₂Ts required to compensate for it.

The expected number of treatments increases as smoking increases (Fig. 3). The top line drives treatment until the probability of at least some wound healing with that number of treatments or more has reached the 90% threshold. We call this the expected level of treatment. The lower line is the number of treatments needed to drive the probability of failure down to 50%. We have arbitrarily defined this as the minimal number of treatments. The actual number of treatments any particular patient will need to achieve some healing is more likely to be closer to the top line than the bottom because many of the failures had their program terminated by amputation.

From Fig. 3 we see that a person with the characteristics of a patient who benefited from treatment and has a smoking history of 10 pack-years or less will most likely require between 14 and 23 HBO₂Ts. This is the non-smoking baseline. At 20 pack-years it increases to 17–28, at 40 pack-years it is 24–39, and at 60 pack-years it is 34–54. Clearly, the greatest impact is on the upper line, which is the level of treatment most likely to ensure a favorable outcome. The horizontal portion at the extreme right side of each curve is where the ramp function becomes horizontal.

The cost of hyperbaric oxygen therapy: The price of HBO₂T may vary widely from one facility to another. Medicare currently allows approximately $360 per treatment. In a recent article, an average cost of $470 plus physician supervisory fees was reported. We use $500 per treatment as a reasonable estimate of the per/treatment billing, which is viewed as a surrogate for cost. Detailed cost records were not reviewed as a part of this study.

Figure 4 computes the difference between the non-smoking baseline and the projected minimal number of HBO₂Ts multiplied by the incremental cost of an additional treatment (not the average cost). This graph shows that heavy smoking can increase the minimal cost of treatment by as much as $20,000, although the range of $2,000 to $7,000 is more likely. Expected costs are 1.61 times higher. The average smoker smoked 38 pack-years. This yields an estimated minimal cost increase of $4,430 and an expected cost increase of $7,000 compared to the person who smoked 10 pack-years or less.

Adjusting for transcutaneous oxygen: The average patient described had Pₑₒ₂ in air of 23.5 mmHg. Many patients have a lower Pₑₒ₂ reading (many are below 10) and others are higher. Because the effects of Pₑₒ₂ on outcome are also nonlinear, the effects of smoking are greater for patients with low initial Pₑₒ₂ because relatively more treatments are needed to overcome the smoking effect. Figure 5 shows the combined effects of Pₑₒ₂ and pack-years of smoking on the number of treatments needed to achieve the minimal number of treatments. The
<table>
<thead>
<tr>
<th>Demographic Component</th>
<th>Estimated Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. United States population</td>
<td>271 million, 1999</td>
</tr>
<tr>
<td>2. Number having diabetes, 5%</td>
<td>13.55 million</td>
</tr>
<tr>
<td>3. Number of those developing chronic foot problems, 25%</td>
<td>3.388 million</td>
</tr>
<tr>
<td>4. Number of those requiring hospitalization in a given year, 6%</td>
<td>203,250</td>
</tr>
<tr>
<td>5. Number requiring HBO₂T, assume 5%</td>
<td>10,163</td>
</tr>
<tr>
<td>6. Number of smokers receiving HBO₂T, 50%</td>
<td>5,081</td>
</tr>
</tbody>
</table>

Estimated annual cost of smoking @ $500 per HBO₂T $22.36 to $35.57 million/yr

DISCUSSION

The research reported in this paper shows statistically significant evidence that for the diabetic patient, smoking is an important risk factor in the healing of wounds requiring HBO₂T. Furthermore, the effects of smoking are independent of the PₑO₂ measured at the wound, and so they can be modeled as separate risk factors. The multivariate model of treatment outcome can then be used as a predictive tool to estimate how many more HBO₂Ts would be needed to counteract the negative effects of smoking.

These effects can be economically significant. The estimated incremental cost of treatment and physician fees is between $4,400 and $7,000 for the average smoker when calculated at the rate of $500 per treatment. This does not include the cost of lost work time, travel, dressings, and supplies. The average smoker (38 pack-years) is estimated to have at least 8 more treatments and is likely to have 13 more treatments than a medically similar nonsmoker. Assuming one treatment daily, 5 days per week, this translates into 1.6 to 2.6 more weeks of therapy.

The aggregate estimated annual cost of smoking is quite large. It has been reported that 5-6% of the United States population will develop diabetes (10,11), and 25% of those will develop chronic foot problems (12). Levin (13) estimated that 6% of those with chronic foot problems will require hospitalization each year because of a foot ulcer; in a French study, Wattel (14) estimated 14%. The proportion of these patients requiring HBO₂T is unknown, but if even 5% present for HBO₂T and half of those are smokers, then the added costs at $500 per HBO₂T are projected to be between $22 and $35 million dollars per year (Table 3). Admittedly, this is a rough estimate, but it brings into focus the importance of smoking as a significant factor in the efficacy of wound healing interventions such as hyperbaric oxygen therapy.

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