Failure of low-level laser therapy to boost healing of venous leg ulcers in surgically and conservatively treated patients

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Keywords
LLLT, venous leg ulcers, wound healing

Summary
Objective: To evaluate in a randomized open-label clinical trial the ability of adjuvant low-level laser therapy (LLLT) to improve healing of venous leg ulcers in surgically and conservatively treated patients. **Patients and methods:** Eighty three patients with venous leg ulcers were included in this study. Patients in groups 1 and 2 were treated surgically while patients in groups 3 and 4 were treated conservatively. Patients in groups 1 and 3 were additionally treated with the LLLT (GaAlAs laser, 810 nm, 4 J/cm^2, 65 mW) once daily, 6 times a week for 7 weeks. **Results:** After therapy comparison of completely healed wounds, statistically significant differences were seen between groups 1 and 3 ($p=0.02$), 1 and 4 ($p=0.02$), 2 and 3 ($p=0.02$), 2 and 4 ($p=0.02$) in favor of groups 1 and 2. Comparison of the relative change of wound total surface area indicated statistically significant differences between groups 1 and 3 ($p=0.002$), 1 and 4 ($p=0.002$), 2 and 3 ($p=0.002$), 2 and 4 ($p=0.002$) in favor of groups 1 and 2. Comparison of the other parameters also demonstrated a more efficient therapy effects in groups 1 and 2 than in group 3 and 4. There were no statistical differences in all examined parameters between groups 1 and 2 ($p>0.05$), 3 and 4 ($p>0.05$). **Conclusion:** The application of the LLLT does not enhance healing of venous leg ulcers in surgically and conservatively treated patients. A well conducted surgical operation is much more efficient than conservative pharmacological procedures.

Phlebologie 2008; 37: 241–246

Schlüsselwörter
LLLT, venöse Ulcera cruris, Wundheilung

Zusammenfassung
Ziel: Beurteilung aufgrund einer randomisierten klinischen Studie der Effektivität einer adjuvanten Low-level-Lasertherapie zur Heilung venösen Ulcera cruris bei chirurgisch und konventionell behandelten Patienten. Studienendpunkte waren die Anzahl der komplett verheilter Wunden und die klinischen Parameter, die den Ausgang voraussagen ließen. **Patienten, Methoden:** Die Studie beinhaltet 83 Patienten mit venösen Ulcera cruris. Die Patienten in Gruppe 1 und 2 wurden chirurgisch behandelt, in Gruppe 3 und 4 konventionell. Zusätzlich wurden die Patienten der Gruppen 3 und 4 mit dem LLLT (GaAlAs laser, 810 nm, 4 J/cm^2, 65 mW) einmal täglich an 6 Tagen der Woche für 7 Wochen behandelt. **Ergebnisse:** Die Anzahl der komplett geheilten Wunden ergab folgende Unterschiede: signifikant mehr Heilungen in den Gruppen 1 als 3 ($p=0.02$), 1 als 4 ($p=0.02$), 2 als 3 ($p=0.02$), und 2 als 4 ($p=0.02$). Gleiche Verhältnisse ergaben sich bezüglich der kompletten Wundenoberfläche: Gruppe 1 besser als 3 ($p=0.002$), 1 besser als 4 ($p=0.002$), 2 besser als 3 ($p=0.002$), und 2 besser als 4 ($p=0.002$). Der Vergleich weiterer Parameter demonstrierte deutlich bessere Therapieeffekte in den Gruppen 1 und 2 im Gegensatz zu Gruppen 3 und 4. In Gruppen 1 und 2 ($p>0.05$), 3 und 4 ($p>0.05$) gab es in allen untersuchten Parametern keine statistisch signifikanten Unterschiede. **Schlussfolgerung:** Die Anwendung des LLLT führt zu keiner Steigerung der Heilungsergebnisse bei Patienten mit venösen Ulcera cruris, die chirurgisch und konservativ behandelt wurden. Eine gut durchgeführte chirurgische Operation ist deutlich effizienter bezüglich des Heilungsprozesses als konservative pharmakologische Prozeduren.

Die Low-level-Lasertherapie ist ohne Einfluss auf die Heilung venöser Ulcera cruris bei chirurgisch und konventionell behandelten Patienten

Mots clés
LLT, ulcères variqueux, cicatrisation de plaie

Résumé
Objectif : Il s'agit d'évaluer l'amélioration ou non de la cicatrisation d'ulcères variqueux, chez des patients traités chirurgicalement ou de manière conservatrice, par une étude randomisée ouverte évaluant l'usage d'un laser à basse fréquence (low-level laser therapy : LLLT). Patients et méthode : 83 patients souffrant d'ulcères variqueux ont été inclus dans cette étude. Deux groupes: (1 et 2) ont été traités de manière chirurgicale et deux autres groupes (3 et 4) ont eu un traitement conservateur. Les groupes 1 et 3 ont reçu en plus un traitement par LLLT (laser GaAlAs, 810 nm, 4J/cm^2, 65 mW) une fois par jour, six jours par semaine, pendant 7 semaines. **Résultat :** Après traitement et guérison complète des ulcères, une différence significative est apparue entre les groupes 1 et 3 ($p=0,02$), 1 et 4 ($p=0,02$), 2 et 3 ($p=0,02$), 2 et 4 ($p=0,02$) en faveur des groupes 1 et 2. La comparaison de la modification relative de la surface totale de l'ulcère a été significative entre les groupes 1 et 3 ($p=0,002$), 1 et 4 ($p=0,002$), 2 et 3 ($p=0,002$), 2 et 4 ($p=0,002$) en faveur des groupes 1 et 2. La comparaison des autres paramètres ont démontré un traitement plus efficace dans les groupes 1 et 2 que dans les groupes 3 et 4. Il n'y a pas eu de différence significative dans tous les paramètres examinés entre les groupes 1 et 3 ($p>0,05$), 3 et 4 ($p>0,05$). **Conclusion :** L'application d'un traitement par LLLT n'améliore pas la cicatrisation des ulcères variqueux chez des patients traités de manière chirurgicale ou conservatrice. Une intervention chirurgicale bien conduite est plus efficace qu'un traitement conservateur.

Echec d'un traitement par laser à basse fréquence (low-level laser therapy : LLLT) pour accélérer la cicatrisation d'ulcères variqueux chez des patients traités de manière chirurgicale ou conservatrice

Received: March 3, 2008; accepted in revised form: September 22, 2008

Low-level laser therapy (LLLT) is well known, but still very controversial treatment. Lasers produce electromagnetic radiation that is unusual only by its monochromaticity, polarization, and coherency (2). However, some researchers maintain that LLLT has some unique characteristics. The most important of these is that its effects result from the interaction of electromagnetic radiation with human tissues (2, 6, 8, 14). By definition, LLLT takes place at irradiation intensities so low that the biological effects in tissues are thought to occur as a direct result of the irradiation than by a heating effect (non-thermal events). This restraint means that irradiation-induced temperature elevations is minimal, not more than 0.5 ^{0}C (2, 8).

Low-level lasers have an output of 1–400 mW (usually 10–120 mW). In practice, the most popular lasers are

- helium/neon (He/Ne) of wavelength 632.8 nm,
- gallium/aluminium/arsenide (GaAlAs) of wavelengths 810, 820 and 830 nm,
- gallium/arsenide (GaAs) of wavelength 904 nm, and
- ruby (Rb) of wavelength 694 nm.

The waveform may be continuous or pulsed (up to 5000 Hz). The energy density (single dose) delivered to a treatment site is between 1 and 10 J/cm^2 (mainly 4 J/cm^2). Irradiation techniques are various and can include static, sweeping, or grid-like patterns over the treatment sites (2).

Most studies have examined the promising effects of LLLT on pain (3, 13, 16), musculoskeletal dysfunction (2, 3), arthritis (4, 16) and neurological functions (2, 3). The utility of this therapy for wound healing application remains controversial. For example, while many of clinical trials find healing of soft tissue wounds significantly improved by irradiation (1, 8, 10, 12), but some (representative and well controlled) do not (6, 11, 15). It is unclear whether LLLT accelerates the wound healing, and if it does, whether any particular treatment regimen is optimal.

In this clinical experiment we investigated the use of LLLT in the treatment of venous leg ulcers. The aim was to evaluate the efficiency of LLLT for healing of venous leg ulcers in surgically and conservatively treated patients. Study endpoints were number of completely healed wounds and the clinical parameters predicting the outcome.

Patients, methods

The methods, the plan and scope of therapy, inclusion of patients into the groups, and other procedures of the scientific research were reviewed, approved, and accepted by the Bioethical Commission of Medical University of Silesia in Katowice, Poland.

A prospective, randomized, controlled clinical trial was conducted from September 2001 to June 2007. Eighty three patients with venous leg ulcers were included in this study. The exclusion criteria were: an ankle brachial pressure index (ABPI) lower than 1.0, diabetes, arteriosclerosis, rheumatoid arthritis, ventricular arrhythmia, cardiac pacemaker, metal implants, pregnancy and after steroid therapy.

- Forty two individuals, who agreed on surgical operation and were qualified for this therapy by research team were allocated into two comparative groups 1 and 2.
- Other individuals, who did not agreed on surgical procedure were allocated into two comparative groups 3 and 4.

Patients were randomly allocated to treatment with compression and drug therapy or compression and drug plus LLLT. Computer generated random numbers were sealed in sequentially numbered envelopes and group allocation was independent of time and persons delivering the treatment. The patient flow through the trial is presented in Figure 1.

Patients in groups 1 and 2 were surgically treated in the General, Vascular, and Transplant Surgery Department at the Medical University of Silesia in Katowice. Patients in groups 3 and 4 were conservatively treated in the Dermatology Department of the Hospital No. 2 in Bytom. Group 1 consisted of 22 patients (14 women, 8 men). After surgical operation they were treated with the LLLT, compression stockings, and drug therapy. Group 2 consisted of 20 patients (12 women, 8 men). After surgical procedure they were only treated with the

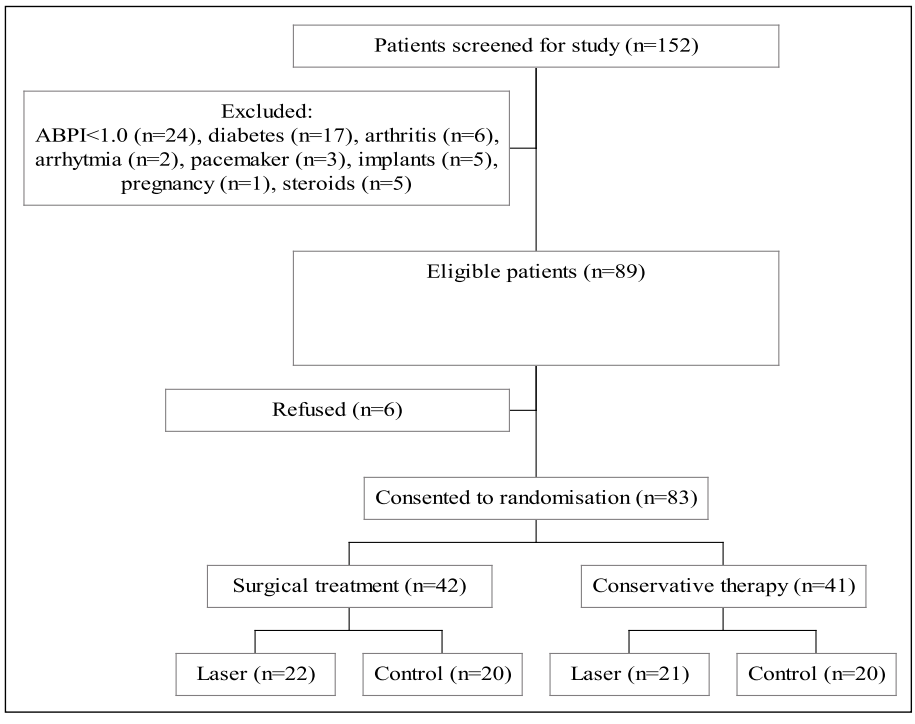

Fig. 1 Patient flow (ABPI: ankle brachial pressure index)

Tab. 1 Characteristics of patients and ulcers

group		1	2	3	4	p
patients	number	22	20	21	20	
age (years)	average SD range	60.10 8.38 48–81	60.66 8.12 48–80	61.02 8.18 47–81	60.13 8.37 43–79	
sex	women men	14 8	12 8	13 8	13 7	
body mass index (kg/cm^2)	average SD range	23.42 3.03 19.04–32.55	25.77 3.78 19.02–33.33	25.01 4.43 21.01–31.35	24.44 5.11 20.11–31.32	
smokers	number	6	5	6	5	
localization of ulcers	medial ankle lateral ankle anterior crural surface posterior crural surface	10 3 5 4	9 3 6 2	10 3 5 3	9 4 4 3	>0.05
duration of disorder (months)	average SD range	30.84 24.22 2–120	32.34 22.89 3–120	30.84 23.09 2–100	30.57 24.12 4–136	
initial wound total area (cm^2)	average SD range	19.17 11.02 6.88–36.01	18.97 13.02 8.01–45.41	16.77 12.02 8.11–44.81	17.92 16.19 9.14–40.09	
initial wound volume (cm^3)	average SD range	2.86 2.01 0.33–13.04	3.11 3.01 0.45–12.44	2.66 2.51 0.40–11.24	3.29 3.05 0.51–12.69	

χ^2 independence test

compression and drug therapy, administered identically as in group 1. Group 3 consisted of 21 patients (13 women, 8 men). They were treated with the LLLT as in group 1, and compression and drug therapy, administered identically as in group 1 and 2. Group 4 consisted of 20 patients (13 women, 7 men). They were only treated with compression and drug therapy, administered identically as in group 1, 2 and 3. Other details of the examined persons and ulcers are shown in Table 1. Patients were evaluated using the CEAP classification of chronic venous insufficiency (Tab. 2).

All ulcers in the groups were diagnosed as venous. In order to rule out the arterial component and to verify the localization of CVI, patients were examined by duplex scanning (EUB 555, Hitachi Inc., Japan). All patients had the symptoms of CVI, i. e. edema, hyperpigmentation and lipodermatosclerosis of the affected limb. The body mass index (BMI) was calculated for all patients. The number of smokers was recorded as well.

Patients in comparative groups were treated with elastic compression stockings (Sigvaris, Gianzoni & Cie AG, Switzerland – certified in Poland) providing pressure 30–40 mmHg at the ankle (5, 10). The stockings were put on the leg at the outpatient clinic every morning and worn whole day (about 10–12 hours); and put off on night. The drug therapy followed a standard regimen. All patients received micronized flavonoid fraction (450 mg diosmin, 50 mg hesperidin), two tablets of 500 mg once daily. The ulcer ground was covered with wet dressings of 0.9% sodium chloride. Dressings were changed once a day and exclusively at the clinic. Before beginning the compression and drug therapy patients in groups 1 and 2 were surgically operated. The spectrum of the following procedure included crossectomy, partial (short) stripping of the greater (GSV) or short (SSV) saphenous vein, local phlebectomy and ligation of insufficient perforators (7).

Tab. 2
Classification of CVI

CEAP class	group 1	group 2	group 3	group 4	p
$C_6E_PA_{S2,3}P_R$	9	8	9	8	>0.05
$C_6E_PA_{S4}P_R$	3	3	3	2	
$C_6E_PA_{S2D13}P_R$	3	3	3	4	
$C_6E_PA_{S3D13}P_R$	2	2	2	2	
$C_6E_PA_{S2,3D13,14P18}P_R$	4	3	3	3	
$C_6E_SA_{S2,3D13,14P18}P_R$	1	1	1	1	
total number of patients	22	20	21	20	

χ^2 independence test

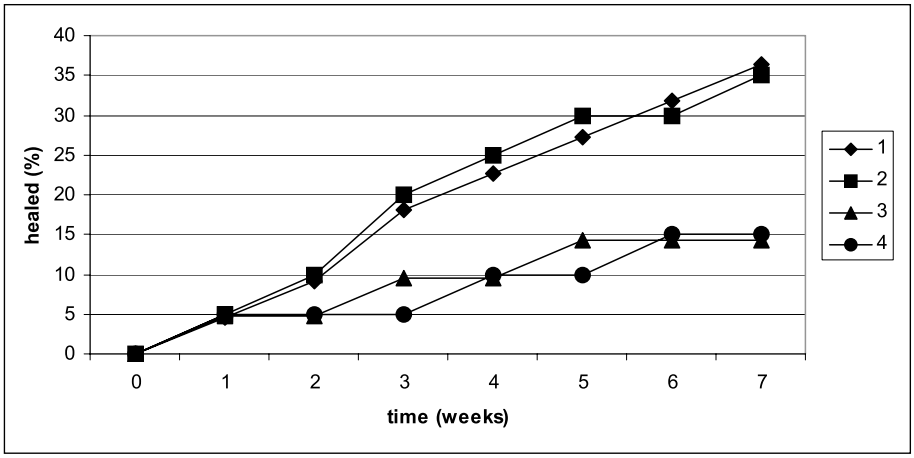

Fig. 2 Dynamics of healing process in all groups

For LLLT in groups 1 (five days after operation) and 3, we used a 810 nm semiconductor GaAlAs laser (CTL – 1106MX, Elektronika i Elektromedycyna sp. z.o.o., Poland), emitting a continuous wave. The laser head was a single diode from High Power Devices Inc., USA). The cross section of the beam emitted from the head was a rectangle sized 2 mm by 5 mm, i. e. 10 mm. The laser was wired to a CTL – 1202S scanner (Elektronika i Elektromedycyna sp. z.o.o., Poland. The laser beam of fixed cross section scanned the surface with a compound movement: in the ordinate axis at a frequency of 20 Hz, and in the abscissae axis at a frequency of 0.5 Hz. The average output of the radiation was 65 mW. The output power was checked every week, using Mentor MA10 apparatus (ITAM, Poland). Scanning frequency was 0.5 Hz. The scanner was placed at a distance of 50 cm from the ulcer surface. The time duration of a single procedure was related to the wound size, and it was adjusted so as to obtain an average dose of 4 J/cm^2.The procedures were repeated once daily, for 6 days a week during 7 weeks. The total time of treatment in all comparative groups lasted seven weeks.

Treatment progress was evaluated by observation of the number of completely healed ulcers, and measuring the area of the ulceration by planimetry of congruent projections of these wounds onto transparency paper using a digitizing pallet. Depth of the ulceration was precisely measured in various points by micrometer. Later, noticed results were transferred to software. The electronic equipment for the measurement of area and volume of the ulcers consisted of the digitizer (Kurta XGT, Altek Inc., USA) wired to a personal computer with modified software C – GEO v. 4.0 thus allowing the calculation of these parameters. Measurements of area and volume were performed in each person before therapy, every week during treatment, and after therapy. From this data, the software calculated the area and volume of tissue deficiency in ulcerations. Measurements were also made of length and perpendicular width dimensions (for observation, the correlation between surface area and linear dimensions). The observation of healing process was supported by precisely calculated relative changes. These indicators were defined as follows:

$$\Delta P\% = (P_I - P_F) \times 100\% / P_I$$

$\Delta P\%$: relative change of the parameter (%); P_I, P_F: initial and final real parameter (length, width in cm, or total surface area in cm^2, or volume in cm^3).

The χ^2 independence test (greatest reliability level) was used for analysis of indicators, which characterized patients in all comparative groups. Differences in relative changes of total surface area, volume, length and width between groups were evaluated with analysis of variance ANOVA and post-hoc Tukey test. Two-sided p values of less than 0.05 were considered to be statistically significant. We also calculated ulcer healing using Kaplan-Meier survival analysis with log rank comparisons (number of completely healed ulcers in time).

Results

The examined groups were homogeneous in terms of patients' characteristics (Table 1 and 2). Kaplan-Meier analysis showed that the effect of therapy on healing did not differ between groups, only in a first week (Fig. 2). After two weeks, the two (9.09%) patients in group 1 were healed completely and also two (10%) in group 2. One (4,76%) patient in group 3 was healed completely and also one (5%) in group 4. After therapy, the eight (36.36%) patients in group 1 were healed completely and seven (35%) patients in group 2 were healed completely. Three (14.28%) patients in group 3 were healed completely and also three (15%) in group 4. Comparison of the treatment efficacy demonstrated statistically significant differences between groups 1 and 3 (p=0.02), 1 and 4 (p= 0.02), 2 and 3 (p= 0.02), 2 and 4 (p=0.02) in favor of groups 1 and 2.

Comparison between groups 1, 2, 3 and 4 in terms of relative change of the total surface area, indicated a significant differences between groups

- 1 and 3 (60.09% vs. 27.85%, p=0.002),
- 1 and 4 (60.09% vs. 28.01%, p=0.002),
- 2 and 3 (60.01% vs. 27.85%, p=0.002),
- 2 and 4 (60.01% vs. 28.01%, p=0.002)

in favour of groups 1 and 2. Comparison between groups 1, 2, 3 and 4 in terms of relative change of the volume, indicated also a significant differences between groups

- 1 and 3 (69.89% vs. 41.85%, p=0.01),
- 1 and 4 (69.89% vs. 41.01%, p=0.01),
- 2 and 3 (68.21% vs. 41.85%, p=0.01),
- 2 and 4 (68.21% vs. 41.01%, p=0.01)

in favour of groups 1 and 2. Comparison between groups 1, 2, 3 and 4 in terms of relative change of the length, indicated a significant differences between groups

- 1 and 3 (43.43% vs. 29.88%, p=0.01),
- 1 and 4 (43.43% vs. 29.82%, p=0.01),

- 2 and 3 (43.05% vs. 29.88%, p=0.01),
- 2 and 4 (43.05% vs. 29.82%, p=0.01)

in favour of groups 1 and 2. Comparison between groups 1, 2, 3 and 4 in terms of relative change of the width, indicated a significant differences between groups

- 1 and 3 (46.55% vs. 30.88%, p=0.006),
- 1 and 4 (46.55% vs. 31.42%, p=0.006),
- 2 and 3 (47.03% vs. 30.88%, p=0.006),
- 2 and 4 (47.03% vs. 31.42%, p=0.006)

in favour of groups 1 and 2 too. There were no statistical differences in all examined parameters between groups 1 and 2 ($p > 0.05$), 3 and 4 ($p > 0.05$).

In all comparative groups the change of wound area occurred simultaneously with changes of linear dimensions. That was beneficial for wound healing, which progressed steadily.

Discussion

In our study LLLT (810 nm, 65 mW, 4 J/cm^2) does not have any stimulatory effect on healing of venous leg ulcers both in surgically and conservatively treated patients.

Our results from surgery indicated that LLLT applied to venous leg ulcers reduced the wound surface area by 60.09% and wound volume by 69.89% of the initial size. In control group, wound surface area decreased by 60.01% and wound volume by 68.21%. Using the same laser in conservatively treated patients we observed that wound surface area decreased by 27.85% and wound volume by 41.85%. In control group, the reduction was 28.01% for surface area and 41.01% for volume.

The LLLT has been only used for the conservative treatment of venous leg ulcers (1, 6, 8, 10 – 12, 15). The investigators were not interested in applying this method in surgical patients. Our study is the first one to implement it. Therefore, our results may only be compared from conservative treatment reports.

Gupta et al. (8) treated nine patients with 12 venous leg ulcers. At the conclusion of the study, the percentage of the initial ulcer area remaining unhealed in the LLLT and placebo groups was 24.4% and 84.7%, respectively ($p \leq 0.001$). The decrease in ulcer area (compared to the baseline) observed in the LLLT and placebo group was 193 mm^2 and 14.7 mm^2, respectively ($p \leq 0.001$). In their opinion the LLLT was an effective modality for the treatment of venous leg ulcers.

Ashford et al. (1) presented two patients with a remarkable response to laser treatment. In case study one, the ulcer size recorded at the start of experiment was 16 mm^2. The ulcer reduced to 15 mm^2 – 91% its original size. In case study two, a similar reduction was observed in 28 days of therapy.

Kleinman (10) has employed several laser types and reported complete healing (assessed by wound closure) in 85.7% of patients over a mean period of 3.5 months. Similarly, Lichtenstein and Morag (12) reported 87% wound closure in patients with venous leg ulcers.

But our findings are consistent with a few critical randomized controlled trials from conservative therapy. In the following study the Kaplan – Meier analysis confirmed that the healing rates did not differ between irradiated and control groups.

For example, Malm and Lundeberg (15), in a placebo controlled study using a GaAs laser, reported no differences in results between the two groups investigated. After 1 month they observed one completely healed ulcers in LLLT group and none in control. After two months they noticed two completely healed ulcers in LLLT group and two in control. After three months they observed four completely healed ulcers in LLLT group and four in control.

Similarly, findings of a controlled study reported by Franek et al. (6) observed that GaAlAs laser irradiation had no advantages over conservative treatment at dosage 4 J/cm^2.

Kokol et al. (11) conducted controlled work using a 685 nm laser. They measured venous leg ulcers planimetrically at baseline (day 1), at the end of therapy (day 28) and two months later (day 90). There were no statistically significant differences in reduction of wound size between the examined groups.

Conclusion

There are no special reasons for application of the LLLT (810 nm, 65 mW, 4 J/cm^2) in enhancement of healing process in venous leg ulcers. In our study the LLLT appeared ineffective and useless. The recommendation for the LLLT seems to be doubtful. The surgical treatment is much more efficient than conservative methods. We believe that successful surgical procedures with standard compression and drug therapy after operation can lead to wound closure, without an enhancement of healing process by the use of LLLT.

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