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Randomized Placebo-Controlled Clinical Trial of Gloves and Stockings Made from Infrared-Emitting Fabric (CELLIANT®) for Transcutaneous Oxygen and Peripheral Blood Flow in Diabetic Patients with Vascular Impairment

Dr. Lawrence A. Lavery, Dr. Michael R. Hamblin and Kathryn Davis

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Randomized Placebo-Controlled Clinical Trial of Gloves and Stockings Made from Infrared-Emitting Fabric (Celliant®) for Transcutaneous Oxygen and Peripheral Blood Flow in Diabetic Patients with Vascular Impairment

Lawrence A. Lavery[1]* Kathryn Davis[1] Seth Casden[2] and Michael R Hamblin[3]

[1]*Department of Plastic Surgery, University of Texas Southwestern Medical Center, Dallas, Texas, USA*
[2]*Hologenix LLC, Santa Monica, USA*
[3]*Laser Research Centre, University of Johannesburg, Doornfontein, South Africa*

Abstract

Objective: To evaluate changes in transcutaneous oxygen ($TcPO_2$) and peripheral blood flow (laser Doppler, LD) in the hands and feet of diabetic patients with vascular impairment when Celliant gloves and stockings are worn.

Methods: We enrolled 20 subjects with a history of diabetes and vascular impairment to be monitored by $TcPO_2$ and LD in the hand and foot at 10-minute intervals over the course of a 1hr treatment with Celliant or placebo gloves and stockings that were applied at the same time but in different sequences with a 1hr interval. The tester and subject were blinded to the type of study garment.

Results: There were no statistically differences between measurements due to the small sample size and variability in the data. However there was a trend for increasing $TcPO_2$ and LD particularly in the foot when comparing placebo garments (first) and Celliant garments (second) at time periods of 50 and 60 minutes.

Conclusion: The 1hr wearing time may have been insufficient for the full effect to be observed, and the 1hr interval between the different garments may be too short to washout the Celliant effect, when the placebo garments were applied second. Further studies are necessary to obtain statistically significant results, and to determine whether Celliant garments could prevent diabetic foot complications.

Keywords: Diabetes • Blood flow • Transcutaneous oxygen • Infrared emitting fabric • Gloves • Stockings

Introduction

Diabetic patients frequently suffer from a combination of peripheral neuropathy and peripheral artery disease, which particularly affects their feet. The neuropathy allows small wounds in the feet to develop into foot ulcers, and the compromised blood flow along with cellular defects in healing caused by high blood glucose levels means that these ulcers are very slow to heal [1]. Infections then develop within the chronic ulcers, which can spread to bones and joints and require treatment with systemic antibiotics [2]. Insufficient penetration of antibiotics into the compromised tissue and the presence of wound biofilms, along with the widespread increase in antibiotic resistance in common bacteria, means that this treatment often fails [3]. In this case foot amputation is the only solution to prevent the development of sepsis and death. Moreover diabetic patients are particularly susceptible to fungal infections of the feet such as onychomycosis. It has been estimated that the lifetime risk for the development of foot ulcers in diabetic patients can be as high as 25% [4] and the risk of amputation is 10-20 times higher than in non-diabetic subjects [5].

***Address for Correspondence:** Lawrence A Lavery, Department of Plastic Surgery, University of Texas Southwestern Medical Center, Dallas, Texas, USA, E-mail: larry.lavery@utsouthwestern.edu*

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In recent years advances in textile technology have allowed the development of biologically active garments. These active garments often rely on the incorporation of infrared-emitting ceramics into the fibers from which they are woven. These garments are different from more conventional sources of infrared (IR) radiation, which rely on the electrically powered heating of a bulb or ceramic panel to emit the radiation. In the case of active garments the only source of energy to power the device is the wearer's own body heat (or any incident radiation from the sun). These mineral materials in the garments (such as silicon dioxide SiO_2, aluminium oxide $Al2O_3$, or titanium dioxide TiO_2) can emit FIR radiation back into the skin. However, the power density in mW/cm^2 is much lower that that measured in IR heat lamps or IR saunas. Nevertheless, even this low power density is sufficient to have beneficial biological effects, especially when worn for a sufficient length of time.

The biological effects of IR radiation are becoming better understood, although there is still some way to go before a complete understanding is achieved [6,7]. The principal absorbing molecule for these IR wavelengths (3-15 μm) is water, which is also the most prevalent compound by weight in all living systems. The penetration of IR wavelengths into living tissue is a controversial subject. Although the penetration depth of ballistic IR photons into tissue is very short (only a few μm), the effective penetration depth of the energy is much deeper (2-4 cm) [8]. The explanation for this marked discrepancy is proposed to be non-radiative energy transmission between adjacent water molecules that enables beneficial effects to occur deep into the tissue. The existence of nanostructured water clusters within cells and tissues as proposed by Gerald Pollack could explain this phenomenon [9]. The theory is that these water clusters could selectively absorb IR radiation producing microscopic conformational changes in protein structure, without any marked tissue heating.

The most common biological effects that have been reported are:

increase in cutaneous blood flow [10]. Increase in transcutaneous oxygen [11]. Reduction in pain [12]. Reduction in inflammation [13]. Improved healing of chronic wounds [14]. Increased sports performance [15] and better sleep [16]. Therefore in the present study we asked whether active IR emitting garments (gloves and stockings) could improve blood circulation in the hands and feet of diabetic individuals with vascular impairment, compared to control placebo garments.

Methods

Patient recruitment

Patients were recruited from those attending the clinic at University Hospital Wound Care Clinic. Dallas, TX. The diagnosis of diabetes mellitus was based on World Health Organization criteria [17]. For the purposes of this study, the diagnosis of peripheral vascular disease was a transcutaneous oxygen measurement < 30 mm Hg taken at the transmetatarsal level on the day of enrollment [18]. The inclusion and exclusion criteria used to determine eligibility are listed in (Table 1). This study was approved by the UT Southwestern Institutional Review Board (IRB # 032015-099) and registered with www.ClinicalTrials.gov as NCT04709419

Randomization

After informed consent was obtained, baseline blood flow measurements using $TcPO_2$ and Laser Doppler were taken for each patient prior to placing the study garments. Patients were randomized to have measurements taken on the left hand and left foot or the right hand and right foot. Each patient had either placebo or Celliant garment applied for 1 hour, followed by a 1-hour wash out period. After this washout, the alternative garment was applied. Patients were randomized to the order of which the garments were applied (placebo then Celliant or Celliant then placebo).

Equipment

Blood flow and tissue oxygenation ($TcPO_2$) were measured using the dual function PeriFlux 5000 System from Perimed Inc. (North Royalton, Ohio) fitted with transcutaneous oxygen module (PF5040) and laser Doppler perfusion module (PF5010). For the $TcPO_2$ measurement, the transcutaneous oxygen electrodes were warmed to 44°C and allowed to equilibrate on the skin for 5 minutes (until stable values were achieved). The resultant values were measured in mmHg [19]. The non-invasive laser Doppler monitor was used to continuously measure tissue blood perfusion. Two stick-on probes similar to standard EKG probes were applied to the skin. The scattered laser light is Doppler shifted by interaction with the moving blood cells. The sampling depth is 200-500 μm. The backscattered light is detected by a photo detector.

Gloves and stockings

The Celliant gloves and stockings were 82% Celliant polyester, 13% nylon and 5% Spandex. Celliant fibers absorb heat generated by the wearer's body by radiation, convection and conduction, and also from the environment, and re-emit the energy as infrared radiation back into the wearer's body. The placebo gloves and stockings were 82% standard polyester, 13% nylon, and 5% Spandex and were visually identical to the active gloves and stockings. Both gloves and stockings had four small holes cut in the area covering the dorsum of the hand and foot to allow the four sensors of the Periflux system (two for $TcPO_2$ and two for LD) to be attached to the skin during the whole 1 hour period of the measurement. (Figure 1). Shows the Celliant and placebo gloves with holes cut into them to allow the attachment of the Periflux probes. The stockings were similarly constructed but are not shown here.

Procedure

Once the baseline measurements were acquired, two study garments (glove and stocking according to the randomization) were applied to the patient's right hand and foot or left hand and foot simultaneously. The patients sat comfortably in a chair during the 1-hour evaluation time. The sensors were then applied to the skin, and $TcPO_2$ and LD measurements were continuously acquired during the 1-hour evaluation period. Values were recorded as the average measurement over 60 seconds at 10-minute intervals on the dorsum of the foot and hand. Additionally, average measurements of the final 2-minute interval of the treatment period were taken. At the end of the first 1-hour evaluation period, the sensors and garments were removed, and the patients remained sitting comfortably for the 1-hour washout period before the second 1-hour evaluation period commenced.

Results

Because there was a large variation in the baseline values of both TCOM and LD measurements on the hand and foot in individual subjects, we calculated the percentage change over the baseline value at each time point for each individual subject and then calculated mean values and SEM error bars. As can be seen in (Figure 2). There was a large amount of error in all the

Table 1. Inclusion and exclusion criteria.

	Inclusion criteria
1	Diagnosis of diabetes mellitus by the World Health Organization Criteria
2	Diagnosis of vascular impairment by $TcPO_2$ measurement
3	Subjects male or female between 18-80 years old.
	Exclusion criteria
1	Patient currently receiving dialysis or having serum creatinine ≥ 3.0 mg/dL.
2	Subjects with active alcohol or substance abuse for six months prior to the start of the study.
3	Patients currently receiving systemic corticosteriods at a dose equivalent to ≥ 10 mg of prednisone per day.
4	Patients currently receiving immunosuppressive drugs.
5	Patients currently receiving radiation therapy.
6	Patients currently receiving cytotoxic drugs.
7	Patients currently receiving antiviral drugs.
8	Patients with a history of malignancy or systemic immunosuppressive disease.
9	Female subjects who are breast feeding, pregnant, or attempting to become pregnant.
10	Subjects considered by the investigator to be disqualified (e.g., acute illness or exacerbation of chronic illness, lack of motivation, or history of poor compliance).
11	Amputation proximal to the tarsometatarsal joint or amputation/surgical debridement has destroyed the venous plexus of the plantar arch.
12	Acute deep venous thrombosis.
13	Active congestive heart failure.
14	Uncontrolled osteomyelitis.
15	Vascular surgery within 4 weeks.
16	Patients with a full thickness skin ulcer.

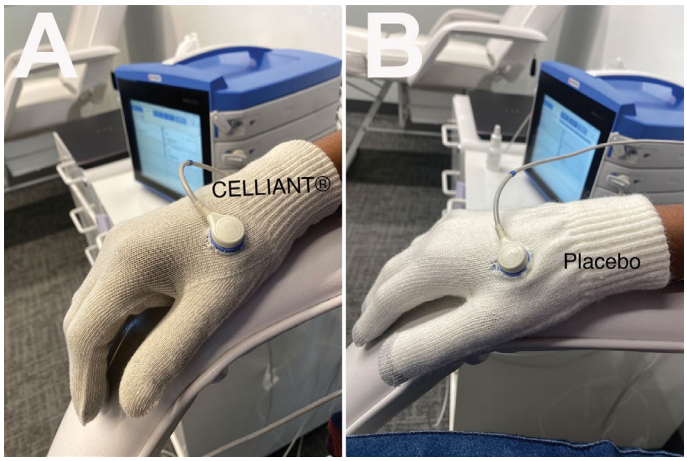

Figure 1. Photograph showing (A) Celliant glove and (B) Placebo glove with a hole cut to allow attachment of the PeriFlux probe.

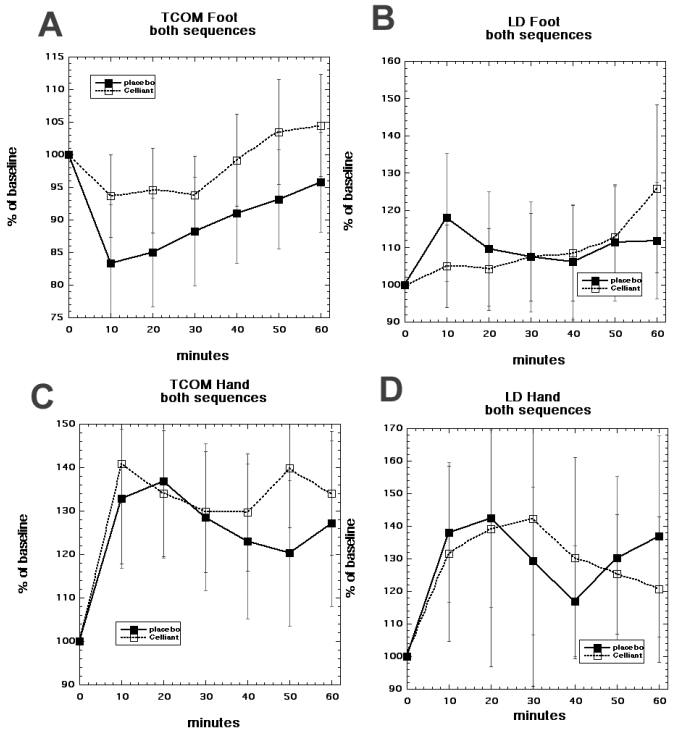

Figure 2. Plots of mean % increase of measured variable over baseline value for each individual subject over the 1-hour interval. In these plots both sequences were included; Celliant first followed by placebo second and placebo first followed by Celliant second. (A) TCOM in foot, (B) LD in foot, (C) TCOM in hand and (D) LD in hand. Values are means and bars are SEM. N=20 subjects.

measurements and no statistically significant differences could be determined. Nevertheless, it can be seen in Figure 2A that there is a trend for the TCOM in the foot to be higher with Celliant stocking compared to placebo stocking at all time points, with the data obtained from both application sequences combined. There is no clear trend visible for LD in the foot (Figure 2B), TCOM in the hand (Figure 2C), or LD in the hand (Figure 2D). We then hypothesized that analyzing combined data from both application sequences may not be the most appropriate method for analysis. For the group that was first treated with Celliant, if the 1-hour wash out period was not long enough to deplete the Celliant-related changes, the relationship between Celliant and placebo measurements may be different than those from the group first treated with placebo. If true, this would mean that the effects of the placebo garment would be contaminated by the lingering effects of the Celliant garment.

To test this hypothesis we plotted the data separately for the two different sequence groups, resulting in only 10 subjects included in each sequence group, as compared to 20 subjects in the combined sequence group (Figure 3). Shows the placebo then Celliant treatment group (Figure 4). Shows the Celliant then placebo treatment group. Figure 3A shows that application of Celliant increases TCOM measurement in the foot; this change is far more pronounced than observed in the combined sequence group (Figure 2A). Moreover, Figure 3B shows that the LD in the foot is higher with Celliant at

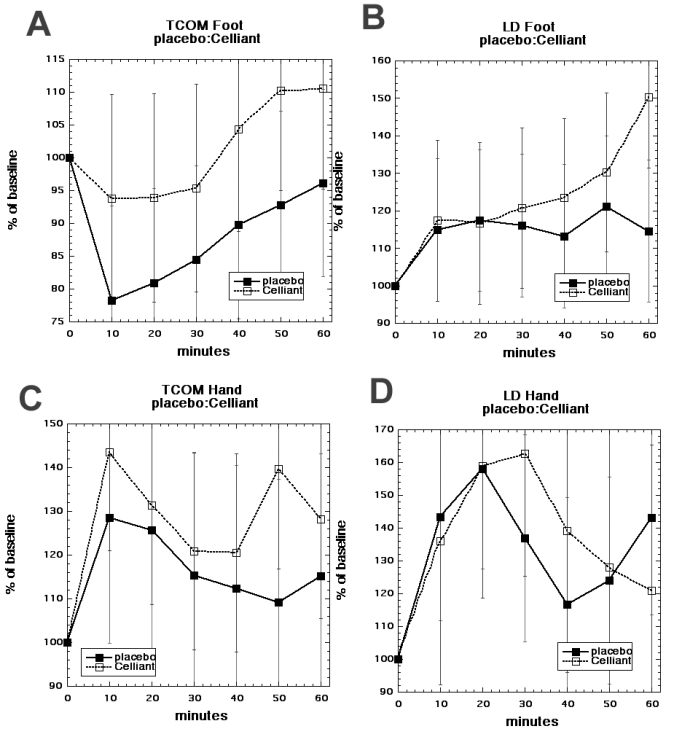

Figure 3. Plots of mean % increase of measured variable over baseline value for each individual subject over the 1-hour interval. In these plots only placebo first followed by ceelliant second is included. (A) TCOM in foot, (B) LD in foot, (C) TCOM in hand and (D) LD in hand. Values are means and bars are SEM. N=10 subjects.

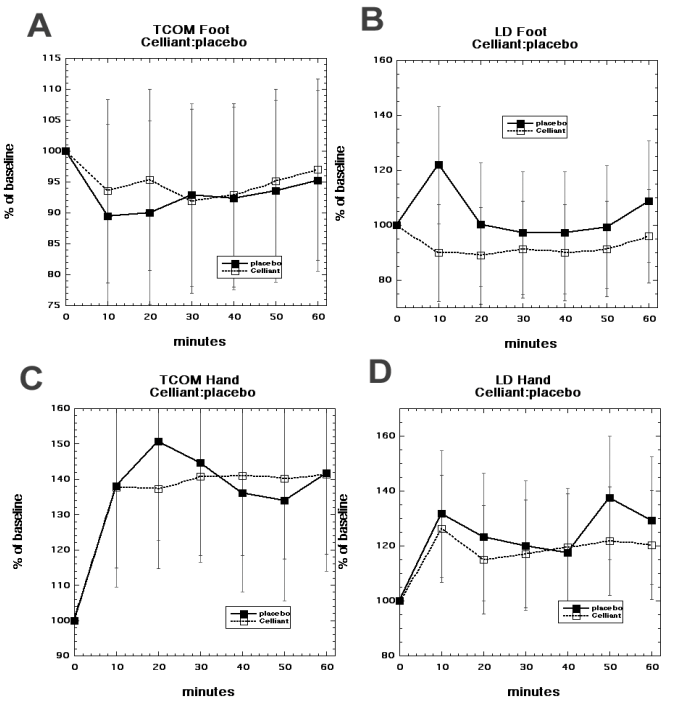

Figure 4. Plots of mean % increase of measured variable over baseline value for each individual subject over the 1-hour interval. In these plots only Celliant first followed by placebo second is included. (A) TCOM in foot, (B) LD in foot, (C) TCOM in hand and (D) LD in hand. Values are means and bars are SEM. N=10 subjects.

the 60 min time point compared to placebo. Figure 3C shows that the TCOM in the hand slightly increases with Celliant application compared to placebo at 50 and 60 minutes. Only Figure 3D showing LD in the hand does not allow any trend for a difference between Celliant and placebo to be discerned. When we examine the same analysis for the group that had application of Celliant before placebo (Figure 4). We can see that all the trends previously described 3, have disappeared. There is virtually no difference between TCOM values in the foot between Celliant and placebo as shown in Figure 4A, despite this being the most pronounced difference seen with the opposite sequence (Figure 3A). This disappearance of any trend for a difference also applies to LD in the foot (Figure 4B), TCOM in the hand (Figure 4C), and LD in the hand (Figure 4D).

Discussion

Despite some notable shortcomings in the experimental design, and the low sample numbers in the trial leading to large variations in the experimental data, we still believe that the results bear some interesting. Firstly, the application time of only one hour was clearly insufficient for the full benefit of the IR emitting fabric to be seen in the measurements of blood flow and tissue oxygenation. In retrospect, the power density of Celliant fabric is very low (only about 0.5 mW/cm^2) compared to IR lamps and IR saunas (about 10-20 mW/cm^2), which are used for about 30 minutes. It was, therefore, unreasonable to expect that such a short wearing time (60 minutes, only twice as long) would have the optimal effects. If the exposure were to be proportional, it would have been necessary to wear both the garments for 24 hours each (with a 24-hour interval in between), which in principle would have been entirely feasible, although somewhat challenging logistically.

Secondly, the decision to randomize the order of wearing (either Celliant first followed by placebo second OR placebo first followed by Celliant second) was probably ill-advised as there was only a one-hour interval between the two 1-hour application sessions. When the Celliant garment was worn first, the full effect had likely not developed by the end of the one-hour period and the effect may have continued over the one-hour washout period and into the placebo-application period. This hypothesis is further supported by the analysis presented in (Figures 3 and 4). Where the Celliant effect becomes much more pronounced when Celliant application followed placebo. A larger, statistically powered study would need to be performed to confirm this hypothesis. These data suggest the effects of the Celliant garments are more pronounced when applied to the foot than when applied to the hand. This is in agreement with the occurrence and severity of peripheral vascular disease and impaired blood flow being much more common in the foot and lower leg of diabetic patients, compared to the hands and lower arms [20]. Although diabetic neuropathy can affect both the feet and the hands, major problems are much more likely to develop in the feet [21]. Moreover, the problems are different in the feet and the hands, with diabetic feet suffering from impaired blood flow, delayed wound healing, and chronic infections, while diabetic hands suffer from poor joint mobility, Dupuytren's contracture, carpal tunnel syndrome, and trigger finger [22].

Although the present study suffered from a low sample size and a high degree of variability in the data, the size of the increase in both tissue oxygenation (~20%) and blood flow (~30%) in the feet after application of Celliant stockings suggests that this benefit could be clinically relevant, if it could be confirmed with statistical significance in a larger clinical trial. Ideally a clinical trial could show that the wearing of Celliant stockings could improve various signs and symptoms of diabetic foot, and even prevent amputations in vulnerable patients. There have been no documented or observed side effects of wearing Celliant stockings, and they are relatively inexpensive compared to conventional pharmaceutical interventions.

Conclusion

Although there were no statistically significant effects of wearing Celliant garments on tissue oxygenation and blood flow in the hands or feet of diabetic subjects, the trends that were observed in favor of Celliant stockings suggest that a larger well-designed clinical trial should be undertaken, and may provide evidence of clinical efficacy in treatment of the diabetic foot.

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Conflict of interest

LAL received sponsored research funding from Hologenix LLC.

SC is a stockholder and employee of Hologenix LLC

MRH received consulting fees and is on the scientific advisory board of Hologenix LLC

Author contributions

LAL. Conceptualization, Methodology, Investigation

KD. Formal analysis

SC. Conceptualization, Resources, Funding acquisition

MRH. Formal analysis, Writing - Original Draft, Writing - Review & Editing

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