Enhanced Healing and Cost-Effectiveness of Low – Pressure Oxygen Therapy in Healing Necrotic Wounds:

A feasibility study of technology transfer

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ABSTRACT

Recent advances in topical hyperbaric oxygen technology identified the use of low-pressure topical hyperbaric oxygen therapy in enhancing wound healing. This study prospectively examined the feasibility of technology transfer from university to Health Maintenance Organization personnel, using topical hyperbaric oxygen therapy to heal necrotic wounds. Fifteen patients with 24 gangrenous and/or necrotic wounds that did not improve or worsened after at least 6 weeks of standard wound care were treated with topical hyperbaric oxygen therapy by trained HMO personnel. Four patients underwent digital amputation for osteomyelitis and/or gangrene followed by topical hyperbaric oxygen therapy. Assessment parameters included wound healing and cost of wound care before and after topical hyperbaric oxygen therapy. Six of the six Level 2 wounds healed within 2 to 4 weeks, nine of the ten Level 3 wounds healed within 4 to 10 weeks, and seven of the eight Level 4 wounds healed within 4 to 12 weeks. The ulcers improved by a mean of 0.829 cm^2 per day. T test (SSPS 7.5) showed significant improvement per day after topical hyperbaric oxygen therapy, $t = 5.217$, $df = 24$, $P < 0.0001$ (95% CI = 1.13 – 0.49). Wound healing with topical hyperbaric oxygen therapy was associated with decreased costs. The results of this support the feasibility of transfer of new wound healing technology from research to HMO personnel.

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Due to the high cost of treating leg ulcers and pressure ulcers in diabetic and nondiabetic patients,[1–3] the healthcare community has developed new strategies for optimizing the quality and cost-effectiveness of traditional wound care paradigms, using strategies that are largely outcome driven.[4] The lack of an effective treatment for nonhealing wounds has led to a federal effort to ensure quality care and eliminate fraudulent claims for noneffective treatments.[5,6] Major factors contributing to the high costs of treating necrotic wounds include their intrinsic tendency to worsen despite treatment and the inadequacy of existing modalities. Recent research has led to a better understanding of the pathophysiology of both these factors in wound healing.

The ease of wound healing is largely based on the adequacy of blood supply. Thus, wounds may be divided into two types: 1) Hypoxic wounds – wounds with inadequate blood supply and transcutaneous oxygen partial pressures ($TcPO_2$) of 0 mm Hg to < 30 mm Hg. These wounds are characterized by the presence of necrotic tissue ($TcPO_2$ from 13 mm Hg to < 30 mm Hg) or gangrenous tissue ($TcPO_2$ from 0 mm Hg to < 13 mm Hg). 2) Nonhypoxic wounds – wounds with relatively adequate blood supply and $TcPO_2$ ranging from 30 mm Hg to 40 mm Hg. These wounds are characterized by the absence of necrotic tissue.

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Hypoxic wounds do not heal because angiogenesis in these wounds cannot be sustained since reperfusion/reoxygenation injury destroys endothelial cells when hypoxic tissues are re-exposed to oxygen in the air (ie, at the wound-air junction). Free radicals (reactive oxygen species), generated by resumption of oxidative phosphorylation during reperfusion or reoxygenation of free radical quencher-depleted hypoxic tissues, cause oxidant injury.[7,8] In the presence of adequate blood supply; however, oxidative-phosphorylation generated oxygen free radicals are quenched by an abundant supply of free radical quenchers – superoxide dismutase, catalases, and reduced glutathione.[9] Conversely, in hypoxic tissues with inadequate blood supply, the supply of free-radical quenchers falls short of that required to quench free radicals generated when re-exposed to oxygen. The survival of unquenched free radicals cause further tissue injury, thus inhibiting angiogenesis, which results in wound healing failure. The presence of recurrent necrotic tissue at any wound surface is an indicator that the wound is of the hypoxic type, and therefore, recalcitrant and unlikely to heal.

This study assesses the cost-effectiveness of implementing a novel breakthrough technology using low-pressure oxygen in wound healing. Some evidence shows that this technique, developed in academia, may stimulate wound healing by improving angiogenesis even in hypoxic wounds (M.C.Y. Heng, unpublished data, 1999). The objective of this study is to examine the feasibility of transfer of knowledge and expertise regarding the use of this new technology from university-based researchers to Health Maintenance Organization (HMO) personnel in order to achieve effectiveness in wound healing and cost savings.

Methods

Study population. This study is a single center, prospective study performed at an acute care hospital operated by an HMO. Inclusion criteria included (a) men and women 18 years and older in an acute care hospital; (b) presence of recalcitrant wounds (unchanged or worsened for 6 or more weeks before THOT treatment), characterized by a necrotic or gangrenous base, with severity classification Levels 2 to 4;[10] and (c) recruitment within a stipulated 3-month period. Selection criteria excluded patients with untreated systemic infections, extensive gangrene, and those who died of their comorbid diseases within 10 days of recruitment. Also excluded were patients who showed improvement (by chart review and clinical examination) under standard wound care. Because topical hyperbaric oxygen therapy (THOT) has not been shown to benefit chronic osteomyelitis without concomitant ostectomy (M.C.Y. Heng 1999, unpublished data), these cases were also excluded.

Study protocol. This study is a 3-month prospective cohort study to assess the healing rate and cost-effectiveness of treating necrotic/gangrenous wounds in diabetic and nondiabetic patients with THOT. In this study, the researchers compared the post-THOT with the pre-THOT improvement in ulcer size to assess efficacy of THOT in wound healing.

Cost savings reported refer to the difference between the cost of wound care with THOT (without whirlpool and pulsed lavage, but with dressings, antibiotics, debridement, and support surfaces as needed) and the cost of standard wound care without THOT (with whirlpool and pulsed lavage, plus dressings, antibiotics, debridement, and support surfaces as needed). Cost savings at various time points accounts for the percentage of wounds healed at these time points.

Study procedures.

Topical hyperbaric oxygen therapy. The researchers used a novel version of low pressure THOT in which the pressure range was different from that previously reported.[11] This recently FDA-approved technique involves delivering oxygen via a pleated polyethylene bag that is 48 inches by 84 inches, open at one end, and closed on three

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KEY POINTS

- This prospective pilot study examined the use of topical hyperbaric oxygen therapy (THOT) on 15 acute care HMO patients with recalcitrant wounds: 24 gangrenous or necrotic wounds following standard wound care for at least 6 weeks.
- The researchers found significant improvements in wound healing, taking wound severity into account, when THOT was utilized, with an overall healing rate of 22/24 ulcers by 12 weeks.
- In this study, THOT was associated with decreased wound care costs over standard wound care at all levels of wound severity.
- THOT technology was transferred from an academic setting to an acute care HMO setting by careful inservicing and training of HMO personnel.

sides. In this study, the patient's legs and trunk were inserted into the bag, with the open end fitting over the patient's trunk, reaching to the level of the patient's nipple area. The bag was secured with 3-inch tape. Oxygen, from a piped source or from an H tank, was allowed to flow into the bag at the rate of 15 L/min. The intra-bag pressures were maintained within a narrow range at all times at pressures at least 10 mm below capillary filling pressures. The protocol required treatment for 4 h/day, 4 consecutive days each week, over a 4-week period. This was followed by a 2-week rest period. If the patient's wound(s) was unhealed within 6 weeks, THOT therapy was repeated.

Wound care personnel training at the HMO facility. Two nurses were trained for 3 months in the "hands-on" application of THOT for wound therapy by university-based research personnel (M.C.Y. Heng). They were then sent out to train other nurses (for 2 hours initially, followed by weekly supervision for 3 weeks) in an acute care hospital managed by a Health Maintenance Organization. Research personnel gave two lectures (one for the nurses and the other for physicians and surgeons) on the theory, indications, and contraindications of THOT in wound healing. Contraindications of THOT include developing gangrene, which should be stabilized before debridement and THOT; uncontrolled diabetes, which should also be stabilized before debridement and THOT; and untreated or uncontrolled infections, including sepsis.

Surgical procedures and antibiotic therapy. Necrotic tissue was initially debrided by sharp debridement, which was repeated as often as necessary for recurrence. Between sharp debridements, wounds were debrided by whirlpool or pulsed lavage in the standard wound care control group only. Infected ulcers were treated with oral or intravenous antibiotics. Osteomyelitis was treated with intravenous antibiotics and surgery, including ostectomy if necessary, to remove the infected bone. The diagnosis of osteomyelitis was made using the "probing to the bone" technique[12] and/or leukocyte scanning with ^{111}In.[13] Gangrenous digits or forefoot were treated by partial amputation, with subsequent treatment of the skin defect with THOT.

Pressure reduction procedures and devices. All patients were turned twice hourly and had protective footwear for all foot ulcers. Specialty beds and mattresses were used, as needed (ie, replacement mattresses for Level 2 ulcers and low-air-loss beds for deeper ulcers). These routine pressure-reduction measures were instituted both before and after THOT.

Dressings. Wet-to-dry saline dressings were prescribed for necrotic or purulent wounds, and hydrocolloid dressings for wounds with minimal necrotic tissue (ie, for wounds directly following debridement or those showing improvement). The dressings were changed 1 to 3 times daily as needed, based on the presence of infection, necrotic tissue, undermining, and the amount of exudate. The frequency of dressings decreased to once daily or less as the ulcers healed. The dressings and their indications were similar for ulcers in the pre- and post-THOT period, with the exception of calcium alginate dressings, which were found to be unnecessary in the post-THOT ulcers.

Measurements.

Ulcer size measurements. Before treatment was initiated, wounds were observed and charted as part of standard care for 6 weeks (1.5 months) or more without improvement, with a mean time of 3.65 months (SD = 4.44). Median time was 3 months: 5 wounds = 1.5 months; 2 wounds = 2 months; 14 wounds = 3 months; 1 wound = 4 months; 1 wound = 6 months; and 1 wound = 24 months without improvement. Chart review of pre-treatment wound descriptions reported that 10 of 24 wounds were "worse" or "more necrotic." The remaining 14 wounds were reported as having "no change." Standard care during the pre-THOT period was similar to the post-THOT period with respect to the criteria for turning (twice hourly), use of support surfaces, sharp debridement, whirlpool, pulsed lavage, and antibiotic therapy.

Ulcer size was assessed at the initiation of THOT treatment and weekly until healing occurred. The healing status was assessed at the end of 12 weeks in ulcers that were unhealed after discharge from the acute unit and/or transitional care unit. Surface area was determined by measuring ulcer diameter at the wound surface at its two greatest diameters.

Severity grading of wounds. The severity of the wounds was determined using a combination of the National Pressure Sore Advisory Panel Pressure Sore Criteria for Staging of Ulcers[14] and the clinical severity grading system for diabetic foot ulcers.[10]

In this study, Level 2 ulcers were infected ulcers that were covered partially or completely with yellow necrotic slough, extending to a depth of up to 3 mm. Level 3 ulcers were infected ulcers with yellow or black (gangrenous) necrotic tissue, extending from subcutaneous

tissue to deep fascia. These wounds were often undermined (usually < 2 cm), but were without bone involvement. Level 4 ulcers were deep ulcers with necrotic or gangrenous tissue and were usually infected, with deep undermining (> 4 cm) involving muscle, tendons, joint capsule, or bone. Gangrenous digits or forefoot, which after amputation leave deep skin defects down to bone, were also classified as Level 4 ulcers.

Data analysis. All ulcers eligible for treatment showed no change or worsening over the 6- to 12-week period prior to THOT, and were considered to demonstrate zero improvement per day. A two-tailed *t* test (SSPS 7.5) was performed to test whether the improvement per day in ulcer healing was significantly different from zero (unchanged or worse). Change per day was calculated for each ulcer by subtracting the ulcer size (cm^2) at the end of treatment from the ulcer size at initiation of treatment and dividing by the number of days in treatment. This measure provides comparable information for all ulcers: those that healed, those that improved, but did not heal by the end of the study, and those that became worse. Possible differences among Levels 2, 3, and 4 wounds were tested using one-way analysis of variance (ANOVA), with post-hoc Tukey tests comparing improvement rate among levels. Usual paired *t* tests to measure wound improvement pre- and post-THOT treatment were not possible for several reasons. First, prior to enrollment in the study, standardized procedures for measuring and reporting wound size were not followed for all patients. Some patients had verbal chart indications of wounds that were "unchanged" or worse, but no recorded wound measurements for as much as 3 months prior to the onset of treatment. Thus, it was not possible to calculate pre-treatment improvement (or worsening) as change per day. Second, given the severe nature of these wounds and the availability of a potentially effective treatment, withholding treatment long enough to

TABLE 1
SITE DISTRIBUTION AND SEVERITY OF WOUNDS

Ulcer Location	Level 2	Level 3	Level 4
Leg	2	3	4
Trochanter	1	3	
Ischium	2		
Sacrum	1		
Mid-back		3	
Foot		1	1
Hand			4
			1

TABLE 2
COMORBID DISEASES

THOT-Treated Characteristics	Number of Events/Patients (N = 15)
Diabetes mellitus	11
Peripheral vascular disease	13
Coronary heart disease	15
Hypertension	14
Spinal cord injury	1
Systemic infections	2
Osteomyelitis*	4

** Concomitant digital amputation/ostectomy to remove infected bone.*

establish a comparable pre-treatment change measure was not reasonable. Finally, given that patients were enrolled only if they showed no improvement or worsening with standard wound care, it was expected that the pre-treatment change per day would be approximately zero or slightly negative and would have a very small variance.

Paired *t* tests comparing pre- and post-THOT treatment change per day would likely violate assumptions of homogeneity of variance. The assumption of zero pre-treatment change as comparison for post-treatment change was deemed a justifiable statistical procedure, and also presented a conservative estimate of the condition of those patients who were becoming worse before THOT treatment was initiated.

Healthcare utilization costs are based on previously published data from the Market-Scan® claims database containing medical and pharmacy prescription data on more than 7 million people,[10] taking into account diagnosis-related group (DRG) based utilization costs and reimbursements based on eligible International Classification of Disease codes, 9th Edition (ICD9) and CPT procedure codes, adjusted for the 1992 Consumer Price Index.[10] The following mean itemized costs obtained from DRG-based utilization rates and reimbursements by severity level were used[10]: hospital payments/stay – $7,778/stay in acute care unit (2 weeks), $1,479/stay in transitional care unit (4 weeks), and $450 for outpatient payments for Level 2 wounds; $11,126/stay in acute care unit, $2,824/stay in transitional care unit, and $1,156 for outpatient payments for Level 3 ulcers; and $14,258/stay in acute care unit; $13,947/stay in transitional care unit; and $1,845 for outpatient payments for Level 4 ulcers. Adding THOT costs to mean DRG costs by ulcer severity (Levels 2 to 4) for hospitalized patients and correcting for healing, the authors obtained the THOT-treated DRG-based costs/episode.

The authors also analyzed costs utilizing the following direct costs to the HMO facility: (a) Costs of air beds were

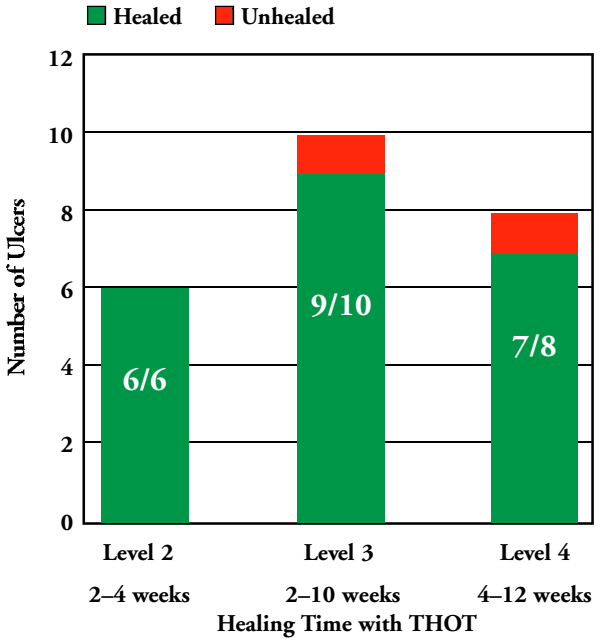
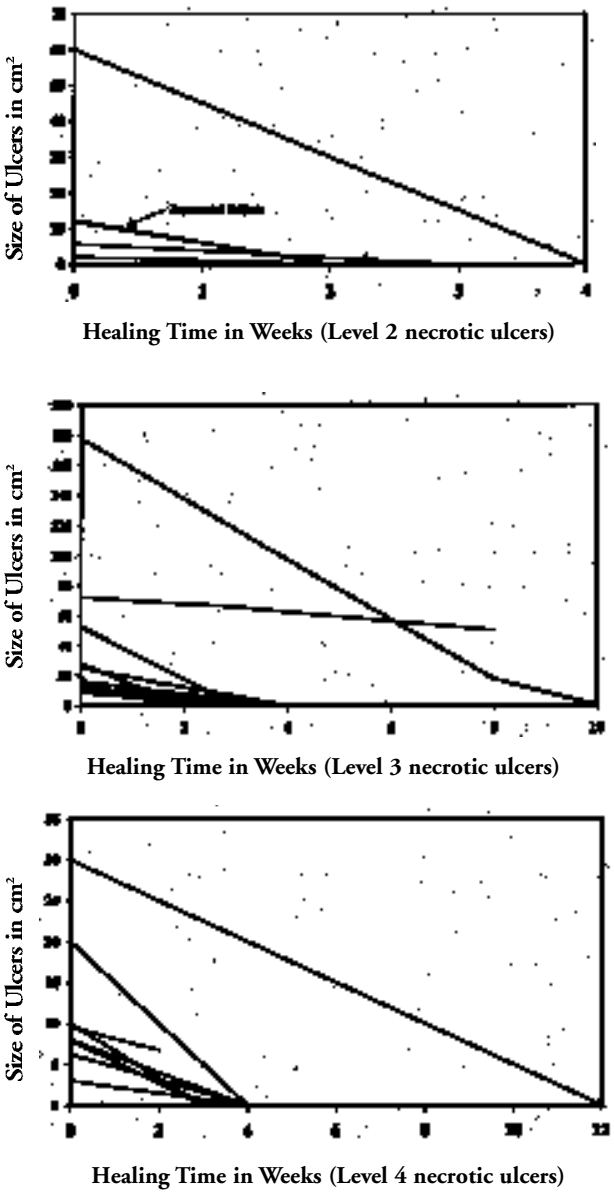


Figure 1
This figure summarizes the healing status of Level 2 to 4 necrotic and/or gangrenous wounds treated with THOT in an acute care hospital setting. Of Level 2 ulcers, healing occurred in 6 of 6 ulcers within 2 to 4 weeks; of Level 3 ulcers, 9 of 10 healed within 2 to 10 weeks; of Level 4 ulcers, 7 of 8 ulcers (including 4 ulcers with osteomyelitis and or gangrene requiring digital/forefoot amputation) healed within 4 to 12 weeks.



Figures 2a, 2b, and 2c
These charts demonstrate the healing of necrotic ulcers using THOT in (a) Level 2 ulcers (n = 6), (b) Level 3 ulcers (n = 10), and (c) Level 4 ulcers (n = 8). The y axis refers to ulcer size in cm² and the x axis refers to time of THOT treatment with rest periods in weeks.

capitated to $45/day; (b) costs of dressing changes (including nursing costs) ranged from $100/day to $200/day, depending on the number of dressing changes required; (c) cost of debridement procedures was as follows: sharp debridement ($500), whirlpool ($112), and pulsed lavage ($75); (d) digital amputation was $6,000 ($1,500 for surgery, $500 for anesthesia, and $4,000 for hospital stay); and (e) THOT costs were $185/treatment. Apart from the cost of digital amputation, costs for hospital stays were not included in the cost analysis for wound care.

Using these direct itemized costs, the authors computed cost/ulcer/day, which includes the cost of THOT, in Level 2, 3, and 4 ulcers and treatment time in weeks/months in the hospitalized study cohort using itemized costs of wound care. They then compared these costs against the cost of wound care/day at the zero healing rate (at best) observed in the previous 6 weeks to 3 months (control period) prior to THOT.

Results

Study cohort. During the stipulated 3-month recruitment period, inclusion criteria identified 21 patients (17 diabetic) with 44 necrotic or gangrenous wounds (8 Level 2, 15 Level 3, and 21 Level 4) for possible treatment with THOT. Selection criteria excluded 3 patients (all diabetic) with sepsis (6 ulcers: 1 Level 2 and 5 Level 4), who died within 10 days of presentation, and 3 patients (13 ulcers: 2 Level 3 and 11 Level 4) with extensive gangrene and/or untreated chronic osteomyelitis. The study cohort consisted of 15 patients (8 male, 7 female, 11 diabetic), ranging from 56 to 92 years of age (mean 76.4 years, SD 15.0 years), with 24 wounds (19 diabetic) treated with THOT. Of the 24 wounds, 6 were categorized as Level 2, 10 were Level 3, and 8 were Level 4. Table 1 (see page 56) summarizes the ulcer location and severity.

Comorbidity. Since the blood-flow, vascular status, and presence of anemia are important covariates, comorbid conditions associated with impaired vascular status, increased thrombotic tendency, or decreased blood-flow or oxygen carrying capacity in the patients are listed in Table 2 (see page 56).

Clinical wound healing with THOT. Clinical data on the healing rate of gangrenous/necrotic ulcers treated with THOT are summarized in Figures 1 and 2. Following THOT, all 6 Level 2 ulcers (all diabetic) healed between 2 and 4 weeks with THOT. Among these were 2 ischial and 2 leg ulcers and 1 trochanteric and 1 sacral ulcer. Eight of 10 Level 3 ulcers (3 sacral, 3 heel, 3 leg, and 1 mid-back) were diabetic. Of the Level 3 ulcers, 9 of 10 healed between 2 and 10 weeks with THOT. Of the Level 4 ulcers (4 foot, 2 heel, 1 hand, and 1 mid-back), 4 of 8 were diabetic, with 7 of 8 healing between 4 and 12 weeks with THOT.

Osteomyelitis and/or gangrene complicated 4 Level 4 ulcers, and all 4 healed with digital or partial foot amputation followed by THOT. Overall, 22 of 24 ulcers were

TABLE 3
DRG-BASED WOUND CARE COSTS PER EPISODE

DRG-Based Utilization Costs/Episode in Hospitalized Patients

	Control* Patients (Outcome)	THOT-Treated Patients (Outcome)
Level 2 ulcers		
Acute care costs (2 weeks)	$7,778	$5,002
	$1,479	$423
Transitional care costs	$450	0
Outpatient costs		$1,480
THOT costs	**$9,707**	**$6,905**
Total cost/ulcer	(0% healed at 4 weeks)	(100% healed at 4 weeks)
Level 3 ulcers	$11,126	$7,651
Acute care costs	$2, 824	$1,000
Transitional care costs	$1,156	$130
Outpatient costs		$2,220
THOT costs	**$15, 106**	**$11,001**
Total cost/ulcer	(0% healed at 6 weeks)	(80% healed at 6 weeks)
Level 4 ulcers	$14,258	$11,098
Acute care costs	$13,947	$2, 223
Transitional care costs	$1,845	$230
Outpatient costs		$2,960
THOT costs	**$30,050**	**$16,511**
Total cost/ulcer	(0% healed at 12 weeks)	(83.3% healed at 12 weeks)

** Recalcitrant ulcers prior to THOT; costs based on DRG-based utilization costs and payments.*[10]

healed by 12 weeks. Only 2 of 24 ulcers (a Level 3 leg ulcer and a Level 4 mid-back ulcer) were unhealed at the end of 12 weeks.

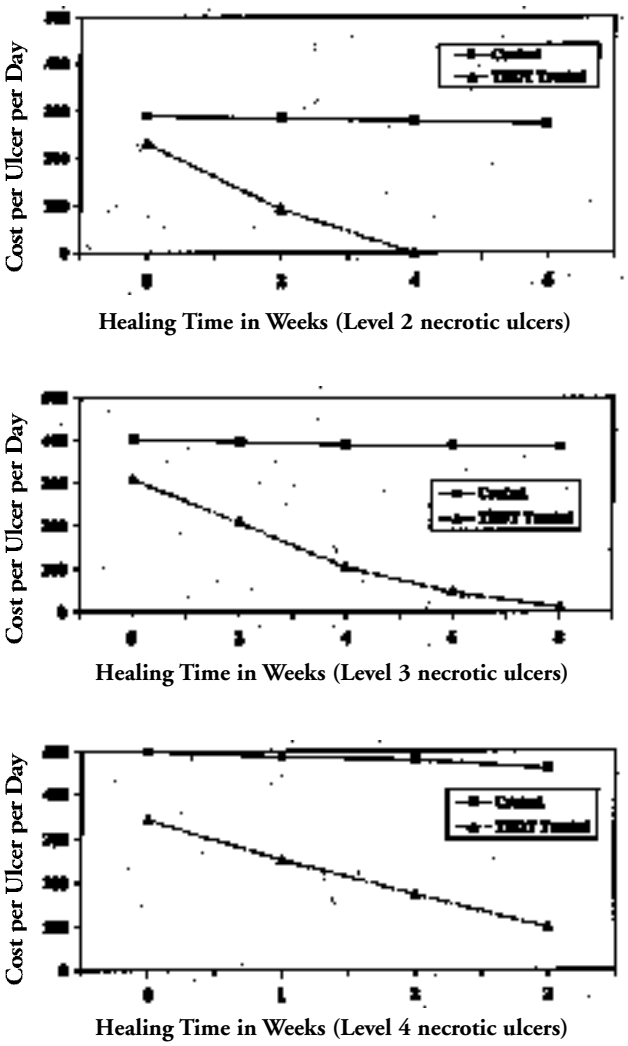
Wound measurements. Before THOT treatment, mean ulcer size (n = 24) was 24.69 cm^2 (SD = 37.3, range = 2.16 to 177.60 cm^2). For each level of severity, ulcer sizes were as follows: Level 2 – 17.4 cm^2 (SD = 21.28), Level 3 – 39.32 cm^2 (SD = 53.21), and Level 4 – 11.86 cm^2 (SD = 8.8). After THOT was instituted, 22 of 24 ulcers healed. The unhealed ulcers were 4.0 cm^2 and 6.76 cm^2 respectively. The change in ulcer size in THOT-treated Levels 2 to 4 wounds is summarized in Figures 2a to 2c.

Improvement per day was calculated by subtracting the size of the ulcer at the end of THOT from the size of ulcers at the beginning of THOT and dividing by the number of days of THOT treatment. The estimated improvement per day was a way to provide comparable data for ulcers that healed and those that did not. A positive value reflects healing, while a negative value reflects worsening.

Twenty-four ulcers (all levels of severity) had a mean improvement per day of 0.829 cm^2. This was significantly greater than zero improvement prior to THOT, $t = 5.217$, $df = 24$, $P < 0.0001$, with upper and lower 95% CI = 1.13 to 0.49. Improvement per day was then compared across ulcer Levels. Level 2 ulcers (n = 6) had a mean improvement of 0.87 cm^2/day (SD = 0.70), Level 3 ulcers (n = 10) improved 1.21 cm^2/day (SD = 0.95), and Level 4 ulcers improved 0.33 cm^2/day (SD = 0.22). ANOVA comparing ulcer Levels was marginally significant, $F_{2,21} = 3.36$, $P < 0.054$. However, the Levene test of homogeneity of variance showed that this assumption was not met (Levene statistic = 6.07, $P = 0.008$).

Analyses of variance performed on the log-transformed (improvement per day) data revealed Levene statistic = 0.98, $P = 0.907$, showing homogeneity of variance across ulcer Levels. Significant differences in log-transformed (improvement per day) data were also found across ulcer Levels, $F_{2,21} = 4.41$, $P < 0.025$. Post hoc comparisons showed significantly greater improvement in Level 3 than Level 4 ulcers ($P = 0.021$), but no significant differences between Level 2 and Level 3 ulcers ($P = 0.99$) or Level 2 and Level 4 ulcers treated with concomitant surgery ($P = 0.247$).

Analyses were repeated for the 19 ulcers from diabetic patients. These ulcers had a mean improvement per day of 0.924 cm^2 (SD = 0.846). This was significantly greater than zero improvement prior to THOT, $t = 4.76$, $df = 18$, $P < 0.0001$, with upper and lower 95% CI = 1.331 to 0.516. Level 2 ulcers (n = 6) improved 0.87 cm^2/day (SD = 0.70), Level 3 (n = 8) improved 1.29 cm^2/day (SD = 1.06), and Level 4 ulcers improved 0.40 cm^2/day. (SD = 0.71). One-way ANOVA comparing improvement per day across ulcer stages was not significant, $F_{2,18} = 1.898$, $P = 0.182$. However the difference between Levels 3 and 4



Figures 3a, 3b, and 3c
These figures summarize the itemized cost/ulcer/day for the following necrotic/gangrenous wounds: (a) Level 2 ulcers, (b) Level 3 ulcers, and (c) Level 4 ulcers. Decreased cost/ulcer/day at various time points reflect necrotic wound healing. Control costs were computed from the same itemized costs, with adjustments at various time points as the ulcers healed.[15]

would have been detected if 16 or more cases per group had been included, based on alpha = 0.05 and 80% power. The minimum improvement observed was 0.154 cm^2/day; none of the diabetic ulcers became worse with THOT.

Cost of healthcare utilization. The study compared total costs of utilization per episode of ulceration of treatment with THOT versus treatment without THOT, using DRG-based ICD9 mean reimbursements in published controls.[10]

The results are summarized in Table 3. Itemized costs/ulcer/day for Level 2 to 4 ulcers treated with THOT were plotted against time and compared to costs of treating the recalcitrant controls prior to THOT.

The data are summarized in Figures 3a to 3c. The cost savings at the 4-week and 3-month time points reflect healing of the recalcitrant necrotic ulcers treated with THOT.

Discussion

The results in this pilot study show that THOT is capable of healing necrotic and gangrenous ulcers of all levels of severity; the rate of healing with THOT appears to be more rapid than that previously observed with less severe ulcers.[15] In addition, results achieved in the HMO setting are similar to those achieved in a university-based research setting (M.C.Y. Heng, unpublished data, 1999). Although preliminary, these results show that knowledge and expertise regarding the use of THOT are easily taught and can be successfully implemented by other nurses and physicians, with excellent results in wound healing.

This study also stresses that patients with uncontrolled diabetes, untreated or inadequately treated systemic infections, particularly sepsis, should be adequately treated prior to the institution of THOT. In addition, patients with osteomyelitis without concomitant removal of the infected bone are unlikely to respond to THOT. Conversely, relatively minor surgery involving removal of the infected bone and/or gangrene by digital amputation followed by THOT resulted in wound healing without having to resort to major amputation.

Cost analysis shows considerable cost savings with THOT in necrotic ulcers that have a tendency to worsen rather than heal. Cost savings were observed at all levels of severity. The total cost of healing this group of mainly diabetic ulcers with THOT also compares well with DRG-based reimbursements of diabetic ulcers not treated with THOT.[10,16] Reimbursements for diabetic patients with ulcers have been shown to range from $16,100 to $63,100 or more per episode.[10,16]

Speculating on the mechanisms by which THOT achieves wound healing in hypoxic wounds is interesting. In hypoxic wounds, the deficient blood supply prevents regeneration of free-radical quenchers, such as superoxide dismutase, catalases, and reduced glutathione,[9] resulting in reduced capacity to neutralize reactive oxygen species released when such tissues are reperfused or reoxygenated by oxygen. In such tissues, new blood vessels fail to grow since endothelial cells are destroyed by unopposed free radicals. Unopposed free radicals generated by oxidative

stress and by pH-dependent reperfusion and reoxygenation injury initiate cell death (apoptosis and necrosis) by activating mitochondrial permeability transition; the opening of the mitochondrial megapore causes leakage of cytochrome c into the cytoplasm; thus, activating caspase 3, which triggers the death cascade.[17] At the therapeutic range, hyperbaric oxygen sequesters free radicals by cross-linking them to mono unsaturated lipids in the tissues,[18,19] thus protecting new blood vessels from oxidant injury. However, if the oxygen pressures are too high, new blood vessels are also destroyed by oxygen toxicity.[20–22] By avoiding the higher oxygen pressures at which the production of oxygen free radicals are increased,[23] the unique range of low oxygen pressures utilized by THOT protects the newly formed blood vessels from oxygen toxicity. In addition, by not elevating $TcPO_2$ in the hypoxic tissues, THOT does not blunt the hypoxic stimulus for angiogenesis, keeping in mind that hypoxia is one of the most potent stimuli for angiogenesis. Furthermore, by keeping pressures below 10 mm Hg above ambient, THOT ensures adequate blood-flow through the capillaries; capillary blood-flow is retarded by pressures greater than 22 mm above ambient.

The ability of HMO personnel to heal recalcitrant necrotic/gangrenous wounds by using THOT and the cost savings they were able to achieve in this study supports the feasibility of technology transfer of new wound healing techniques from academic to HMO personnel. - OWM

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