Comparison Low-Level Laser Therapy (LLLT) of 10J/cm^2 and 5 J/cm^2 Energy Density for Healing Diabetes Foot Ulcer

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Abstract
Background*: Diabetic foot ulcer is a problem in patients with diabetes mellitus (DM). One adjuvant therapy that can enhance wound healing is Low-Level Laser Therapy (LLLT), but there is no established guideline regarding the dosage. In Indonesia, there has been no study comparing the energy density of LLLT on diabetic ulcer healing*
Methods*: This is an experimental study on 28 subjects with a randomized diabetic foot ulcer. Group A received standard treatment of ulcer and LLLT 5J/cm2. Group B received standard treatment of ulcer and LLLT 10J/cm2.*
Results*: The difference in wound size between group A and group B were 4.15 mm2 and 7.5 mm2 (p=0.178). The healing rate of group A and group B were 4.15 (-10-34.5) mm2/4 weeks and 7.5 (-2.8-34) mm2/4weeks (p=0.168).*
Conclusions: *There was no statistically significant difference between the group receiving LLLT 5J/cm^2 or 10 J/cm^2 in diabetic foot ulcer healing.*
Keywords: *Diabetic foot ulcer, laser therapy, LLLT, wound healing*

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Perbandingan Densitas Energi *Low-Level Laser Therapy* (LLLT) 10J/cm² dengan 5 J/cm² terhadap Penyembuhan Luka Kaki Diabetes

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Abstrak

***Latar Belakang**: Luka kaki diabetes merupakan masalah umum pasien diabetes melitus (DM). Salah satu terapi adjuvan yang dapat mempercepat penyembuhan luka adalah Low- Level Laser Therapy (LLLT), namun belum ada pedoman pasti mengenai dosisnya. Di Indonesia belum ada penelitian yang membandingkan densitas energi terhadap penyembuhan luka diabetes.*

***Metode**: Studi eksperimental ini dilakukan pada 28 subyek dengan luka kaki diabetes yang telah dirandomisasi. Kelompok A mendapat perawatan luka rutin dan LLLT 5J/cm². Kelompok B mendapat perawatan luka rutin dan LLLT 10J/cm². Dilakukan intervensi selama 4 minggu dengan frekuensi 2x/minggu.*

***Hasil:** Selisih ukuran luka setelah intervensi antara kelompok A dan B adalah 4.15 mm² dan 7.5 mm² (p=0.178). Total kecepatan pemulihan luka kelompok A dan B adalah 4.15(-10-34.5) mm²/4 minggu dan 7.5(-2.8-34) mm²/4 minggu (p=0.168).*

***Kesimpulan**: Pemberian LLLT dengan 5J/cm² maupun 10J/cm² tidak memberikan efek bermakna secara statistik terhadap penyembuhan luka kaki diabetes.*

***Kata Kunci**: luka kaki diabetes, terapi laser, LLLT, penyembuhan luka*

Background

Diabetes mellitus (DM) is a metabolic disorder with increasing blood sugar levels. Diabetic foot ulcer (DFU) is the most common problem in patients with DM. Based on the International Working Group of Diabetic Foot (IWGDF), DFU is a combination of infections, ulceration and tissue destruction in the legs associated with neuropathy and peripheral arterial disease in the lower extremities in patients with DM.[1] The prevalence of DFU among patient with DM was 4-27% and it is expected to rise in the coming years.[2] If DFU not treated properly can lead to infection, amputation and even death. Routine wound management includes infection and amputation care, which can also contribute to increasing medical expenses each year. The mortality rate of post-amputation DM was 14.3% in a year and 37% in 3 years. It shows that DFU still being a major health problem.[3–5]

Low-level Laser Therapy (LLLT) is an alternative modality that is considered to give a significant effect on chronic wound healing. LLLT is an electromagnetic wave that produces light with one wavelength. In an in-vitro study, LLLT can stimulate collagen formation, DNA synthesis and improve disrupted tissue function. Mechanisms of LLLT include increasing the production of ATP from mitochondria, stimulating the synthesis of protein, the proliferation of fibroblasts and macrophage, increasing serotonin and endorphins, increasing anti-inflammatory effects and circulation, decreasing cell membrane permeability thereby causing hyperpolarization, increasing lymphatic flow and reducing edema.[6,7]

To date, there is no guideline for treatment on DFU using a laser. Research by Kajagar *et al* found that routine of LLLT therapy with a dose of 2-4 J/cm2 for 15 days, can accelerate the healing process of DFU.[8] Other research by Kaviani *et al* found that 23 patients with DFU who received LLLT therapy with wavelengths of 685 nm and energy density of 10 J/cm2 showing speed-up of the wound healing process in chronic DFU, especially at 4th week.[6] The aims of this research to comparing the difference

in the effectiveness of healing DFU using LLLT with 5J/cm2 and10 J/cm2.

Method

This is an experimental study conducted at the diabetic foot polyclinic of Cipto Mangunkusumo General Hospital during July - November 2017. The sample size was 30 people. Studies were required consecutively and were placed in a group randomly. Inclusion criteria were patients with DFU that diagnosed by an internist, with PEDIS criteria (Perfusion: Ankle brachial index (ABI) 0.7 - 1.3; Extent: <10 cm2; Depth: superficial, not deeper than the dermis; Infection: no infection; Sensation: normal or disturbed). Exclusion criteria were comorbidities (eg, malignancy, immunocompromised, severe infections, blood clotting disorders, bleeding, severe vascular or other neuromuscular disorders), fractures that require surgical intervention at the laser application site, a history of laser therapy at least 2 months before the study and presence of laser contraindications (eg pregnancy, malignancy, 4-6 months post-radiotherapy, epilepsy and febrile). The drop out criteria are patients who have experienced extraordinary response or side effects from the laser that cannot be tolerated. Hyperpigmentation at the site of therapy, or did not attend therapy three times in a row.

Ethics approval for this study was obtained from the Ethics Committee of the Faculty of Medicine, University of Indonesia no. 285 / UN2.F1 / ETIK / 2017. Subjects were explained about the goals and benefits of the study and were asked to sign informed consent. Subjects were divided into 2 groups. The group A is a group using LLLT diode, 400 mW, 830 nm with 5 J/cm2 and group B is a group using 10 J/cm2. Both groups received standard wound and laser treatments twice a week for 4 weeks.

The wound was cleaned with 0.9% NaCl solution and debrided by nurses at the Poliklinik Kaki Diabetes. The wound was covered by thin transparent plastic. The wound edges were printed on tracing paper using a black marker at pre and post-debridement. The wound area was assessed using the paper tracing measurements then executed to millimeter paper blocks. The laser continues performed by scanning technique on the edges and the bottom of the wound. The wound was covered again by sterile gauze. The area of the wound will be evaluated every weekend for 4 weeks. The difference in the size of the wound will be taken from a wound area in pre-debridement at the beginning and the end of the week. Then, the data were processed using SPSS software version 20.0 (IBM Corporation; Armonk, New York). The level of significance for hypothesis testing is p d" 0.05.

Result

A total of 30 individuals, with a ratio of female and male (78.6%: 21.4%), were enrolled in this study. Each group had 1 subject drop-out. The mean age of the subjects in group A was 53 years old while group B was 58.79 years old (p = 0.134). The mean duration of DM in these subjects was 13.97 ± 8.54 years. The median value of the wound period in this study was 2.5 weeks by a range of duration for 0 to 104 weeks. The characteristics of the research subjects are summarized in Table 1.

Table 1. Demographic Characteristic of Subject

Characteristic	Group A n=14 n (%)	Group B n=14 n (%)
Ages	53 years	58.79 years
Duration of DM	13.93 years	14.01 years
Duration of Ulcer	3 week (0-104)	2 week (0-104)
Sex	2 (14.3)	4 (28.6)
BMI	12 (85.7)	10 (71.4)
	5 (35.7)	1 (7.1)
	5 (35.7)	5 (35.7)

	Obesity I	3 (21.4)	4 (28.6)
	Obesity II	1 (7.1)	4 (28.6)
ABI	Normal	12 (85.7)	9 (64.3)
	Mild obstruction	2 (14.3)	5 (35.7)
Sensibility disability	No	8 (57.1)	2 (14.5)
	Yes	6 (42.9)	12 (85.7)
Control of glucose level	Good	5 (35.7)	4 (28.6)
	Moderate	4 (28.6)	1 (7.1)
	Bad	5 (35.7)	9 (64.3)
Smoking	No	13 (92.9)	11 (78.6)
	Mild	0 (0)	1 (7.1)
	Moderate	1 (7.1)	2 (14.3)
Amputation	No	13 (92.9)	8 (57.1)
	Yes	1 (7.1)	6 (42.9)
Location of ulcer	Dorsal pedis	1 (7.1)	3 (21.4)
	Plantar pedis	1 (7.1)	4 (28.6)
	Ankle	7 (50)	0 (0)
	Digital pedis	5 (35.7)	7 (50)

Note: BMI: Body Mass Index; ABI: ankle-brachial index

In group A, there was a significant difference median size of DFU between before therapy and therapy at the end of week 4. At the end of week 1 to week 3, there was a reduction in wound size compared to before treatment, but not statistically significant.

In group B, the wound size decreased statistically significant every week from 1st to 4th week. Complete wound closure was achieved in 5 subjects (35.7%) at the end of week 1. At the end of week 3, 8 subjects (57.1%) had completed therapy since the wound closure was adequate.

Table 2. Median of DFU Size of Group A in The End of Each Week

Size of ulcer	Median (mm²)	P
Baseline	5.55 (1.6 – 40)	
1st weekend	3.9 (0 – 45.3)	0.116
2nd weekend	3.95 (0 - 25.9)	0.285
3rd weekend	2.45 (0 – 50)	0.213
4th weekend	0.5 (0 – 49.7)	0.012

There was decrease in the size of DFU each group after 4 weeks of laser administration, which is 4.15 (-10 - 34.5) mm2 in group A and 7.5 (-2-34) mm2 in group B. There was no significant difference in the decrease in DFS in both group A and group B after 4 weeks (p = 0.178).

In this study, several factors cannot be restricted, such as age, blood sugar control, ABI, BMI, sensibility disorders, history of amputation,

Table 3. Median of DFU Size of Group B at The End of Each Week

Size of ulcer	Median (mm^2)	P
Baseline	8.75 (1.4 - 42.3)	
1st weekend	3.40 (0 - 27)	0.002
2nd weekend	3.35 (0 - 22.7)	0.001
3rd weekend	0 (0 - 18.4)	0.001
4th weekend	0 (0 - 16.9)	0.002

smoking history, and wound location. These confounding factors were analyzed through multivariate tests to find out whether they could influence research results between the two groups. After statistical tests were performed, confounding variables in this study have proven not to provide a bias statistically in the two study groups.

Discussion

LLLT is a low-intensity laser or diode that can be used as an adjuvant therapy to stimulate vascular circulation, collagen formation, and decrease bacterial colonization in DFU. The laser converts fibroblasts into myofibroblasts for the contraction of granulation tissue and accelerates wound epithelialization. Lasers also cause vasodilation by triggering the relaxation of smooth muscle. The vasodilation increases oxygen in the cells target, and therefore it will increase immune cells, endothelial cells, and accelerate healing as well.[9,10]

Table 4. Wound Size of Two Group at The End of Each Week

Size of ulcer (mm^2)	Group A	Group B	P
Baseline (0 minggu)	5.55 (1.6 – 40)	8.75 (1.4 - 42.3)	0.550
1st weekend	3.9 (0 – 45.3)	3.40 (0 - 27)	0.659
2nd weekend	3.95 (0 - 25.9)	3.35 (0 - 22.7)	0.652
3rd weekend	2.45 (0 – 50)	0 (0 - 18.4)	0.468
4th weekend	0.5 (0 – 49.7)	0 (0 - 16.9)	0.690
Difference of size	4.15 (-10 – 34.5)	7.5 (-2 – 34)	0.178

Although LLLT has been widely used, it is still controversial as therapy because (1) the underlying biochemical mechanism is not fully understood and (2) the parameters such as wavelength, energy density, pulsation structure and time of light given, are too broad to study. Incorrect parameters will decrease the effectiveness of therapy or even cause side effects. This unexpected result is due to an inappropriate dose. Therefore, parameter selection is very important to reach the optimal dosage for each application.[11] Laser parameters used in this study were diode light, 860 nm, 400 mW power with the duration of laser radiation adjusted to the area of wound and energy density. In this study, the two energy densities were classified in LLLT because the parameters used were wavelengths of < 1064 nm and output power <500 mW. By using high output power, the duration of therapy is faster. Various studies have used LLLT and examined the effect of lasers on wound healing. They found that 2-12 J / cm2 had the effect of migrating and proliferating fibroblast cells so it can accelerate wound healing.[8,9,12,13]

Furthermore, LLLT improves the tissue at the base of the wound through DNA synthesis, increasing mitochondrial performance, so it can provide good oxygenation and reduce ROS. Recommended treatment doses for LLLT do not exceed 4-5 J/cm2 and the inhibitory effect can occur at exposure to 20 J/cm2.[14] However, some

other studies[6,15,16] get results contrary to this recommendation where 10 J/cm² to 30 J/cm² still shows a positive effect of LLLT on wound healing without any side effects. This study also obtained similar results; an energy density range of 10-30 J / cm2 can have more positive effects than other dose levels.

A study showed a reduction in wound size after giving LLLT therapy once a day for 15 days with a wavelength of 850 nm, strength density of 60 mW/cm2, energy 2-4 J/cm2 compared to the control group that only received standard treatment from DFU such as wound management with saline, antibiotics, immobilized casts and wound excision if needed. Wounds are measured by moving the printed wound from transparent paper to paper box. After 15 days of therapy, there was a significant reduction in injuries in the intervention group (40.24 ± 6.3 mm2 vs 11.87 ± 4.28 mm2, p <0.001).[8]

A study showed the effectiveness of LLLT on DFU, using a wavelength of 685 nm, strength density of 50 mW/cm2, energy 10 J/cm2, radiation duration of 200 seconds) while the control group received a placebo. Therapy is given for 6x / week for 2 weeks. The study showed that there was a significant reduction in wound size in the group (58 ± 10.4% vs 23.5 ± 14.1%, p = 0.046). There was a tendency for faster wound healing time in the intervention group (11 weeks vs. 14 weeks).[6]

In this study, there was no statistically significant difference in the treatment of LLLT for 4 weeks, either with 5 J/cm2 or 10 J/cm2 (4.15mm2: 7.5mm2; p = 0.178). Within each LLLT group, there were significant differences in the size of DFU wound healing after 4 weeks of therapy. However, in group B, a significant improvement in DFU was found since the end of week 1. Therefore, it can be considered that LLLT therapy with a dose of 10 J/cm2 has a positive impact on wound healing from the start compared to LLLT with a dose of 5 J/cm2. Besides, no side effects or unexpected events were found in both groups, so it can be concluded that LLLT in DFU with a dose of 10 J/cm2 can heal faster, but it is not better than a dose of 5 J/cm2 in terms of wound size and time of wound recovery after the administration of therapy for 4 weeks.

Conclusion

There was no significant difference in the healing of DFU using 5 J/cm2 and 10 J/cm2 after 4 weeks of LLLT therapy. The energy density of 5 J/cm2 is easier to use because it has faster exposure time and better safety. However, the energy density of 10 J/cm2 can be considered, especially in DFU patients with hard to heal wounds or low socioeconomic status who found it hard to take routine control in medical facilities, since the positive effects can be seen after 1 week of therapy. In this study, both the two energy densities are safe to use, without any side effects. However, to reduce the risk of side effects due to overdosing, LLLT with an energy density of 5 J/cm2 is more recommended.

Suggestion

DM is a multifactorial disease, so the characteristic subjects were heterogeneous. Further research is needed using more subjects, more strict follow-up and inclusion criteria so that the background of the subjects can be more homogeneous in both groups. Moreover, evaluation of vascular disorders in DM should use TcPO2 which is a noninvasive test and has better sensitivity in assessing the condition of blood micro-circulation in the skin than ABI. Assessment of wound size should be done using software technology that has a high accuracy value in measuring wound area and granulation area.

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