Biomodulation induced by fluorescent light energy versus standard of care in venous leg ulcers: a retrospective study

Objective: The recently completed EUREKA study confirmed the efficacy and safety profile of fluorescent light energy (FLE) in treating hard-to-heal wounds. To supplement the EUREKA prospective, observational, uncontrolled trial results, researchers selected one of the EUREKA clinical centres to conduct a retrospective analysis of matching wound care data for 46 venous leg ulcers (VLU) patients who had received standard wound care over a five-year period, compared with 10 EUREKA VLU subjects.
Method: The study centre selected 46 patients with VLUs based on the matching criteria (wound age and size, patient's age and gender). They compared the healing rates of these matching VLUs with 10 VLU patients treated at the same centre during the EUREKA study.
Results: The EUREKA patients had larger and significantly older wounds ($p<0.05$) and significantly more risk factors ($p<0.05$) than the matching wounds. However, they had better outcomes (EUREKA: 40% versus matching group: 7% for full wound closure by 16 weeks). No wound breakdown was observed at 16 weeks in the EUREKA group, compared with 25% in the matching group. No EUREKA patient developed infections requiring antibiotics, compared with 37% in the matching group. EUREKA wounds had a mean relative wound area regression (RWAR) of 32% at week six and 50% at week 16, compared with –3% at week six and –6% at week 16 for the matching group.
Conclusion: These findings show that the system based on FLE was well-tolerated and efficacious, with better clinical outcome results compared with the wounds analysed in this retrospective matching study and treated with standard of care alone.
Declaration of interest: S. Fauverghe is an employee of KLOX Technologies. M. Romanelli and V. Dini are medical consultants for KLOX Technologies. The authors have no other conflicts of interest.

biophotonics • chromophores • fluorescence biomodulation • fluorescent light energy • FLE • hard-to-heal wounds • light • photoacceptors • photobiomodulation therapy • phototherapy • venous leg ulcers

Hard-to-heal wounds present significant challenges to physicians worldwide, impose a significant financial burden on the health-care system and contribute to morbidity and mortality, particularly in ageing populations.[1] For populations aged 45–65 years, the incidence of hard-to-heal wounds is estimated at 120 per 100,000 people, and increases to 800 per 100,000 people over 75 years of age.[2–4] Venous leg ulcers (VLU) are the most common hard-to-heal wounds, accounting for 80% of cases[5,6] and recurring in 70% of cases, with a median time-to-ulcer recurrence of 60 days.[7,8] VLUs occur when inadequate venous return results in sustained venous hypertension in the lower leg. This chronic condition, the prevalence of which increases with age,[9] has numerous consequences involving inappropriate remodelling of venous vessels and dermal inflammatory alterations, leading to superficial tissue breakdown and ulcerations. This latter complication contributes to greatly reduced quality of life (QoL) for affected patients,[10] justifying the high need for improving therapeutic strategies, in addition to efficient venous compression.

In several experiments and controlled studies, low energy level light (LELL) treatments, such as photobiomodulation (PBM)[11–14] showed promise as therapies for the treatment of hard-to-heal wounds by stimulating the wound healing processes.[15] Fluorescence biomodulation (FB), a form of PBM, is induced by the delivery of fluorescent light energy (FLE) to the skin with a dual-component treatment system: a gel containing chromophores illuminated by an LED lamp. The photons absorbed by the tissue endogenous photoacceptors initiate a cascade of molecular reactions that stimulate the natural wound healing process and have a positive effect on all phases of wound healing (inflammation, proliferation and remodelling).[16]

Studies using FLE on VLUs showed improved healing, particularly for medium- and large-sized ulcers.[18] In addition, the European Wound Management Association (EWMA) guidelines on advanced therapies in wound management stated that enough evidence exists to show PBM's positive action on all phases of wound repair from the first inflammatory stage to the remodelling phase. These guidelines also referenced the EUREKA interim results in describing the positive effects

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of a treatment system based on PBM for the healing of hard-to-heal wounds.[17]

During the EUREKA clinical study ('Evaluation of real-life use of KLOX BioPhotonic System in chronic wound management'), 99 subjects, 52 of whom had VLUs, were recruited during a 15-month period and treated with a FB system. This multicentre, prospective, observational, uncontrolled trial was an evaluation of FLE under real-life conditions and the system consisted of a photo-converter wound gel (known by the brand name of LumiHeal) that contains specific chromophores) to be illuminated by a multi-LED lamp. The EUREKA study[10] was designed to confirm the efficacy and safety of the treatment, to improve QoL in treated subjects, and to determine the system's usability by health professionals. The final results of the EUREKA study confirmed the preliminary analysis, which showed that the system was well tolerated, efficacious (50% of patients with VLUs achieved total wound closure, with a median wound area reduction of 94% at the last study visit, $p<0.001$) and significantly improved QoL using the Cardiff Wound Impact Schedule (CWIS) validated questionnaire (15.4%, $p<0.001$). In addition, the final analysis showed that, after four weeks of treatment, it was possible to significantly predict if the ulcer would decrease in size in response to the study treatment. In the EUREKA study, 81% of the VLUs responded to treatment with a decrease of their wound size area, with 62% of these wounds achieving full closure in the VLU group.

The original EUREKA clinical study using the FLE treatment system together with standard wound care was completed in December 2016. While the study showed an excellent safety and tolerability profile, as well as showing efficacy for VLU patients, the lack of a control group prevented comparison of the results using the FLE system with patients receiving only the standard of care (SoC) at the same centre. This matching retrospective analysis of medical records for patients who presented for an initial VLU assessment over a period of five years partially alleviates this limitation.

The Wound Care Center in Pisa, Italy, one of the clinical trial centres participating in EUREKA, was selected for a retrospective analysis of matching wound care data over a five-year period (2013–2017) for matching patients receiving standard wound care. They identified 46 wounds (the 'matching group') and compared them with the 10 EUREKA study subjects (the 'EUREKA group') who were diagnosed with VLUs at the same centre.

Methods

This study was conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki, ICH/GCPs & ISO 14155:2011 and all applicable local/national regulatory requirements.

Study design and patients

All of the EUREKA study participants from the selected centre (10 in total) were included in the retrospective study. All of these patients were treated for VLUs using FLE plus SoC.

The retrospective study included patients who presented and were treated at the selected centre over a five-year period for VLUs using the centre's SoC. For each patient in the EUREKA trial, every effort was made to match at least three patients with the same characteristics (±20% for continuous variables) of age, gender, age in months of VLU at initial review time-point and size of VLU at initial review time-point, based on the computerised source documents of the centre.

Because all the wounds were treated in the same centre, both groups received similar SoC, mainly dressings (foam/alginate/hydrocolloid/ hydrogel/ hydrofiber), compression (two-layer venous compression bandages, except two patients with one-layer) and regular visits at the hospital. Only the EUREKA group received the FLE treatment system.

A screening database was created, from which 46 patients were identified as meeting the following inclusion criteria:

- Diagnosis of VLU (open leg ulcer with the presence of a venous disease)
- Male or female, 18–85 years of age, ambulatory or hospitalised
- Phototype I to IV based on the Fitzpatrick scale
- Area of ulcer to be treated available in the source documents and between 5–100cm^2 at the first treatment visit.

Patients were excluded from the retrospective matching list under the following conditions:

- Leg ulcers due to mixed vascular disorders
- Wounds grafted or previously or currently treated with FLE
- History of malignancy within the wound or patient with prior diagnosis of malignancy who was less than one-year disease-free
- History of radiation therapy to the wound region.

An independent statistician (Vertical, Paris) reviewed and approved the list of 46 matching wounds.

Once the records were selected, investigators collected specific retrospective data from the source documents for each eligible wound in each analysed record. The form collected the following data:

- Matching of the wounds with the EUREKA wounds they were paired with
- Demography (men/women, patient's age, Body Mass Index (BMI))
- Clinically significant medical history
- Wound characteristics (size and age at the first date of the retrospective analysis)
- Number of prognostic factors of poor healing at study entry (based on initial wound age and wound size)
- Previous wound treatments, including SoC and advanced wound care
- Wound treatments, including SoC, during the retrospective observational period
- Wound trajectories (area in cm^2)

Table 1. Patient demographics (gender and age) at initial treatment visit, all groups

Population	Number	Gender	Mean age at 1st treatment visit (years)	Age at 1st treatment visit (years)	
				<75	≥75
EUREKA group	10	Female: 30% (3) Male: 70% (7)	71.8 (50.8 –85.5)	50.0% (5)	50.0% (5)
Matching group	46	Female: 76.1% (35) Male: 23.9% (11)	72.5 (45.0 – 86.0)	47.8% (22)	51.8% (24)

Source: CL-K1002-P015 database

- Wound breakdowns (if the wound closed during the period of observation)
- Number of wound infections requiring a topical or systemic antibiotic treatment.

Though QoL questionnaires were collected from the patients who participated in the EUREKA study, these data were not available in the patients' charts of the matching group and therefore were not included in this analysis.

Statistical methods

The sample size of the matching group was selected from the list of patient records that met the inclusion criteria and that matched (to the extent possible) with the 10 EUREKA VLUs treated at the selected centre.

The collected data were analysed by an independent statistician using the following variables:

- Matching of the wounds with EUREKA wounds
- Rate of wound closure
- Relative wound area regression (RWAR) over time
- Percentage of wound breakdown after wound closure (if data available)
- Rate of wound infections.

RWAR was analysed using paired t-tests and a $p<0.05$ was considered as statistically significant.

A Kaplan-Meier analysis (survival functions) was used to estimate the mean time of wound closure for all wounds. A regression analysis was also performed to extrapolate RWAR from baseline at week six and week 16. These analyses were conducted using SPSS software package (IBM Inc., US).

Results

Of the selected patient records, 46 were deemed as matching the 10 EUREKA patients. Table 1 shows the relative demographics of each population.

Patients were closely age-matched (a mean difference of <1 year) and there was a mean difference of only 11.2%, within the authorised ranges, between the two groups in terms of wound area. The size of the VLUs in the matching group was on average 16.6 cm^2 at baseline, compared with an average of 18.7cm^2 in the EUREKA group.

Despite all efforts to recruit patients with wounds that matched the EUREKA VLUs, on average, the EUREKA group had older wounds than the matching group at baseline, with the EUREKA group averaging 6.3 months versus 3.2 months for the matching group (Table 2 shows the wound areas and wound age at baseline). Gender distribution was reversed between the two groups. In the EUREKA group, 30% of patients were female, compared with 70% female in the matching group. As gender is not recognised as having an impact on the management of VLUs,[21] the sponsor decided to keep the selected matching patients, the most important criteria being the wounds characteristics (age and size) and subjects' age.

The method for analysing prognostic factors of poor wound healing developed by Margolis et al.,[17–20] was used to identify the healing prognostic of VLUs based on two criteria: area >10cm^2 and ulcer age at study entry (>6 months). Overall, the wounds of the EUREKA group had a higher prognostic factor of poor healing than the matching group at the first treatment visit. Results showed that 65% of the matching wounds had at least one of the prognostic factors of poor wound healing, compared with 100% of the wounds of the EUREKA group ($p<0.05$). Of the matching group, 35% of the wounds had no prognostic factors of poor healing at baseline. Most of the wounds in the two groups (90% of the EUREKA wounds and 63% in the matching group) had a surface area of >10cm^2 at first study visit. Of the wounds in the EUREKA group, 50% were >6 months old at the first study visit, compared with 17% of the matches ($p<0.05$) (Table 3).

Table 2. Wound area and wound duration at initial treatment visit, all groups

	EUREKA group (n=10)	Matching group (n=46)
Wound area (cm^2)		
Mean±SD	18.7±9.0	16.6±11.6
Median	16.1	12.2
Range	7.4–35.0	5.5–49.2
Wound age at first visit (months)		
Mean±SD	6.3±3.7	3.2±2.8
Median	6.9	2.5
Range	0.04–11.1	0.46–12.0

Source: CL-K1002-P015 database; SD—standard deviation

Table 3. Wound area, wound age categories and risk factors at initial treatment visit, all groups

Population	Number	Wound area class		Wound age class		Risk factors*	
		≤10cm²	>10cm²	<6 months	≥6 months	None	1 or 2
EUREKA group	10	10% (1)	90% (9)	50% (5)	50% (5)	0% (0)	100% (10)
Matching group	46	37% (17)	63% (29)	82.6% (38)	17.4% (8)	34.8% (16)	65.2% (30)
p-values	–	–		p<0.05 (EUREKA wounds significantly older)		p<0.05 (EUREKA wounds considered significantly harder to heal)	

Source: CL-K1002-P015 database. *Risk factors as defined by Margolis et al.[19–21]

Table 4. Patient demographics (BMI) at initial treatment visit, all groups

Population	Number	Mean BMI at 1st treatment visit (kg/m²)	Median BMI at 1st treatment visit (kg/m²)	BMI at 1st treatment visit (kg/m²)	
				<25	≥25
EUREKA group	10	28.2 (23.7–41.9)	26.0	30.0% (3)	70.0% (7)
Matching group	46	23.7 (19.5–29.1)	23.6	71.7% (33)	28.3% (13)

Source: CL-K1002-P015 database. BMI—body mass index

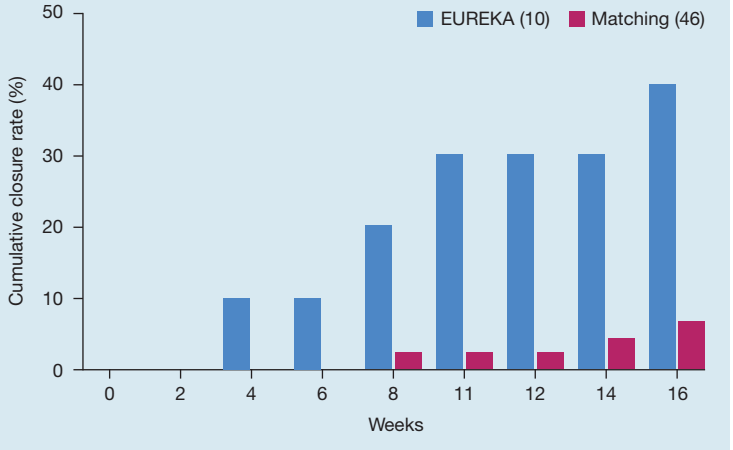
Table 5. Percentages of wound closure and wound breakdown and mean time to wound closure, all groups

Population	Wounds closed at week 16 (%)	% of wound breakdown at week 16 (% of closed wounds)	Mean time to wound closure during the entire study period (weeks)
EUREKA group	4 (40%)	0 (0.0%)	10.5
Matching group	4 (10.6%)	1 (25.0%)	31.6

Source: CL-K1002-P015 database

The risk of poor healing was also higher in the EUREKA group based on the patients' body mass index (BMI). However, BMI was not part of the matching selection criteria. As shown in Table 4, the EUREKA group had a higher BMI on average than the matching group (28.2kg/m² compared with 23.7kg/m² on average), with 70% of the patients of the EUREKA group having a BMI >25, compared with 28% in the matching group.

Fig 1. Cumulative wound closure rates at 16 weeks, all groups



In this retrospective study, it was decided to assess the rate of wound closure at 16 weeks, which corresponds to the study duration in the EUREKA study (treatment period of 12 weeks, followed by a follow-up period of four weeks). After 16 weeks, 40% of the wounds were considered as fully closed by investigators in the EUREKA group. This percentage was only 7% (3/46) in the matching group (Fig 1).

As the retrospective review allowed assessment of the matching group over a period longer than 16 weeks, it was possible to determine the final closure rate—37%. This percentage is quite similar to the one observed at the study end in EUREKA, but with mean times to wound closure of 31.6 weeks compared with 10.5 weeks in the EUREKA group (Table 5).

No wound that closed during the 16-week evaluation period reopened (no breakdown) in the EUREKA group, compared with 25% in the matching group treated with SoC only.

A Kaplan-Meier analysis (survival functions) was used to estimate the mean time of wound closure for all wounds. The estimated mean time of wound closure was statistically significant (p=0.001) in favour of the wounds treated in EUREKA study (13.2 weeks, median not assessable due to the low sample size in the EUREKA group) compared with the wounds of the matching group (69.0 weeks, median was 48 weeks) treated with SoC (p<0.001, Fig 2).

Wound areas at week six and week 16 were estimated by extrapolating the last available data up to these points and then calculating the RWAR from baseline (%). Fig 3 shows that the RWAR was higher for the EUREKA group than for the matching group at both six and 16 weeks. At six weeks, the median RWAR was 13% for the EUREKA group and 12% for the matching group. At 16 weeks, the difference in RWAR between the two groups was much greater, with EUREKA patients showing a median RWAR of 58% and the matching patients showing only 38%. The difference between the two groups was also higher when examining the mean results, with a mean RWAR of 32% and 50% at weeks six and 16 in the EUREKA group, compared with an increase in the wound area (respectively +3% and +6% at weeks six and 16) in the matching group.

Looking more deeply, 30% of the wounds of the EUREKA group had a RWAR of 50% or more at week six, compared with 15% of the matching group. At week 16, 40% of EUREKA wounds had a RWAR of 80% or more, compared with 26% for the matching wounds (Table 7). This result is interesting as the EUREKA group showed older and larger wounds at baseline.

In terms of safety profile, none of the patients of the EUREKA group developed an infection that required antibiotics during the EUREKA study period,[10,18] compared with 37% of the patients of the matching group during the treatment period.

Discussion

In this analysis the EUREKA group had significantly older wounds and carried significantly more risk factors of poor healing ($p<0.05$) than the wounds of the matching group treated with SoC. Despite these differences the EUREKA group had better outcomes after treatment with FLE and SoC versus SoC alone, showing an overall clinical profile that is extremely promising for treating hard-to-heal wounds. By week 16, 40% achieved full wound closure compared with 6.5% of the wounds in the matching group.

The difference between the two groups was also observed in terms of RWAR. As shown in Table 6, 30% of the EUREKA group achieved a RWAR of 50% or more at week six, compared with only 15% in the matching group. This trend continued at week 16, with 40% of the EUREKA wounds reaching a RWAR of 80% or more, compared with 26% in the matching group.

This early difference at week six between the two groups is well aligned with the previously observed healing rate during the EUREKA study.[10,18] If the hard-to-heal wound did not respond in the first weeks of treatment with a reduction in size, meaning no early response, the therapeutic strategy needed to be changed accordingly because the lack of response indicated that the wound needed additional intervention. This has implications for clinical protocols using a treatment with FLE because the health professional could then make early adjustments to the treatment as needed.

No wound breakdown occurred in the EUREKA group, compared with a reopening of 25% of the closed wounds in the matching group. This is of importance, as, once a wound is closed, dehiscence is an undesirable outcome that is frequently observed in VLUs.

These significantly improved outcomes using FLE support the findings of other studies using light-based therapies, which have demonstrated how these modalities can induce changes in the intracellular signalling pathways, regulate nucleic and protein

Fig 2. Kaplan-Meier analysis (survival functions): estimated rates of wound closure for the two groups

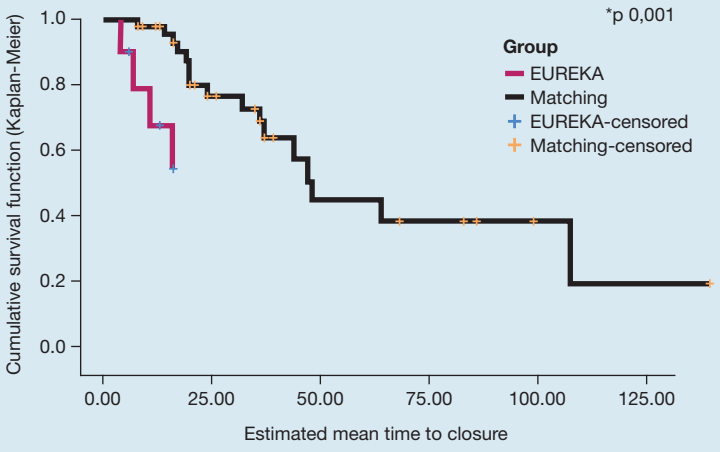
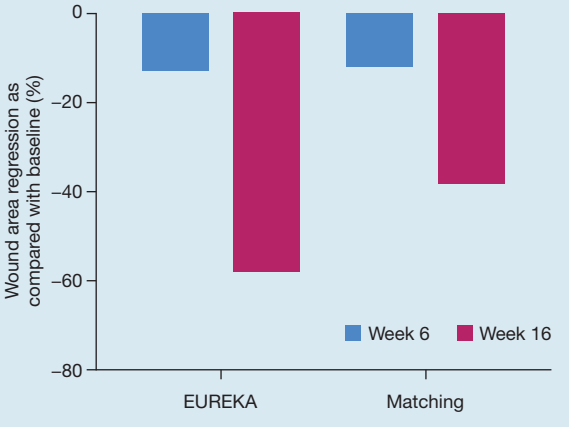


Table 6. Mean RWAR

Population	Number	RWAR ≥50% at week 6		RWAR ≥80% at week 16	
		Yes	No	Yes	No
EUREKA group	10	30.0% (3)	70.0% (7)	40.0% (4)	60.0% (6)
Matching group	46	15.2% (7)	84.8% (39)	26.1% (12)	73.9% (34)

Source: CL-K1002-P015 database; RWAR–relative wound area regression

Fig 3. Median relative wound area regression (RWAR) for the two groups, at weeks six and 16 of treatment



synthesis, and stimulate enzymes and cell progression.[24] These biochemical and cellular changes improve the healing of chronic wounds.[25] It also confirms the potential action of FLE on each phase of wound healing, already demonstrated in preclinical and clinical trials.[17]

In addition, FLE-induced PBM can be considered as a well-tolerated solution for the management of hard-to-heal wounds, including VLUs. Previous studies already described that the system does not generate heat and therefore does not cause an increased temperature in the treated tissues.[26–28] The analysis presented here also reports on the absence of wound infection, which is in line with the tolerability profile of the system based on FLE in the management of hard-to-heal wounds, including VLUs, in the EUREKA group, compared with a 37% infection rate in the matching group, which might be explained by the ability of FLE to modulate the anti-inflammatory responses and control bacterial colonisation and growth.[17]

Limitations

This study was limited to one centre and to patients with VLUs. A retrospective matching study, even when correctly executed, can never completely replace a controlled study. Even with maximum effort to retrospectively find patients with similar parameters, such as SOC and frequency of visits, it can never entirely be the same as it would be during a monitored controlled trial.

Conclusion

Whereas the EUREKA patients in this retrospective study presented with more severe VLUs based on prognostic factors of poor healing, compared with the 46 matching wounds, the EUREKA wounds showed better results than the matching wounds, although all the wounds in the two groups were treated at the same centre with SoC. These results favoured the EUREKA group on many important clinical outcomes:

- Higher rate of wound closure
- Faster closure (shorter time to achieve wound closure)
- Higher rate of RWAR at weeks six and 16
- No wound breakdown after wound closure during the same observation period in the two groups (week 16)
- Higher safety profile (no infections).

These findings support the results of the EUREKA study for patients with VLUs, which showed that the system was well-tolerated and efficacious.[10,18] JWC

References

1 Sen CK, Gordillo GM, Roy S et al. Human skin wounds: a major and snowballing threat to public health and the economy. Wound Repair Regen 2009; 17(6):763–771. https://doi.org/10.1111/j.1524-475X.2009.00543.x
2 Oliverio J, Gero E, Whitacre KL, Rankin J. Wound care algorithm: diagnosis and treatment. Adv Skin Wound Care 2016; 29(2):65–72. https://doi.org/10.1097/01.ASW.0000473132.88076.af
3 Natarajan S, Williamson D, Stiltz AJ, Harding K. Advances in wound care and healing technology. Am J Clin Dermatol 2000; 1(5):269–275. https://doi.org/10.2165/00128071-200001050-00002
4 Robson MC, Steed DL, Franz MG. Wound healing: biologic features and approaches to maximize healing trajectories. Curr Probl Surg 2001; 38(2):A1–A140. https://doi.org/10.1067/msg.2001.111167
5 Frykberg RG, Banks J. Challenges in the treatment of chronic wounds. Adv Wound Care 2015; 4(9):560–582. https://doi.org/10.1089/wound.2015.0635
6 Collins L, Seraj S. Diagnosis and treatment of venous ulcers. Am Fam Physician 2010; 81(8):989–996
7 Finlayson K, Edwards H, Courtney M. Factors associated with recurrence of venous leg ulcers: A survey and retrospective chart review. Int J Nurs Stud 2009; 46(8):1071–1078. https://doi.org/10.1016/j.ijnurstu.2008.12.012
8 Reeder SW, Eggen C, Maessen-Visch MB et al. Recurrence of venous leg ulceration. Reviews in Vascular Medicine 2013; 1(4):63–65. https://doi.org/10.1016/j.rvm.2013.08.002
9 Margolis DJ, Bilker W, Santanna J, Baumgarten M. Venous leg ulcer: incidence and prevalence in the elderly. J Am Acad Dermatol 2002; 46(3):381–386. https://doi.org/10.1067/mjd.2002.121739
10 Romanelli M, Piaggesi A, Scapagnini G et al.; EUREKA Study Group. Evaluation of fluorescence biomodulation in the real-life management of chronic wounds: the EUREKA trial. J Wound Care 2018; 27(11):744–753. https://doi.org/10.12968/jowc.2018.27.11.744
11 Houreld NN. Shedding light on a new treatment for diabetic wound healing: a review on phototherapy. Scientific World Journal 2014; 2014:1–13. https://doi.org/10.1155/2014/398412
12 Chaves ME, Araújo AR, Piancastelli AC, Pinotti M. Effects of low-power light therapy on wound healing: LASER x LED. An Bras Dermatol 2014; 89(4):616–623. https://doi.org/10.1590/abd1806-4841.20142519
13 Hamblin MR, Demidova TN. Mechanisms of low level light therapy. SPIE Proc 2006; 6140:1–12
14 Avci P, Gupta A, Sadasivam M et al. Low-level laser (light) therapy (LLLT) in skin: stimulating, healing, restoring. Semin Cutan Med Surg 2013; 32(1):41–52
15 Caetano KS, Frade MA, Minatel DG et al. Phototherapy improves healing of chronic venous ulcers. Photomed Laser Surg 2009; 27(1):111–118. https://doi.org/10.1089/pho.2008.2398
16 Scapagnini G, Marchegiani A, Rossi G et al. Management of all three phases of wound healing through the induction of fluorescence biomodulation using fluorescence light Energy. Proc SPIE 10863. Photonic Diagnosis and Treatment of Infections and Inflammatory Diseases 2019; II:108630W. https://doi.org/10.1117/12.2508066
17. Piaggesi A, Läuchli S, Bassetto F, et al. Advanced therapies in wound management: cell and tissue based therapies, physical and bio-physical therapies, smart and IT based technologies. (EWMA document) J Wound Care 2018; 27(Sup6a):S1-S137. https://doi.org/10.12968/jowc.2018.27.Sup6a.S1
18 Romanelli M, Piaggesi A, Scapagnini G et al. EUREKA study – the evaluation of real-life use of a biophotonic system in chronic wound management: an interim analysis. Drug Des Devel Ther 2017; 11:3551–3558. https://doi.org/10.2147/DDDT.S142580
19 Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. The accuracy of venous leg ulcer prognostic models in a wound care system. Wound Repair Regen 2004; 12(2):163–168. https://doi.org/10.1111/j.1067-1927.2004.012207.x
20 Margolis DJ, Kantor J, Santanna J et al. Risk factors for delayed healing of neuropathic diabetic foot ulcers: a pooled analysis. Arch Dermatol 2000; 136(12):1531–1535. https://doi.org/10.1001/archderm.136.12.1531
21 Margolis DJ, Berlin JA, Strom BL. Which venous leg ulcers will heal with limb compression bandages? Am J Med 2000; 109(1):15–19. https://doi.org/10.1016/S0002-9343(00)00379-X
22 Margolis DJ, Berlin JA, Strom BL. Risk factors associated with the failure of a venous leg ulcer to heal. Arch Dermatol 1999; 135(8):920–926. https://doi.org/10.1001/archderm.135.8.920
23 Tang XL, Chen HL, Zhao FF. Meta-analytic approaches to determine gender differences for delayed healing in venous leg ulcers. Phlebology 2016; 31(10):744–752. https://doi.org/10.1177/0268355515616702
24 Lavi R, Shainberg A, Friedmann H et al. Low energy visible light induces reactive oxygen species generation and stimulates an increase of intracellular calcium concentration in cardiac cells. J Biol Chem 2003; 278(42):40917–40922. https://doi.org/10.1074/jbc.M303034200
25 de Freitas LF, Hamblin MR. Proposed mechanisms of photobiomodulation or low-level light therapy. IEEE J Sel Top Quantum Electron 2016; 22(3):348–364. https://doi.org/10.1109/JSTQE.2016.2561201
26 Agostinis P, Berg K, Cengel KA et al. Photodynamic therapy of cancer: an update. CA Cancer J Clin 2011; 61(4):250–281. https://doi.org/10.3322/caac.20114 Medline
27 Huang YY, Chen AC, Carroll JD, Hamblin MR. Biphasic dose response in low level light therapy. Dose Response 2009; 7(4):358–383. https://doi.org/10.2203/dose-response.09-027.Hamblin
28 Huang YY, Sharma SK, Carroll J, Hamblin MR. Biphasic dose response in low level light therapy - an update. Dose Response 2011; 9(4):dose-response.1. https://doi.org/10.2203/dose-response.11-009.Hamblin