Lasers in Medical Science (2022) 37:919–928
https://doi.org/10.1007/s10103-021-03335-9

ORIGINAL ARTICLE

Treatment of diabetic foot ulcers in a frail population with severe co-morbidities using at-home photobiomodulation laser therapy: a double-blind, randomized, sham-controlled pilot clinical study

Amir Haze[1] · Lilach Gavish[2] · Ofer Elishoov[1] · Dorit Shorka[1] · Tamir Tsohar[1] · Yechiel N. Gellman[1] · Meir Liebergall[1]

Received: 1 March 2021 / Accepted: 3 May 2021 / Published online: 29 May 2021

Abstract

Purpose To evaluate the safety and efficacy of an at-home photobiomodulation (PBM) device for the treatment of diabetic foot ulcers (DFUs) in a frail population with severe comorbidities.

Methods Prospective, randomized, double-blind, sham-controlled pilot study. Patients (age = 63 ± 11 years, male:female 13:7) with insulin-dependent diabetes type 2, neuropathy, peripheral artery disease, significant co-morbidities, and large osteomyelitis-associated DFUs (University of Texas grade ≥ III) were randomized to receive active ($n = 10$) or sham ($n = 10$) at-home daily PBM treatments (pulsed near-infrared 808 nm Ga-Al-As laser, 250 mW, 8.8 J/cm^2) for up to 12 weeks in addition to standard care. The primary outcome was the %wound size reduction. The secondary was adverse events.

Results With the numbers available, PBM-treated group had significantly greater %reduction compared to sham (area [cm^2], baseline vs endpoint: PBM 10[20.3] cm^2 vs 0.2[2.4] cm^2; sham, 7.9 [12.0] cm^2 vs 4.6 [13.8] cm^2, p=0.018 by Mann–Whitney U test). Wound closure > 90% occurred in 7 of 10 PBM-treated patients but in only 1 of 10 sham patients (p=0.006). No adverse device effects were observed.

Conclusions Photobiomodulation at home, in addition to standard care, may be effective for the treatment of severe DFUs in frail patients with co-morbidities and is particularly relevant at these times of social distancing. Our preliminary results justify the conduction of a larger clinical trial. ClinicalTrials.gov: NCT01493895.

Keywords Diabetic foot ulcer · Photobiomodulation · Low-level laser therapy · Frail elderly · Wound healing

Amir Haze and Lilach Gavish have contributed equally.

✉ Lilach Gavish
lilachg@ekmd.huji.ac.il

Amir Haze
amir.haze@mail.huji.ac.il

Ofer Elishoov
ofer@hadassah.org.il

Dorit Shorka
dori@hadassah.org.il

Tamir Tsohar
tamirt@hadassah.org.il

Yechiel N. Gellman
Yechielg@hadassah.org.il

Meir Liebergall
LIEBERGALL@hadassah.org.il

[1] Orthopedic Department, Hadassah-Hebrew University Medical Center, POB 12000, 9112001 Jerusalem, Israel

[2] Institute for Research in Military Medicine (IRMM) of the Faculty of Medicine, The Hebrew University of Jerusalem, POB 12272, Jerusalem 9112001, Israel

Introduction

The global prevalence of diabetes is on the rise and with it an increase in prevalence of diabetic foot ulcers (DFU) [1]. Patients with diabetes have a 12–25% lifetime risk of developing a DFU which precedes 85% of all lower limb amputations. The 5-year mortality rate for an amputee is over 40% [2]. A variety of interventions have been used for treatment of DFUs [1, 3], but these recalcitrant wounds are difficult to manage and pose a heavy economic burden [4].

The majority of the studies designed to evaluate novel technologies for treatment of diabetic foot ulcers, recruit patients that have adequately controlled diabetes and adequate arterial perfusion with relatively uncomplicated ulcers (University of Texas grading I or II), and few comorbidities [5]. However, many of the patients that arrive at hospital wards, including our department, arrive with insulin-dependent diabetes, peripheral artery disease, and neuropathy and have complicated ulcers, including osteomyelitis with multiple co-morbidities. Moreover, after standard, primary wound treatment

at the hospital, most patients with DFUs require frequent follow-up visits to the hospital clinic over a period of several weeks. This poses significant inconvenience with logistics that are often very challenging as well as safety issues at these times of social distancing and self-isolation of frail elderly patients with diabetes. The availability of a treatment that can be administered at home is therefore of great benefit.

Photobiomodulation (PBM), previously termed low-level laser therapy, is the application of non-ionizing visible to near-infrared optical radiation to tissues. The photons are absorbed by endogenous chromophores eliciting photochemical events without creating thermal damage [6, 7].

Acceleration of wound healing is one of the first indications for which PBM was used, and one of the most thoroughly studied. PBM has been shown to affect multiple molecular pathways related to wound healing [8] including: increasing mitochondrial activity and ATP levels; promotion of proliferation and migration of keratinocytes, endothelial cells, fibroblasts, and vascular smooth muscle cells; increasing collagen synthesis; and modulation of expression and secretion of relevant chemokines and cytokines. Similar effects of PBM were also found in a variety of experiments in diabetes models (see review [9]). A recent systematic review of randomized controlled studies evaluating PBM for treatment of DFUs concluded that efficacy is generally positive with no associated adverse events (AEs) [5]. The authors of the review concluded that this technology has significant potential to become a portable, minimally invasive, easy-to-use, and cost effective modality for treatment of DFU [5]. Randomized clinical trials reported after publication of that systematic review provided substantial additional supportive evidence [10–17].

A practical limitation for the use of this modality is the requirement of frequent treatment sessions. Most PBM studies applied treatment at least 3 times a week at the clinic. Thus, the current study was designed to evaluate the safety and efficacy of an "over-the-counter" consumer PBM device at home as an adjuvant to standard treatment (compared with sham-device) for healing diabetic foot ulcers in complicated, frail patients with severe comorbidities.

Materials and methods

Design overview

This study was a single-center, prospective, randomized, double-blind, sham-controlled, parallel-group proof of concept study evaluating the safety and efficacy of a photobiomodulation device (B-Cure Laser, Good Energies, Haifa, Israel) at home for treatment of diabetic foot ulcers in addition to standard care. Patients with diabetic foot ulcers and comorbidities were randomized to receive active or sham treatments in addition to standard care (wound cleaning, debridement, culture based antibiotic therapy when necessary, PolyMem silver bandage [Polymem, Fort Worth, TX, USA]), and offloading or footwear adjustment when required. Patients were treated everyday (excluding Saturdays) at home by professional caregivers until complete ulcer closure or up to 12 weeks, the earlier of the two. In every visit to the clinic, study physicians measured the wound area, inspected the wound for safety issues, and investigated any side effect reported by the patients. All adverse events were recorded. The primary endpoint was the percent reduction in wound size from baseline to endpoint. The secondary outcome was the occurrence of treatment-related adverse events. No changes in the trial assessments or measurements took place after the trial commencement.

Ethical approval

This clinical trial (ClinicalTrials.gov: NCT01493895) was approved by the clinical trial ethical review board of the Hadassah Medical Organization (0122–11-HMO) prior to recruitment. All patients provided written informed consent before entering the study.

Setting and participants

Patients were recruited from the inpatient and outpatient foot and ankle orthopedic service of Hadassah Medical Organization in Jerusalem from December 2013 to August 2015. Eligibility was determined according to the following criteria:

Inclusion: 21–75 years of age; male or female; documented diabetes mellitus with an active chronic foot ulcer that has been treated over 3 weeks without improvement, size of the wound – greater than 3 cm^2, and an ankle brachial index (ABI) > 0.6

Exclusion: Pregnancy or presence of cancerous comorbidity.

In the initial approved protocol, the required ulcer size was limited to 1–8 cm^2, and patients with osteomyelitis were excluded. However, since the patient population that normally arrives at the service had severe comorbidities and larger ulcers, the clinical group decided to modify the eligibility criteria to include ulcers with an area of 3 cm^2 and above. These modifications took effect before initiation of patient recruitment. See Table 1 for patient characteristics by groups.

The individual measurements collected in this study and details of diabetes status and care (according to Jeffcoat et al. [3]) are reported in the Online Resource Tables S1 and S2.

Randomization and blinding

Simple randomization was performed by a third-party statistician using a computer-generated randomization list. At

Table 1 Baseline patient characteristics by group allocation

	Sham ($n=10$)	Active ($n=10$)	Total ($n=0$)
Age (mean ± SD) [years old]	61 ± 11	65 ± 11	63 ± 11
Gender (male:female)	7:3	6:4	13:7
Osteomyelitis	10 of 10	9 of 10	19 of 20
Renal function by eGFR stages*			
Stages 1 and 2 (GFR ≥ 60)	4	5	9
Stages 3 and 4 (GFR < 60)	3	2	5
Dialysis	3	3	6
CRP (normal < 0.5) [Mg%], mean [95%CI]	7.8 [−0.3,15.9]	6.7 [−0.1, 13.5]	7.3 [2.5, 12.1]
Albumin (normal 35–50)[Gr/l]	32.8 [29.0,36.5]	29.6 [26.9, 32.2]	31.4 [29.1, 33.7]
Hemoglobin (normal: male 14–18; female 11–14)[Gr%]	10.8 [9.4, 12.1]	10.0 [9.1, 10.8]	10.4 [9.6, 11.2]
WBC (4–10)[10^9/l]	10.4 [7.0, 13.9]	9.4 [6.1, 12.8]	9.9 [7.8, 12.1]
Previous amputation	5 of 10	6 of 10	11 of 20
PAD	9 of 10	9 of 10	18 of 20
No pulse	7 of 10	7 of 10	14 of 20
Ambulatory status	8 independent	7 independent	15 independent
	1 walker	2 walker	3 walker
	1 wheelchair	1 wheelchair	2 wheelchair
Neuropathy	10 of 10	10 of 10	20 of 20
Revascularization**	3 of 10	3 of 10	6 of 20
Deformity***	2 of 10	2 of 10	4 of 20
Footwear/offloading	3 of 10	3 of 10	6 of 20
Additional co-morbidities (#patients)	HTN (4), HL (4), IHD (4), DiabRet (4), HyperTH (1), Psych (1), PsorAr (1)	HTN (8), HL (5), IHD (1), CHF (1), AF (1), DVT (2), DiabRet (1), HyperTh (1), Psych (3)	

*National Kidney Foundation (NKF) classification; **including catheterization or bypass prior to recruitment, ***midfoot Charcot with rocker bottom; one patient in the active group did not have GFR information; *HTN* hypertension; *HL* hyperlipidemia; *IHD* ischemic heart disease; *CHF* chronic heart failure; *AF* atrial fibrillation; *DVT* deep vein thrombosis; *DiabRet* diabetic retinopathy; *HyperTh* hyperthyroidism; *Psych* psychiatric (also dementia, depression, etc.); *PsorAr* pshoriatic arthritis

the first home visit of each patient, the caregiver contacted the statistician to receive a group allocation. The caregiver would then record this allocation in the patient's files.

Patients, caregivers, and evaluators were blinded to group allocation. The wavelength of the B-cure laser is in the near-infrared range and therefore is barely visible. Moreover, both the active and sham devices emit a sound every 3 seconds and glow with a green light when they operate. The physicians that measured the ulcers were not present at the time of the treatment or device allocation.

Standard treatment

All treatments were carried out by a third-party professional caregiving service (Sal Nursing Services, Yavne, Israel) at home or by the ward nurses. Ulcers were treated daily regardless of the treatment that was used until then. The wound was checked for infection, deterioration, or any negative developments. Standard wound care included rinsing in 0.9% saline, cleaning with antiseptic soap under a stream of warm water, and drying with absorbable disposable paper towels. Debridement was performed in cases of necrotic tissue. Laser therapy (see below) was then administered followed by wound dressing with PolyMem Silver. Offloading and/or footwear adjustment was supplied according to the physician's instructions. The experimental standard treatment was an improvement over previous self-treatment/community nurse weekly treatment, and we therefore expected that patients in both placebo and active groups would benefit from the treatment regardless of group allocation.

Laser therapy

The home-use PBM device used in this study (B-Cure Laser, Good Energies, Haifa, Israel) is sold over the counter without prescription and has a CE mark, Israel Ministry of Health (AMAR), and Health Canada approvals for several

indications including accelerating wound healing and specifically for treatment of diabetic ulcers.

The light source was a pulsed near-infrared 808-nm Ga-Al-As laser, with a mean output power of 80 mW (peak power of 250 mW with a 33% duty cycle) and irradiation area of 4.5×1 cm^2 which accumulates to 1.1 J/cm^2 per minute.

The device was applied by direct contact with the wound. Each application consisted of 8 minutes per area (total energy of 8.8 J/cm2), until all areas of the wound were irradiated. The part of the device that was in contact with the wound was cleaned thoroughly with 70% alcohol prior to application.

Wound size measurements

Following identification of the wound edges and measurement by the ruler technique by blinded evaluators (AH, OE, and TT), the surface area of the wound was calculated by multiplying the maximum perpendicular length by the maximum width of the wound bed in cm^2 [18]. The measurements were documented during the visit.

Statistical analysis

The analysis was performed using intention-to-treat principles.

Continuous variables were reported as mean [95%CI] or median [interquartile range (IQR)]. Categorical data were reported as counts and percentages. Safety assessments included the number, type, and severity of adverse events as outlined in the Common Terminology Criteria for Adverse Events (CTCAE) version 5.

The wound size at the endpoint (time of complete closure or 12 weeks, the earlier of the two) was compared to baseline. Percent wound closure was categorized using a 90% cut-off: closure $\leq 90\%$ or $> 90\%$. For missing data, imputation using last observation carried forward (LOCF) was used.

Normality of distribution was based on Shapiro–Wilk (SW) test of normality ($p > 0.1$). The signed rank test or paired Student *t* test (according to the SW test) was applied for analyzing the change (baseline to endpoint) in wound area within group. The exact Wilcoxon Mann–Whitney *U* (MW-*U*) test or unpaired Student *t* test (according to the SW test) was used to compare baseline wound sizes and percent wound closure between the study groups. Fisher's exact test (FET) was applied for analyzing the differences in percent of patients who demonstrated over 90% wound closure. Unless otherwise specified, all statistical testing was 2-sided and performed using a significance level of 0.05. Post-hoc power analysis for 10 patients in each group achieved 82.3% power at 0.05 significance level to detect a difference between group proportions of 0.6 based on the results of the 90% wound closure contingency table, using the one-sided Fisher's exact test. Statistical analysis was performed by an unaffiliated statistical service company (Medistat inc, Tel-Aviv, Israel) with SAS® v9.3 (SAS Institute, Cary NC, USA).

Results

Accountability

Twenty-one patients participated in the study and were allocated to receive either active irradiation ($n = 11$) or sham ($n = 10$) treatments in addition to standard care. The group allocation code was opened only at the end of the study. Of the 11 patients in the active irradiation group, 1 decided to withdraw prior to receiving treatment and therefore was not included in the analysis. All 20 remaining patients were included in the analysis. See CONSORT diagram of the patient flow through the different stages in Fig. 1.

Baseline characteristics (Table 1 and Table 2)

Twenty ($n = 20$) predominantly elderly patients (average ± SD [range]: age 63 ± 11 [38–88] years, ratio male:female 13:7) that arrived at our clinic had insulin-dependent diabetes type 2 for at least 10 years and were not on a regular follow-up in the community were recruited. Patients were all neuropathic (based on gross sensation test), mostly (18 of 20) with peripheral artery disease (based on pulses palpation and Doppler evaluation), more than half with previous amputations; some had midfoot Charcot with rocker bottom deformity; some underwent previous revascularization procedures and arrived at the clinic in various ambulatory states. After hospitalization, patients were linked to local community diabetes clinics where they were followed on a regular basis and received standard care including offloading and footwear adjustment if required. The patients represented a characteristic population of hospitalized diabetic foot patients which usually suffer from other significant co-morbidities including hypertension, hyperlipidemia, and heart disease as well as varying degrees of renal failure, malnutrition, low hemoglobin, and inflammation. See baseline characteristics by group allocation in Table 1 and individual data in Online Resource Table S1.

All wounds were considered chronic showing no signs of healing with standard care for a minimum of 3 weeks. The median surface area of the wounds was 8 cm^2 (minimum to maximum 3 to 54 cm^2) and was evenly distributed between medium (3–10 cm^2) and large (> 10 cm^2) in both groups. Most wounds appeared on the plantar surface of the foot with more wounds at the forefoot in comparison to the mid- and hind foot. The majority of ulcers were deep

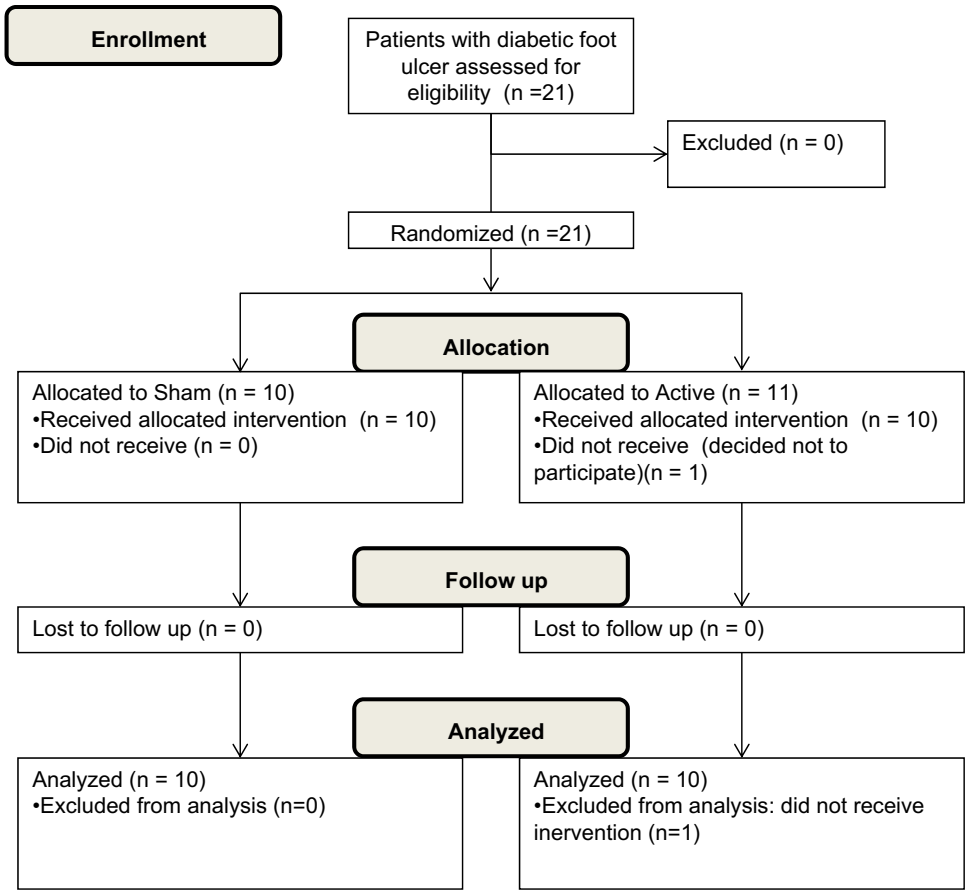

Fig. 1 CONSORT patient flow diagram

with osteomyelitis (determined by probing to bone and/or changes seen by X-ray) or abscess formation (University of Texas grade III A/B). See Table 2 for ulcer characteristics by group allocation and Fig. 2 for examples of 2 ulcers.

Efficacy (Table 3, Fig. 2)

With the numbers available, no significant difference could be detected in baseline wound surface area ($p = 0.81$ by MW-U test). However, a significant reduction in wound area was observed in the active group (wound size [cm^2] median [IQR] baseline vs endpoint: 10 [20.3] vs 0.2 [2.4], $p = 0.002$ by exact sign ranks test) but not in the sham group (7.9 [12.0] vs 4.6 [13.8], $p = 0.63$). Direct comparison of percent closure at the study termination showed a significant healing effect of active laser treatment over sham treatment (%closure, active vs sham, median [IQR]: 97% [20] vs 49% [79],

Table 2 Characteristics and classifications of diabetic foot ulcers

	Sham ($n = 10$)	Active ($n = 10$)	Total ($n = 20$)
Initial surface area of ulcer, median [IQR](range) [cm^2]	7.9 [12.0] (3.8–54.0)	10.0 [20.2] (3.0–25.0)	9.6 [16.0] (3–54.0)
Surface area, *n* (%)			
Medium (3–10 cm^2), large (> 10 cm^2)	5, 5	5, 5	10, 10
Location			
Left : right	6:4	7:3	13:7
Dorsal:Plantar	2:8	1:9	3:17
Forfoot:Midfoot:Hindfoot	5:3:2	6:3:1	11:6:3
Ulcer classifications: University of Texas grading			
Grade IIA: Ulcers penetrates to capsule or bone	1	1	2
Grade IIIA/B: Ulcer that penetrates to bone or a deep abscess	9	9	18

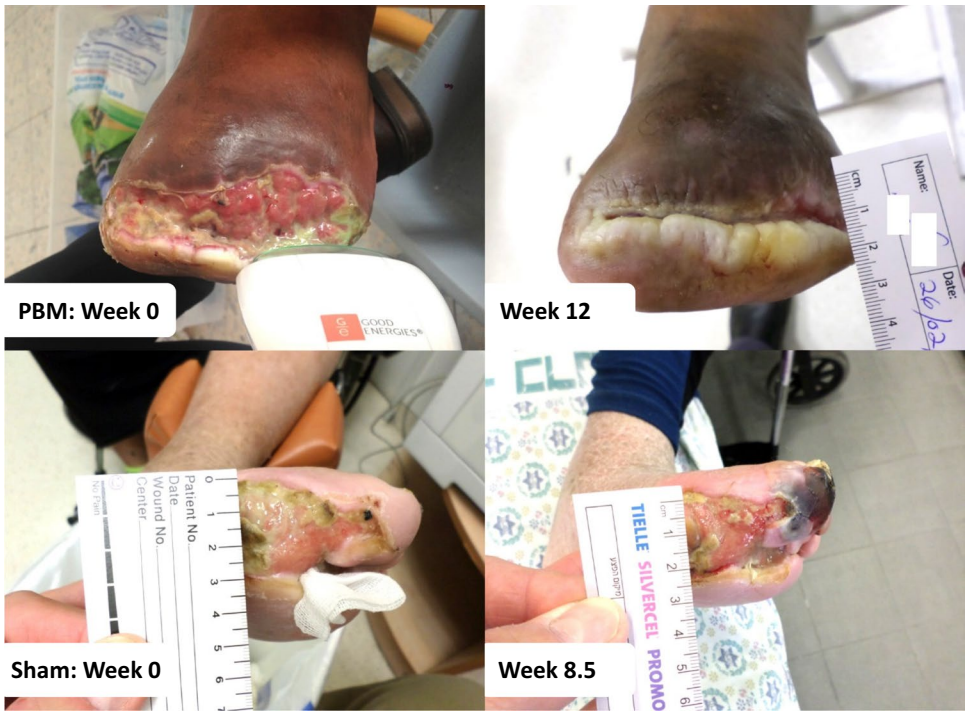

Fig. 2 Diabetic foot ulcers submitted to active or sham photobiomodulation (PBM) treatment at home (before/after). Upper panel: DFU of a patient in their early 70's, treated with active PBM. Laser device seen in the picture. Note near complete closure of the wound at 12 weeks. Lower panel: DFU of a patient in their 50's, treated with sham PBM. Note deterioration of wound by 8.5 weeks that led to transmetatarsal amputation

$p = 0.018$ by MW-U test). The full individual data set can be found in the Online Resource Table S2. See Fig. 2 for an example of DFU from baseline to endpoint in a patient receiving active treatment and a patient receiving sham treatment. Percent wound closure was categorized using a 90% cut-off: closure ≤ 90% or > 90%. At the endpoint, 7 of 10 patients of the active group demonstrated over 90% closure, whereas only 1 patient of 10 of the sham group demonstrated the same ($p = 0.006$ by Fisher's exact test). Complete wound healing was achieved by 5 of 10 patients in the active group but only 1 of 10 patients in the sham group ($p = 0.051$ by Fisher's exact test).

Safety (Table 4)

During the study, 13 adverse events (AEs) were observed in 8 of 20 patients, of which 7 were serious AEs (SAEs) occurring in 6 of the patients. None of the AEs was considered device related. SAEs included 1 death (sham group), 6 hospitalizations of which 2 were due to infection leading to amputation (both in the sham group), 1 due to deterioration of the ulcer that did not lead to amputation, 1 was due to arterial occlusion that required catheterization, and 2 were not related to the wound including a psychotic attack on the background of schizophrenia and development of an ulcer on the untreated leg. Adverse events that were not considered SAEs included ulcer infection, burning sensation in area of treatment (that occurred in a sham patient), and development of necrotic tissue that required debridement. The total number of AEs and SAEs per group was 2 and 3, respectively, for the active group, and 4 and 4, respectively, for the control group. See Table 4 for a summary of safety events by group.

Table 3 Wound area – baseline vs endpoint

	Sham ($n = 10$)				Active ($n = 10$)				
	Baseline	Endpoint	%Closure	p*	Baseline	Endpoint	%Closure	p*	p**
Median [IQR]	7.9 [12.0]†	4.6 [13.8]	49.4 [79.1]	0.625	10 [20.3]	0.2 [2.4]	97.3 [20.0]	0.002	0.018
Range	3.8 to 54.0	0.0 to 66.5	− 275 to 100		3.0 to 25	0.0 to 6.0	31.3 to 100		
Mean ± SD	15.5 ± 17.1	12.5 ± 20.2	16.7 ± 110.4	0.470	12.4 ± 9.2	1.5 ± 2.4	84.6 ± 24.4	0.006	0.087
Lower, upper 95%CI	3.2, 27.7	− 1.9, 26.9	− 62.3, 95.6		5.8, 19.0	-0.2, 3.2	67.1, 102.1		

All measurements in cm^2 *baseline vs endpoint, 2-sided paired test – sign rank test for median, paired Student t test for mean; **active vs sham – 2-sided unpaired test – Wilcoxon Mann–Whitney U test for median, unpaired Student t test for mean with separate variances as determined by Levine's test for equality of variances; †$p = 0.81$

Table 4 Safety results by group

	Description	CTCAE (Grade)	Sham	Active
Adverse events	Infection	Severe (G-3)	3	1
	Ischemia	Severe (G-3)	0	1
	Burning sensation	Mild (G-1)	1	0
	Total		4	2
Serious adverse events	Death	Severe (G-5)	1	0
	Hospitalization – infection leading to amputation	Severe (G-4)	2	0
	Hospitalization – deterioration of wound not leading to amputation	Severe (G-3)	0	1
	Hospitalization – occlusion of vessel requiring catheterization	Severe (G-3)	1	0
	Hospitalization – general, not related to treated wound	Severe (G-3)	0	2
	Total		4	3

Discussion

This is the first double-blind randomized controlled study that evaluates the safety and usefulness of daily photobiomodulation treatments with the B-Cure Laser at home for the treatment of DFUs in a frail population of patients with diabetes and severe comorbidities. With the limitation of the small sample size, we report that this treatment protocol was safe and effective. No device-related adverse events were observed, and percent closure was significantly greater in the active group compared to sham-treated controls.

Safety

The issue of safety related to photobiomodulation for treatment of DFUs was examined in each of 12 previous randomized controlled trials [10–17, 19–22] including more than 450 patients. Similar to our findings, no adverse device effects (ADEs) were reported in any of those studies, even in a case series report of patients with severe DFUs (MW grade III–IV) [23]. Moreover, previous studies using the same device as the one used in this study also did not report any ADEs. In those studies, PBM was applied up to twice daily for 1–3 weeks at home for other indications including pain reduction related to temporomandibular disorder [24, 25] and treatment of postoperative paresthesia [26]. Finally, studies with other home-use PBM devices that also included multiple frequent treatment administrations for various indications (e.g. pain and related symptoms, cognitive dysfunction, wound healing, diabetic macular edema, and post-procedural side effects, reviewed in [27]), also reported no ADEs, further supporting the lack of device-related complications seen in the current study.

Efficacy and practical considerations

Favorable effects of PBM on diabetic foot ulcer, including accelerated healing and/or increased incidence of complete closure, were shown previously [10, 11, 13–17, 19–22]. It should be pointed out that the treatment protocols in those studies required frequent visits to the clinic, mostly daily or 3 times a week. Such frequency is difficult to achieve in a real-life situation both because arriving to the clinic is difficult for patients with DFUs and because of the limited availability and time required of the clinical team to administer the treatment.

Recently, 2 reports described the application of the same device used in this study for the treatment of diabetic ulcers by the patients themselves achieving complete healing. In both reports, the patients were elderly (67–84 years old) and had various co-morbidities, albeit not renal failure, and ulcers were less severe, not involving osteomyelitis. Raizman and Gavish [28] describe 4 patients with diabetic wounds that self-treated with the study device 3–5 sessions a week for 6–10.5 min per session until closure of the wounds 1–3 weeks after onset of treatment. Merigo et al. [29] describe a single patient with several diabetic ulcers that used the device daily, twice a day for 15 min each session, during 30 days until achieving complete healing. In the current study, the treatment was administered at home, albeit by a professional caregiver, thus avoiding the necessity of visiting the clinic, but still benefitting from trained personnel.

This treatment is not part of the medical insurance, and it is therefore important to be aware of the cost for the patient. Since the treatments are self-applied, the only expense is the device itself which may reach up to $900 (according to the manufacturer) depending on the payment model (rented or bought). In other indication (i.e., after dental procedures), certain clinics and hospitals lend out devices (G. Ross and C. Fornaini, personal communications).

Mechanisms

Healing of the DFU is impaired by neuropathy and by compromised micro- and macro-circulatory perfusion leading to local hypoxic conditions and excessive inflammation [30]. The compromised perfusion around the DFU is due

in part to diabetic-related red blood cell deformation [31] and aggregation in rouleau structures [32] that obstruct and finally destroy the capillary beds [33]. There are several known biological effects of PBM that may explain the favorable results on diabetic wound healing seen in this study and reported by others. In vitro, PBM was shown to stimulate vascular cell proliferation including endothelial cells [34–36], smooth muscle cell [37], and fibroblasts [38, 39]; induce VEGF secretion [40]; and stimulate nitric oxide release and gene expression of NO synthase (NOS) [35, 41]. PBM was also shown to stimulate proliferation, migration, and collagen production, as well as to reduce apoptosis and pro-inflammatory cytokines in experimental settings of cell cultures grown in high concentration of glucose [9]. In studies of streptozotocin-induced diabetes in rats, PBM was shown to improve tensiometric properties within healing wounds [42] and protect against excessive inflammatory tissue response [43].

PBM may attenuate compromised perfusion based on the following findings: In vitro, PBM was shown to improve RBC deformity [44]. Ex vivo, PBM was shown to increase vasodilatation in blood vessels of diabetic mice that was abolished after addition of NOS inhibitor or after denuding the vessels from the endothelial cells [45]. In vivo, PBM was found to restore vasodilatation in a diabetic mouse model of endothelial dysfunction [45] and stimulate angiogenesis in a flap model in diabetic rats [46]. In humans, PBM was shown to improve the microcirculatory blood flow by inducing arteriolar vasodilatation that results in both immediate and long-lasting increased capillary flow and tissue perfusion in healthy individuals [47, 48] and in patients with diabetes [49, 50]. As in animal studies, in humans, this effect was found to be abolished with nitric oxide (NO) inhibitors [48, 49].

Thus, by re-establishing tissue perfusion in the vicinity of the wound, reducing inflammation, and increasing vascular cell proliferation and angiogenesis, PBM may positively affect the metabolism of the surrounding cells, thereby promoting active and accelerated healing.

Pilot trial limitations

First, the 12-week time frame of the study was determined according to FDA guidelines for evaluation of interventions for treatment of chronic wounds including diabetic foot ulcer [51]. However, this time frame was not sufficient to achieve complete wound healing in many of these complicated cases – only 5 of 10 cases of the active group were completely healed by 12 weeks, but additional 2 cases had 90–95% healing at that time point indicating that additional time would have potentially allowed additional wounds to complete closure. Second, the number of study participants was small, and therefore, in order to reach conclusive evidence, a larger study should be conducted. The sample size of the future study will be based on the results found in this pilot study. Finally, the ruler technique that was used in this study to assess the wound size is the most commonly used method in the clinic for this purpose but is imprecise for ulcers of irregular shapes and might have rendered some of the measurements inaccurate. However, all measurements were conducted under blinding and therefore are not expected to insert bias of one group over the other.

Conclusions

In summary, the findings from this small double-blind randomized proof of concept clinical trial support the view that photobiomodulation at home in addition to standard care is safe in patients with severe diabetic foot ulcers and co-morbidities. The encouraging results of efficacy add to growing evidence in the literature indicating the usefulness of this modality for the treatment of diabetic foot ulcers. Transferring the treatment from the clinic to the patient's home is both feasible and convenient for the patient, promoting improved compliance and cost-effectiveness as well as increases patient safety, particularly at these times of social distancing and self-isolation of frail elderly patients with diabetes. Our preliminary results justify the conduction of a larger clinical trial.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10103-021-03335-9.

Acknowledgements We would like to thank Vladimir Heiskanen of the University of Helsinki for access to the photobiomodulation comprehensive database (http://www.bitly.com/PBM-database).

Author s' contribution AH, OE, TT, YNG, and ML conceived the study and designed the trial; AH, OE, and TT were responsible for patient recruitment and clinical evaluations, DS was involved with the treatment and collected data, LG validated and analyzed the data, conducted literature review, and together with AH drafted the original manuscript. AH, TT, YNG, LG, and ML reviewed the manuscript critically. AH takes responsibility for the paper as a whole. All authors gave final approval for the version to be published.

Funding The manufacturer of the device provided active/sham devices and payment for third-party services (caregivers, statistical analysis) and provided a camera for the study. The manufacturer was not involved in the collection or analysis of the data.

Code availability Not applicable.

Declarations

Ethics approval This clinical trial (ClinicalTrials.gov: NCT01493895) was approved by the clinical trial ethical review board of The Hadassah Medical Organization (0122–11-HMO) prior to recruitment.

Consent to participate. All patients provided written informed consent before entering the study.

Consent for publication Figure 2 contains feet from 2 patients. The pictures were taken during 2014. Both patients are deceased; one died in 2015 and the other in 2018. The text was anonymized by omitting the exact age and gender from the legend. There is no additional identifiable data in the photos.

Data sharing The individual measurements collected in this study and details of diabetes status and care (according to Jeffcoat et al. [3]) are reported in Supplementary Tables S1 and S2.

Conflict of interest LG is paid as a consultant by the manufacturer of the device to give recommendations for treatment protocols. This was not relevant in this study. All other authors declare no competing interests.

References

1. Armstrong DG, Boulton AJM, Bus SA (2017) Diabetic foot ulcers and their recurrence. N Engl J Med 376(24):2367–2375. https://doi.org/10.1056/NEJMra1615439
2. Thorud JC, Plemmons B, Buckley CJ, Shibuya N, Jupiter DC (2016) Mortality after nontraumatic major amputation among patients with diabetes and peripheral vascular disease: a systematic review. J Foot Ankle Surg 55(3):591–599. https://doi.org/10.1053/j.jfas.2016.01.012
3. Jeffcoate WJ, Vileikyte L, Boyko EJ, Armstrong DG, Boulton AJM (2018) Current challenges and opportunities in the prevention and management of diabetic foot ulcers. Diabetes Care 41(4):645–652. https://doi.org/10.2337/dc17-1836
4. Everett E, Mathioudakis N (2018) Update on management of diabetic foot ulcers. Ann N Y Acad Sci 1411(1):153–165. https://doi.org/10.1111/nyas.13569
5. Tchanque-Fossuo CN, Ho D, Dahle SE, Koo E, Isseroff RR, Jagdeo J (2016) Low-level light therapy for treatment of diabetic foot ulcer: a review of clinical experiences. J Drugs Dermatol 15(7):843–848
6. Chung H, Dai T, Sharma SK, Huang YY, Carroll JD, Hamblin MR (2012) The nuts and bolts of low-level laser (light) therapy. Ann Biomed Eng 40(2):516–533. https://doi.org/10.1007/s10439-011-0454-7
7. Anders JJ, Lanzafame RJ, Arany PR (2015) Low-level light/laser therapy versus photobiomodulation therapy. Photomed Laser Surg 33(4):183–184. https://doi.org/10.1089/pho.2015.9848
8. Gavish L (2013) Chapter 50: Low-Level laser therapy for wound healing. In: Hamblin M, Huang Y (eds) Handbook of Photomedicine. Boca Raton: CRC Press.,
9. Houreld NN (2014) Shedding light on a new treatment for diabetic wound healing: a review on phototherapy. ScientificWorldJournal 2014:398412. https://doi.org/10.1155/2014/398412
10. Carvalho AF, Feitosa MC, Coelho NP, Rebelo VC, Castro JG, Sousa PR, Feitosa VC, Arisawa EA (2016) Low-level laser therapy and Calendula officinalis in repairing diabetic foot ulcers. Rev Esc Enferm USP 50(4):628–634. https://doi.org/10.1590/S0080-623420160000500013
11. El-Kader S, M., Ashmawy E, M. (2015) Impact of different therapeutic modalities on healing of diabetic foot ulcers. Eur J Gen Med 12(4):319–325
12. Feitosa MC, Carvalho AF, Feitosa VC, Coelho IM, Oliveira RA, Arisawa EA (2015) Effects of the low-level laser therapy (LLLT) in the process of healing diabetic foot ulcers. Acta Cir Bras 30(12):852–857. https://doi.org/10.1590/S0102-86502015012000010
13. Mathur RK, Sahu K, Saraf S, Patheja P, Khan F, Gupta PK (2017) Low-level laser therapy as an adjunct to conventional therapy in the treatment of diabetic foot ulcers. Lasers Med Sci 32(2):275–282. https://doi.org/10.1007/s10103-016-2109-2
14. Ortíz MCS, Villabona EH, Lemos DMC, Castellanos R (2014) Effects of low level laser therapy and high voltage stimulation on diabetic wound healing. Rev Univ Ind Santander Salud [online] 46(2):107–117
15. Frangez I, Nizic-Kos T, Frangez HB (2018) Phototherapy with LED shows promising results in healing chronic wounds in diabetes mellitus patients: a prospective randomized double-blind study. Photomed Laser Surg 36(7):377–382. https://doi.org/10.1089/pho.2017.4382
16. Priyadarshini LMJ, Babu KEP, Thariq IA (2018) Effect of low level laser therapy on diabetic foot ulcers: a randomized control trial. Int Surg J 5(3):1008–1015
17. Sangma MB, Selvaraju S, Marak F, Dasiah SD (2019) Efficacy of low level infrared light therapy on wound healing in patients with chronic diabetic foot ulcers: a randomised control trial. Int Surg J 6(5):1650–1653
18. Flanagan M (2003) Wound measurement can it help us to monitor progression to healing? J Wound Care 12(5):189–194. https://doi.org/10.12968/jowc.2003.12.5.26493
19. Kajagar BM, Godhi AS, Pandit A, Khatri S (2012) Efficacy of low level laser therapy on wound healing in patients with chronic diabetic foot ulcers-a randomised control trial. Indian J Surg 74(5):359–363. https://doi.org/10.1007/s12262-011-0393-4
20. Kaviani A, Djavid GE, Ataie-Fashtami L, Fateh M, Ghodsi M, Salami M, Zand N, Kashef N, Larijani B (2011) A randomized clinical trial on the effect of low-level laser therapy on chronic diabetic foot wound healing: a preliminary report. Photomed Laser Surg 29(2):109–114. https://doi.org/10.1089/pho.2009.2680
21. Landau Z, Migdal M, Lipovsky A, Lubart R (2011) Visible light-induced healing of diabetic or venous foot ulcers: a placebo-controlled double-blind study. Photomed Laser Surg 29(6):399–404. https://doi.org/10.1089/pho.2010.2858
22. Minatel DG, Frade MA, Franca SC, Enwemeka CS (2009) Phototherapy promotes healing of chronic diabetic leg ulcers that failed to respond to other therapies. Lasers Surg Med 41(6):433–441. https://doi.org/10.1002/lsm.20789
23. Maiya AG, Kumar AS, Hazari A, Jadhav R, Ramachandra L, Hande HM, Rajgopal SK, Maiya SG, Kalkura P, Keni LG (2018) Photobiomodulation therapy in neuroischaemic diabetic foot ulcers a novel method of limb salvage. J Wound Care 27(12):837–842. https://doi.org/10.12968/jowc.2018.27.12.837
24. Del Vecchio A, Floravanti M, Boccassini A, Gaimari G, Vestri A, Di Paolo C, Romeo U (2019) Evaluation of the efficacy of a new low-level laser therapy home protocol in the treatment of temporomandibular joint disorder-related pain: a randomized, double-blind, placebo-controlled clinical trial. Cranio:1–10. https://doi.org/10.1080/08869634.2019.1599174
25. Fornaini C, Pelosi A, Queirolo V, Vescovi P, Merigo E (2015) The "at-home LLLT" in temporo-mandibular disorders pain control: a pilot study. Laser therapy 24(1):47–52. https://doi.org/10.5978/islsm.15-OR-06

26. Merigo E, Rocca JP, Oppici A, Cella L, Fornaini C (2017) At-home laser treatment of oral neuronal disorders: Case reports. J Clin Exp Dent 9(4):e595–e598. https://doi.org/10.4317/jced.53373
27. Gavish L, Houreld NN (2019) Therapeutic efficacy of home-use photobiomodulation devices: a systematic literature review. Photobiomodul Photomed Laser Surg 37(1):4–16. https://doi.org/10.1089/photob.2018.4512
28. Raizman R, Gavish L (2020) At-home self-applied photobiomodulation device for the treatment of diabetic foot ulcers in adults with type 2 diabetes: report of 4 cases. Can J Diabetes 44(5):375–378. https://doi.org/10.1016/j.jcjd.2020.01.010
29. Merigo E, Tan L, Zhao Z, Rocca J-P, Fornaini C (2020) Auto-administered photobiomodulation on diabetic leg ulcers treatment: a new way to manage it? Case Rep Med 2020:7428472. https://doi.org/10.1155/2020/7428472
30. Davis FM, Kimball A, Boniakowski A, Gallagher K (2018) Dysfunctional wound healing in diabetic foot ulcers: new crossroads. Curr Diab Rep 18(1):2. https://doi.org/10.1007/s11892-018-0970-z
31. Buys AV, Van Rooy MJ, Soma P, Van Papendorp D, Lipinski B, Pretorius E (2013) Changes in red blood cell membrane structure in type 2 diabetes: a scanning electron and atomic force microscopy study. Cardiovasc Diabetol 12:25. https://doi.org/10.1186/1475-2840-12-25
32. Ziegler O, Guerci B, Muller S, Candiloros H, Mejean L, Donner M, Stoltz JF, Drouin P (1994) Increased erythrocyte aggregation in insulin-dependent diabetes mellitus and its relationship to plasma factors: a multivariate analysis. Metabolism 43(9):1182–1186. https://doi.org/10.1016/0026-0495(94)90063-9
33. Singh M, Shin S (2009) Changes in erythrocyte aggregation and deformability in diabetes mellitus: a brief review. Indian J Exp Biol 47(1):7–15
34. Schindl A, Merwald H, Schindl L, Kaun C, Wojta J (2003) Direct stimulatory effect of low-intensity 670 nm laser irradiation on human endothelial cell proliferation. Br J Dermatol 148(2):334–336
35. Chen CH, Hung HS, Hsu SH (2008) Low-energy laser irradiation increases endothelial cell proliferation, migration, and eNOS gene expression possibly via PI3K signal pathway. Lasers Surg Med 40(1):46–54
36. Kipshidze N, Nikolaychik V, Keelan MH, Shankar LR, Khanna A, Kornowski R, Leon M, Moses J (2001) Low-power helium: neon laser irradiation enhances production of vascular endothelial growth factor and promotes growth of endothelial cells in vitro. Lasers Surg Med 28(4):355–364
37. Gavish L, Perez L, Gertz SD (2006) Low-level laser irradiation modulates matrix metalloproteinase activity and gene expression in porcine aortic smooth muscle cells. Lasers Surg Med 38(8):779–786. https://doi.org/10.1002/lsm.20383
38. Hawkins D, Abrahamse H (2006) Effect of multiple exposures of low-level laser therapy on the cellular responses of wounded human skin fibroblasts. Photomed Laser Surg 24(6):705–714. https://doi.org/10.1089/pho.2006.24.705
39. Houreld N, Abrahamse H (2007) Irradiation with a 632.8 nm helium-neon laser with 5 J/cm2 stimulates proliferation and expression of interleukin-6 in diabetic wounded fibroblast cells. Diabetes Technol Ther 9(5):451–459
40. Tuby H, Maltz L, Oron U (2006) Modulations of VEGF and iNOS in the rat heart by low level laser therapy are associated with cardioprotection and enhanced angiogenesis. Lasers Surg Med 38(7):682–688. https://doi.org/10.1002/lsm.20377
41. Gavish L, Perez LS, Reissman P, Gertz SD (2008) Irradiation with 780 nm diode laser attenuates inflammatory cytokines but upregulates nitric oxide in lipopolysaccharide-stimulated macrophages: implications for the prevention of aneurysm progression. Lasers Surg Med 40(5):371–378. https://doi.org/10.1002/lsm.20635
42. Bagheri M, Amini A, Abdollahifar MA, Ghoreishi SK, Piryaei A, Pouriran R, Chien S, Dadras S, Rezaei F, Bayat M (2018) Effects of photobiomodulation on degranulation and number of mast cells and wound strength in skin wound healing of streptozotocin-induced diabetic rats. Photomed Laser Surg 36(8):415–423. https://doi.org/10.1089/pho.2018.4453
43. Kilik R, Lakyova L, Sabo J, Kruzliak P, Lacjakova K, Vasilenko T, Vidova M, Longauer F, Radonak J (2014) Effect of equal daily doses achieved by different power densities of low-level laser therapy at 635 nm on open skin wound healing in normal and diabetic rats. Biomed Res Int 2014:269253. https://doi.org/10.1155/2014/269253
44. Mi XQ, Chen JY, Liang ZJ, Zhou LW (2004) In vitro effects of helium-neon laser irradiation on human blood: blood viscosity and deformability of erythrocytes. Photomed Laser Surg 22(6):477–482. https://doi.org/10.1089/pho.2004.22.477
45. Keszler A, Lindemer B, Weihrauch D, Jones D, Hogg N, Lohr NL (2017) Red/near infrared light stimulates release of an endothelium dependent vasodilator and rescues vascular dysfunction in a diabetes model. Free Radic Biol Med 113:157–164. https://doi.org/10.1016/j.freeradbiomed.2017.09.012
46. Santos NR, dos Santos JN, dos Reis JA, Jr., Oliveira PC, de Sousa AP, de Carvalho CM, Soares LG, Marques AM, Pinheiro AL, (2010) Influence of the use of laser phototherapy (lambda660 or 790 nm) on the survival of cutaneous flaps on diabetic rats. Photomed Laser Surg 28(4):483–488. https://doi.org/10.1089/pho.2009.2500
47. Gavish L, Hoffer O, Rabin N, Halak M, Shkilevich S, Shayovitz Y, Weizman G, Haim O, Gavish B, Gertz SD, Ovadia-Blechman Z (2020) Microcirculatory response to photobiomodulation – why some respond and others do not: a randomised controlled study. Lasers Surg Med 52(9):863–872
48. Samoilova KA, Zhevago NA, Petrishchev NN, Zimin AA (2008) Role of nitric oxide in the visible light induced rapid increase of human skin microcirculation at the local and systemic levels II healthy volunteers. Photomed Laser Surg 26(5):443–449. https://doi.org/10.1089/pho.2007.2205
49. Samoilova KA, Zhevago NA, Menshutina MA, Grigorieva NB (2008) Role of nitric oxide in the visible light induced rapid increase of human skin microcirculation at the local and systemic level I diabetic patients. Photomed Laser Surg 26(5):433–442. https://doi.org/10.1089/pho.2007.2197
50. Schindl A, Schindl M, Schon H, Knobler R, Havelec L, Schindl L (1998) Low-intensity laser irradiation improves skin circulation in patients with diabetic microangiopathy. Diabetes Care 21(4):580–584
51. Administration FaD (June 2006) Guidance for industry chronic cutaneous ulcer and burn wounds — developing products for treatment. Rockville, MD