An evaluation of the efficacy of Transdermal Continuous Oxygen Therapy in patients with recalcitrant diabetic foot ulcer.

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Abstract:

A retrospective single-site, non-comparative, observational study was initiated in a Canadian outpatient clinic to test the efficacy of Transdermal Continuous Oxygen Therapy (TCOT) in patients with hard to heal diabetic foot ulcers.

Eleven patients with fourteen ulcers participated in the study. Standard moist wound care, including cleansing and debridement where indicated, was used with TCOT as an adjunct. The average wound size upon enrollment was 4.07 cm2 (range 0.04 cm2 - 26.66 cm2). The mean age of the wounds prior to TCOT treatment was 19.1 weeks (range: 2 – 50).

Of the 14 ulcers, a total of 12 ulcers (86%) closed within, on average, 46 days (range: 13 -119). The two remaining lesions showed re-epithelialization of 90.5% and 87.5%, although both patients were non-compliant with regard to off-loading.

As part of a comprehensive wound treatment program, TCOT contributed to positive wound closure outcomes in patients with recalcitrant diabetic foot ulcers.

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Introduction

The International Diabetes Federation estimated that in 2007, 246 million adults suffered from diabetes mellitus in the adult population, representing 6.0% of adults between 20 and 79 years, with the highest rate found in the North American region (9.2%) and European Region (8.4%)[1]. The global prevalence of diabetes is estimated to reach 380 million in 20 years[1], with 15% of all diabetic adults developing a diabetic foot ulcer in the course of their life.[2] Diabetic foot ulcers can cause considerable stress, anxiety, and reduction in quality of life. Diabetic patients have high levels of morbidity and mortality[3] and the ulcers can be expensive to treat.

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Forty to 70% of all non-trauma related lower extremity amputations are believed to be directly related to diabetes and the economic cost of (caring for) a diabetic foot ulcer in Western countries is estimated at $7,000 - $10,000, with amputations costing as much as $65,000[4]. In 2007, the world was estimated to spend at least US$ 232 billion to treat and prevent diabetes and its complications. By 2025, this amount is expected to exceed US$ 302.5 billion.[4]

While prevention of the development of a diabetic foot ulcer is extremely important, many different options for treatment of a diabetic foot ulcer exist. The standard of care includes proper glucose management, off-loading, the treatment of infection including osteomyelitis, surgical correction of a Charcot foot, vascular reconstruction, proper debridement and other aspects of wound care.[3 5-7]
In some patients with difficult to heal wounds, oxygen supply may never meet oxygen demand, thereby preventing wound healing. Importantly, in all phases of wound healing oxygen plays a central and crucial role.[8] It is crucial in most cellular functions associated with wound healing, including energy metabolism, neovascularization, fibroblast proliferation and the production of a (neo)matrix.[9] Oxidative burst is a core reaction that occurs to kill microorganisms. [10] The bactericidal activity of granulocytes depends on high amounts of oxidants and the adequacy of oxidative killing has been shown to be directly proportional to local oxygen tensions.[11] The tensile strength of incisional wounds was shown to increase with increasing oxygen concentrations, with optimal wound healing achieved at 100% oxygen at atmospheric pressure[12] and, furthermore, the epithelialization rate also depends on oxygen tension.[12]

Conversely, hypoxemia, caused by disrupted vasculature, is a key factor that limits wound healing.[13] Thus, the availability of oxygen to a wound is of extreme importance for the healing process to progress, but the macro- and microangiopathy occurring in diabetes may negatively influence oxygen supply and oxygen pressure.[14-16]

Description of the test device

TCOT is the continuous delivery of a very low dose (3mL/hour) of 99% pure oxygen directly to the wound site. The oxygen is metabolized at the cellular level and stimulates epithelialization, the development of granulation tissue, glycosaminoglycan production, and collagen synthesis[17]. TCOT can be initiated in any care setting, allowing the patient to be ambulatory.

A self-contained miniature device (EPIFLO®) continuously produces oxygen. The device utilizes state-of-the-art 'fuel cell' technology, in conjunction with a polymer membrane to concentrate the oxygen from the ambient air to nearly 100% for continuous 24/7 delivery. The device measures 5 cm x 2.5 cm x 4 cm, weighs about two-ounces and can be attached to clothing by a tape or strap, worn on a belt, or stored in a pocket. Pure oxygen generated at the anode of the device is delivered to the wound site through a 152 cm (60") #5 French cannula. The end of the cannula is placed onto the wound site and covered with an occlusive or compression dressing. Additional dressings may be used, depending upon wound conditions such as the amount of exudate, the presence of infection and/or maceration, and the depth and site of the wound. Dressing changes usually take place every 3-5 days.

The device provides a silent, continuous, slow flow of oxygen (3 ml/h) for 15 days. Dressings do not inflate and the patient has no sense of oxygen movement. The oxygen delivered is at a low flow rate, so the wound will not dry out.

Study Objective and Design

The objective of this study was to retrospectively analyze the efficacy of TCOT in hard-to-heal diabetic foot ulcers in a Canadian outpatient clinic. Patients with a diabetic foot ulcer that previously had been treated with standard of care methods, without success with regard to healing and/or re-epithelialization of their ulcer were included in the evaluation.

TCOT was used as an adjunct to standard care, which included wound cleansing, debridement (if and when necessary, and including osteomyelitis if present), antibiotic therapy, if and when indicated, off-loading, and local wound management, as well as proper diabetes management.

EPIFLO® was used according to manufacturer's instructions and for Health Canada (Medical Device Class II) approved indications.

The ulcers were cleaned with sterile saline and debridement was performed as necessary. The EPIFLO® oxygen concentrator was placed in the "on" position and the oxygen delivery tube directed onto the center of the wound. A small foam dressing was placed beneath the cannula just outside the periwound area to prevent the cannula from pitting the skin.

The cannula was then secured in place with surgical tape and covered with an absorbent dressing. The wound, cannula and absorbent dressing (if needed) were covered with a secondary foam dressing and the outside of the dressing was secured with a thin film dressing to occlude the recipient site. Finally, the cannula was attached to the study device and this was then usually placed on the patient in a pocket. The device was changed every 15 days, according to the manufacturers' recommendations. All wounds were evaluated at least on a weekly basis for assessment of healing progress.

Results

Eleven patients with an average age of 62.9 years (range: 38 - 93) with 14 diabetic foot ulcers were included in this evaluation. The average duration of the ulcers prior to enrollment into this evaluation was 19.1 weeks (range: 2 - 50). The average size of the ulcers was 5.0 cm^2 (range: 0.04 - 26.7). Six Ulcers (43%) were on a toe, 3 (21%), on the plantar surface, 2 (15%) on the heel, 2 (15%) on a metatarsal area and 1(7%) on the distal leg. (Table1)

Table 1 : Prevalence of Wound Location

Location	N	Prevalence (%)
Plantar surface	3	21
Toe	6	43
Heel	2	15
Distal leg	1	7
Meta-tarsal	2	14

Due to rounding, percentages may not add up to 100

Most patients had received adjunct treatment prior to enrollment in this evaluation, with negative pressure wound therapy (NPWT) being the most common modality. Other previously used adjunctive measures included the application of low intensity laser and hyperbaric oxygen therapy.

Many patients suffered from serious co-morbidities, including peripheral vascular disease (N=2, 18%), end stage renal disease (N=2, 18%), osteomyelitis (N=3, 27%), edema (N=1, 9%), and coronary artery disease (N=1, 9%). One patient (9%) had a smoking habit. (Table 2)

Table 2 : Prevalence of Co-morbidities

Location	N	Prevalence (%)
Peripheral vascular disease	2	18
End stage renal disease	2	18
Osteomyelitis	3	27
Edema	1	9
Coronary arterial disease	1	9
Smoking habit	1	9

Twelve out of 14 ulcers (86%) healed completely within an average of 46 days (range: 13 -119). (Figure I).

Figure I

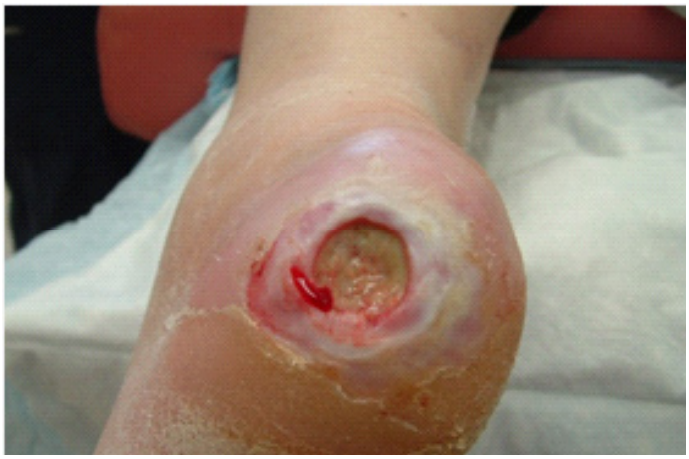
The average duration of the healed ulcers prior to re-epithelialization was 15.5 weeks (Figure I).

The two remaining ulcers (14%) showed an average reduction of 89% of the wound area (90.5% and 87.5% respectively), although patient compliance in these two patients was poor with regard to following off-loading guidelines.

Figures 2a through 3b are illustrations of the typical healing progress, observed in this evaluation.

Case history, patient I

Figure 2a

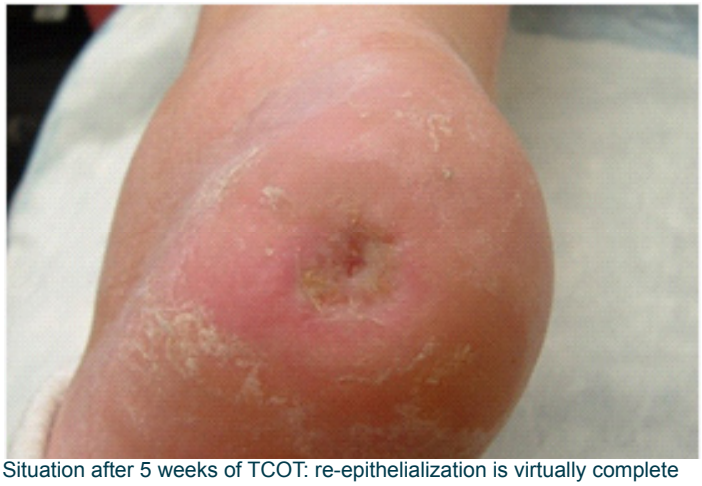


A 59 year old male with type I diabetes mellitus and neuropathy. A previous attempt to revascularize had failed.

Neuropathic ulcer on the left heel, measuring 3.0 cm x 3.0 cm x 11 mm. The wound bed was filled with spongy slough which was removed with water jet debridement.

Situation after NPWT was used for a total of 13 weeks: no improvement (Figure 2a)

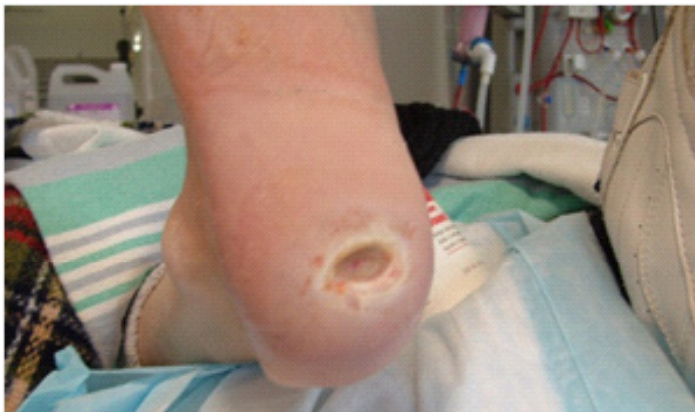
Figure 2b



Situation after 5 weeks of TCOT: re-epithelialization is virtually complete (Figure 2b)

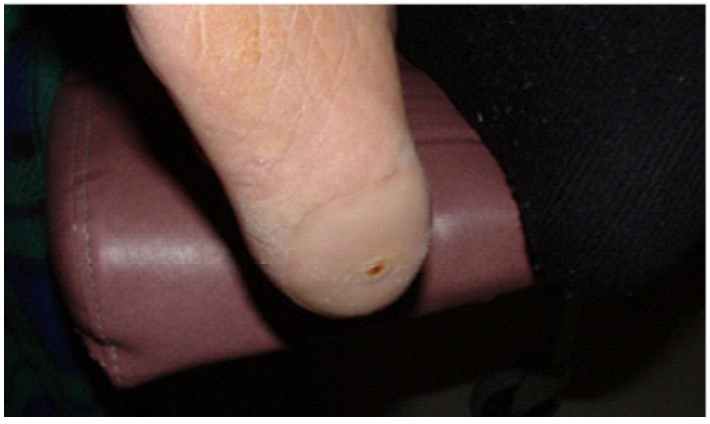
Case history, patient 2

Figure 3a



A 60 year old male with type 1 diabetes mellitus and 6 years of renal failure for which dialysis is performed. The ulcer had been in existence for 16 weeks prior to EPIFLO treatment (Figure 3a).

Figure 3b



After 5 weeks of EPIFLO® the lesion is virtually healed (Figure 3b).

Discussion

The application of oxygen to a wound is used in many different ways, including hyperbaric oxygen and topical delivery in an oxygen chamber. Both methods only deliver oxygen intermittently. Hyperbaric oxygen (HBO) uses a large stationary chamber to deliver a high flow (600 L/hour) of oxygen at 2.0 to 3.0 times atmospheric pressure. The mechanism of action is respiratory and relies on systemic perfusion and diffusion. The patient is confined to the chamber at a facility for 1.5 to 2.0 hours per day, 4 to 5 days per week. Wound dressings are changed after each treatment. HBO seems to be effective for certain diabetic foot ulcers, particularly those of Wagner grade 3 or higher.[3 7, 18-20] However, although cost effective [21] the therapy is expensive[22] , has an impact on the quality of life, and can severely limit mobility.

Topical oxygen therapy is delivered via a disposable or reusable limb chamber connected to an oxygen tank. The mechanism of action is localized diffusion and the therapy provides an intermittent treatment utilizing a medium flow (60 L/hour) of oxygen at a pressure slightly higher than ambient. Like hyperbaric oxygen, the patient is confined to a specific location (topical limb chamber and oxygen tank) in a clinical setting or at home for 1.5 to 2.0 hours per day, 4 to 5 days per week. Wound dressings are changed after each treatment. Topical oxygen therapy, in combination with low level laser therapy has been found to be beneficial.[23 24]

However, as mentioned, both therapies severely restrict patient mobility. In addition, the infrastructure required for systemic HBO therapy and the need for (disposable) limb chambers for topical oxygen may contribute to the cost of these types of treatment.

TCOT with the EPIFLO® chamber provides a continuous delivery of a very low dose of 99% pure oxygen directly to the wound site. Since the delivery device is small and portable, patients are not confined to a specific space or treatment room, which may contribute to a better quality of life (i.e. independence of movement) and more possibilities to continue regular activities of daily living, including work.

More important than continued mobility, the results found in this study indicate the high level of efficacy of TCOT in patients with indolent diabetic foot ulcers with a complete re-epithelialization in 86% of all cases within an average of 46 days. In this context, it is interesting that one patient had an untreated contralateral ulcer that remained unhealed while the TOCT treated ulcer healed. When the second ulcer was subsequently treated with TOCT, it started to show improvement as well (data on the second ulcer are not included in this evaluation). In the two patients in whom healing was not complete, 90.5% and 87.5% re-epithelialization occurred, in spite of the fact that they were non-compliant with regard to prescribed off-loading.

In addition to the positive healing results, the use of TCOT may also contribute to cost reduction by promoting faster healing and reducing costs associated with treatment (i.e. nursing time, dressings and the use of expensive equipment such as hyperbaric oxygen chambers): the actual EPIFLO® device only needs to be changed every 15 days and is relatively low-cost when compared to both ways of delivering alternative oxygen therapies. An overall reduction of morbidity may also lead to a reduction of necessary hospitalization which, in Canada, is reported to cost approximately $CDN 1000 per day per bed. When the costs of medical care, such as nursing time, physician consultation, antibiotics, and more frequent dressing changes are factored in, potential hospitalization related cost savings are even more substantial.

A number of therapies, not aimed at the delivery of extra oxygen to the wound, have become popular. These include the application of modern dressings[25], active therapies,[26 27] and NPWT[28] (Table 3).

Table 3: COMPARISON OF VARIOUS RECENT TREATMENTS FOR DIABETIC FOOT ULCER

Author	Veves et al. [27]		Driver et al[26]		Jude et al., [25]		Blume et al.[28]	
ARM	Treatment Promogran*	Control	Treatment Autologel**	Control	Treatment Hydrofiber+	Control	Treatment NPWT	Control
n	138	138	40	32	67	67	169	166
Age (Years)	58 (23-85)	59 (37-83)	56.4 (31-75)	57.5	58.9±12.6	61.1 ± 11.4	58±12	59 ±12
Male/Female (%)	69/31	78/22	80/20	84/16	62.4±109.2	79/21	83/17	73/27
Wound duration prior to treatment (weeks)	13 (4-364)	13 (4-624)	N/A	N/A	62.4±109.2	72.8 ± 135.2	28.3 ± 46.2	29.4 ± 52.3
Baseline wound area (cm2)	2.5 (0.2-27.4)	3.1 (0.1-42.4)	4.0 (0.4-24)	3.2	3.1 ± 4.1	4.2 ± 7.8	13.5 ± 18.2	11 ± 12.7
Time to wound closure (weeks)	7 ± 0.4	5.8 ± 0.4	N/A (median time = 6.4)	(0.5-15.8)	7.5 ± 0.3	8.2 ± 0.2	N/A (KM¶ median for 75% closure = 8.3)	11.1 ± 5.6
% closed	37.0	28.3	32.5	N/A	31.3	22.4	43.2	28.9

*Systagenix Wound Management, Quincy, MA, USA
** Cytomedix, Rockville, MD, USA
+ ConvaTec, Skillman, NJ, USA
¶ Kaplan-Meier

Conclusion

The results of this study indicate that the use of TCOT as an adjunctive therapy may significantly increase wound healing and re-epithelialization in patients with indolent diabetic foot ulcers. Patients using the device benefit from a continuous flow of oxygen to their wound and are not confined to a wound treatment room in a hospital or outpatient clinic: this, in turn, contributes to overall quality of life (patients being independent and ambulant) and may also assist in reducing the overall cost of care.

References

1) International Diabetes Federation (IDF), 2007.

2) Palumbo PJ, Melton LJ, 3rd. Peripheral Vascular Disease and Diabetes. Washington, DC: Government printing office. NIH publication 85-1468, 1985.

3) Jude EB, Unsworth PF. Optimal treatment of infected diabetic foot ulcers. Drugs Aging 2004;21(13):833-50.

4) International Diabetes Foundation (IDF), 2007.

5) Moretti B, Notarnicola A, Maggio G, Moretti L, Pascone M, Tafuri S, et al. The management of neuropathic ulcers of the foot in diabetes by shock wave therapy. BMC Musculoskelet Disord 2009;10:54.

6. Horswell RL, Birke JA, Patout CA, Jr. A staged management diabetes foot program versus standard care: a 1-year cost and utilization comparison in a state public hospital system. Arch Phys Med Rehabil 2003;84(12):1743-6.

7. McCartney T. Wound healing and care in the infected diabetic foot. West Indian Med J 2001;50 Suppl 1:27-8.

8. Gottrup F. Oxygen in wound healing and infection. World J Surg 2004;28(3):312-5.

9) Tandara AA, Mustoe TA. Oxygen in wound healing--more than a nutrient. World J Surg 2004;28(3):294-300.

10) Quinn MT, Gauss KA. Structure and regulation of the neutrophil respiratory burst oxidase: comparison with nonphagocyte oxidases. J Leukoc Biol 2004;76(4):760-81.

11) Cianci P. Advances in the treatment of the diabetic foot: Is there a role for adjunctive hyperbaric oxygen therapy? Wound Repair Regen 2004;12(1):2-10.

12) Niinikoski J. Current concepts of the role of oxygen in wound healing. Annales Chirugiae et Gynaecologia. 90 2001;Supplement 215:9-11.

13) Gordillo GM, Sen CK. Revisiting the essential role of oxygen in wound healing. Am J Surg 2003;186(3):259-63.

14) Breuer HW, Breuer J, Berger M. Transcutaneous oxygen pressure measurements in type I diabetic patients for early detection of functional diabetic microangiopathy. Eur J Clin Invest 1988;18(5):454-9.

15) Amini M, Parvaresh E. Prevalence of macro- and microvascular complications among patients with type 2 diabetes in Iran: a systematic review. Diabetes Res Clin Pract 2009;83(1):18-25.

16) Ditzel J, Standl E. The problem of tissue oxygenation in diabetes mellitus. I. Its relation to the early functional changes in the microcirculation of diabetic subjects. Acta Med Scand Suppl 1975;578:49-58.

17) Said HK, Hijjawi J, Roy N, Mogford J, Mustoe T. Transdermal sustained-delivery oxygen improves epithelial healing in a rabbit ear wound model. Arch Surg 2005;140(10):998-1004.

18) Fife CE, Buyukcakir C, Otto G, Sheffield P, Love T, Warriner R, 3rd. Factors influencing the outcome of lower-extremity diabetic ulcers treated with hyperbaric oxygen therapy. Wound Repair Regen 2007;15(3):322-31.

19) Lyon KC. The case for evidence in wound care: investigating advanced treatment modalities in healing chronic diabetic lower extremity wounds. J Wound Ostomy Continence Nurs 2008;35(6):585-90.

20) Roeckl-Wiedmann I, Bennett M, Kranke P. Systematic review of hyperbaric oxygen in the management of chronic wounds. Br J Surg 2005;92(1):24-32.

21) Guo S, Counte MA, Gillespie KN, Schmitz H. Cost-effectiveness of adjunctive hyperbaric oxygen in the treatment of diabetic ulcers. Int J Technol Assess Health Care 2003;19(4):731-7.

22) Wunderlich RP, Peters EJ, Lavery LA. Systemic hyperbaric oxygen therapy: lower-extremity wound healing and the diabetic foot. Diabetes Care 2000;23(10):1551-5.

23) Landau Z, Schattner A. Topical hyperbaric oxygen and low energy laser therapy for chronic diabetic foot ulcers resistant to conventional treatment. Yale J Biol Med 2001;74(2):95-100.

24) Gorman DF, Harding PE, Roberts AP, Gilligan JE, Capps RA, Parsons DW. Topical hyperbaric oxygen for treatment of diabetic foot ulcers. Diabetes Care 1988;11(10):819.

25) Jude EB, Apelqvist J, Spraul M, Martini J. Prospective randomized controlled study of Hydrofiber dressing containing ionic silver or calcium alginate dressings in non-ischaemic diabetic foot ulcers. Diabet Med 2007;24(3):280-8.

26) Driver VR, Hanft J, Fylling CP, Beriou JM, Autologel Diabetic Foot Ulcer Study G. A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. Ostomy Wound Manage 2006;52(6):68-70, 72, 74 passim.

27) Veves A, Sheehan P, Pham HT. A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. Arch Surg 2002;137(7):822-7.

28) Blume PA, Walters J, Payne W, Ayala J, Lantis J. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. Diabetes Care 2008;31(4):631-6.

29) Margolis DJ, Gelfand JM, Hoffstad O, Berlin JA. Surrogate end points for the treatment of diabetic neuropathic foot ulcers. Diabetes Care 2003;26(6):1696-700.

30) Margolis DJ, Kantor J, Berlin JA. Healing of diabetic neuropathic foot ulcers receiving standard treatment. A meta-analysis. Diabetes Care 1999;22(5):692-5.