EFFECT OF LOW LEVEL LASER IRRADIATION ON INDOLENT ULCERS CAUSED BY BUERGER'S DISEASE; LITERATURE REVIEW AND PRELIMINARY REPORT

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Thromboangiitis obliterans, or Buerger's disease, is a comparatively rare but extremely unsettling condition, associated with very high levels of pain, often with amputation or reamputation the only surgical recourse. Because of its propensity to be found in the younger patient, it is important that the most minimal surgery possible is indicated, owing to the possibility of the patient's being forced to lead a life of invalidism following the drastic surgery usually needed in this disease. The authors present three cases seen in their institute, all of which would probably have required amputation, or reamputation. Low reactive-level laser therapy (LLLT) was applied in an outpatient setting, using a 10 mW helium-neon continuous wave laser, at doses ranging from 0.18 and 2.7 J/cm². Two of the three patients were completely healed, with a one-year follow-up, and the third patient is still undergoing treatment, but with an excellent prognosis. All three patients reported a significant reduction of pain, and demonstrated fast and significant reduction in inflammation and oedema, accompanied by fast and clear demarcation of the necrotic area, and fast granulation of the ulcer's surface. The wounds healed with minimal scarring. Antibiotics had to be used additionally to the LLLT in two of the three reported cases. Infrared thermography was used to evaluate the effect of LLLT on the microvasculature in the affected area, showing on average a 0.9°C increase in temperature. With what is known about the mechanisms of LLLT on the microvasculature, in particular the improvement in blood flow rate, the authors suggest that LLLT provides a noninvasive therapeutic modality for Buerger's disease, or any other condition related to microvascular impairment. Further studies on the photoautoimmune effects of LLLT are also needed, as there is a strong connection between autoimmune processes and this condition.

KEY WORDS Thromboangiitis obliterans Endangiitis obliterans Nicotine Indolent ulcers Gangrene Microcirculation IR-thermography

Introduction

Thromboangiitis obliterans, or Buerger's disease, although rare,^{1,2} is nonetheless remarkable, due to the youth of the patients^{3,4} and the high rate of limb loss.⁵⁻⁹ The pathogenesis of Buerger's disease is, in the final analysis still unknown.¹⁰ Autoimmunological processes are probably involved.¹¹⁻¹⁵ Familiar and geographical predisposition is discussed. Nicotine seems to play an important role.^{16,17} Buerger's disease is primarily a disease of the small and medium sized vessels and affects mostly the lower extremities.^{18,19} The disease is decidedly rare in women.⁵ The great varieties of conventional therapies can be reduced to the therapy of pain, increase in blood flow, antiinflammatory therapy and grafting

for the treatment of the indolent ulcers; but the unattendant pain is mostly the reason of the high amputation rate. Low reactive-level laser therapy, or LLLT, has recently been reported in the effective treatment of pain,²⁰⁻²² there are also many positive reports concerning the stimulating effect of LLLT energy on indolent wounds, and on the increased blood supply not only in the LLLT target area, but also in surrounding, and even contralateral, areas.²³⁻²⁸

Due to these encouraging results and our own good experience with LLLT during the last seven years, we treated three patients with indolent ulcers, and unattendant pain caused by Buerger's disease.

Materials and Methods

Two of the three patients had been light smokers and had stopped smoking years before manifestation of the disease. The third patient, a very heavy

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smoker, did not stop smoking for the whole duration of the treatment. Two patients have been followed up for one year, one patient is still under therapy.

In our institute the patients received LLLT sessions four to five times per week and after clear clinical improvement the regime was reduced to three times a week. The therapy was carried out with a 10 mW HeNe-Laser (Felas Medical laser Med 10/30 Germany). The incident energy intensity dose (IED) was 0.18 and 2.7 J/cm² depending on the wound area and the irradiation time. The dynamic changes in wound healing processes were documented by photographs. With our IR-thermography equipment we could objectively show and record the changes in the condition of the local circulation over a 'region of interest' under LLLT. By 'region of interest' we mean not only that area which has been treated with LLLT, but also the surrounding unirradiated tissue. Figure 1 shows the thermography set-up, with the camera on the left, and the recording/analysis systems on the right and centre. The image is computer-enhanced, and can be recorded either on film or stored on magnetic media until required. The image displayed on the colour monitor in Figure 1 is the same as in Figure 2A below.

Table 1 shows a typical series of thermography data in the form of a print-out, from case 1 below. The temperature rise, after 20 min of LLLT, was standardized at 0.9°C, allowing for standard deviation. Figure 2A is the thermogram of the affected right hand, palmar aspect, of case 1 before LLLT. The black-and-white version is difficult to interpret: the second digit has an area of very low temperature at the tip, and down the finger itself. The area extending from the junction of the thumb and second finger down over the palm to the wrist is also significantly colder than the rest of the surrounding tissue. In Figure 2B, the post LLLT thermography shows a much more balanced distribution of higher temperature over the whole palm and especially in the affected digit. Although the mean temperature rise was computed 0.9°C for the

Figure 1. Infrared thermography recording and storage system. thermogram on screen is same as Figure 2A.

Figure 2. Case 1: 42-year-old female, thrombosis of both palmar digital arteries of right hand: extreme pain, amputation only course.

(A) IR-Thermography on case 1 patient before LLLT.

(B) IR-Thermography on same patient after 20 min LLLT. Mean temperature rise, 0.9°C, but in some spots, as high as 4°C.

'area of interest', in some areas it was as high as 4°C. For full details of the history and treatment of case 1, please see below in the case report section.

Clinically, all patients reported a significant pain reduction even after the first treatment which lasted a maximum of 2 h. With the number of sessions parallel to the extent of wound healing and reduction of inflammatory signs, a continuous reduction of

Table 1. Thermography data printout (case 1)

LS 15 Schwartz Herta vor Beginn der Lasertherapie			
782	SDir.		
78-1.8	nodus		
Maximum	: T = 42.2 C	Minimum	: T = 38.9 C
Mittelw	: T = 41.7 C	Median	: T = 41.8 C
Std.Abw.	: T = 0.6 C	Schiefe	: T = 0.8 C
Anzahl der pixel:145			
L5 18 Schwartz Herta nach 28 min. Lasertherapie			
782 S 78-1.8	Dir. nodus		
Maximum	: T = 43.1 C	Minimum	: T = 48.2 C
Mittelw	: T = 42.5 C	Median	: T = 42.7 C
Std.Abw.	: T = 0.6 C	Schiefe	: T = 0.8 C
Anzahl der pixel:145			
Durchschnittl.			
Temperaturzunahme			
N. 28 min LLLT-T			
8.9 C			

pain could be noticed. This is in keeping with the latency effect reported by other users in other pain entities, and shown by Moore and his colleagues in his double blind crossover trial for LLLT in postherpetic neuralgia.^{29,30}

Case Reports

Case 1

A 42-year-old woman, a secretary in a top position, had stopped smoking one year before the manifestation of Buerger's disease. She underwent thrombosis of both proper palmar digital arteries of the second finger of the right hand. She was in extreme pain, and after six weeks of prostaglandin infusions the pain was still unbearable. Amputation of the finger seemed to be unavoidable. The patient did not want to accept that and looked for an alternative. We decided to try LLLT, and her treatment protocol is seen in Table 2.

Figure 3A is the condition before LLT: typical appearance of severe ischaemic necrosis in the finger. Figure 3B is after 1 month of LLLT, and already the condition has improved. After 2 months the crust sloughed off, leaving an area of healthy granulation with healing progressing well from the wound margins (Figure 3C). We ended the therapy after three months of LLLT-irradiation because of freedom of pain and complete wound healing with a minimal scar, as seen in Figure 3D.

Case 2

The second patient was a 32-year-old man who had undergone amputation of both lower extremities at the mid-thigh two years previously caused by Buerger's disease. Due to a poorly-fitted artificial leg, an ulcer on the right stump appeared, growing bigger and bigger up to an extent of 400 cm² and

8 cm depth, accompanied by heavy inflammation, swelling and uncontrollable pain. The condition on presenting is seen in Figure 4A, and even in black-and-white the severe ulcerative and ischaemic condition is clearly visible. Neither prostaglandin infusions nor sympathectomy could improve the clinical situation. Enucleation of the hip joint was offered to him as the only possibility to get rid of the pain. The patient refused the reamputation and signed himself out of the hospital at his own risk after a six-month stay, and with a very bad prognosis. We decided to apply LLLT, and Table 3 shows the protocol of LLT applied for this patient.

Despite our strong suggestion to do so, this patient did not stop smoking during the 13 months of therapy. In Figure 4B, 3 months after the first LLLT session, the wound is much healthier with good granulation, and the initiation of wound healing from the now healthy margin is clearly visible. After 8 months, only a small central area remains of the granulation tissue, surrounded by completely normal skin (Figure 4C), and in Figure 4D, after 13 months of LLLT, the wound was completely healed, despite the patient's insistence on continuing smoking.

Case 3

The last patient in this small study was a 40-year-old woman, who had suffered from systemic lupus erythematosus (SLE) for 15 years. The first manifestation of Buerger's disease three years previous to her presenting at the authors' institute had led to an amputation of both lower extremities 20 cm below the knee joint. The patient could walk with two artificial legs and managed her household efficiently with little assistance from her family. Eight months before presenting at the authors' clinic, an occlusion of a medium sized vessel on the left stump led to an embolectomy and one month later to an extensive case of gangrene, accompanied

Table 2. LLLT protocol for case 1 patient

Wound area/ irradiated area	Depth of the lesion (cm)	Pain	IED J/cm ²	Frequency of LLL-T	Duration of LLL-T
10 cm ²	1 cm	+	1.8	4 ×/week	3 months

Table 3. LLLT protocol, case 2

Wound area/ irradiated area	Depth of the lesion (cm)	Pain	IED J/cm ²	Frequency of LLL-T	Duration of LLL-T
400 cm ²	8 cm	+	0.18	5 ×/week, after 2 months 3 ×/week	13 months

Table 4. LLLT protocol for case 3 patient

Wound area/ irradiated area	Depth of the lesion (cm)	Pain	IED J/cm ²	Frequency of LLL-T	Duration of LLL-T
40 cm ²	2 cm	+	2.7	4 ×/week	Still going on (8 months)

by incredible pain. Prostaglandin infusions did not bring any clear improvement of the clinical situation. The patient had already been sympathectomized three years previously, and the surgeon wanted to avoid the enucleation of the knee joint due to the expected instability and the unavoidable change from an active and comparatively mobile housewife to a life-long wheelchair patient. One year previous to presenting, a very small, but indolent ulcer on the other stump had healed easily under LLLT, so the surgeon in charge of the patient asked for our assistance. The LLLT protocol for case 3 is seen in Table 4.

The pretherapy condition is seen in Figure 5A, a gangrenous stump 20 cm distal to the knee. Figure 5B shows the condition after only 1 week of LLLT. As seen in the previous two cases, LLLT encourages the formation of a healthy eschar, under which good granulation tissue forms. In case 3, this eschar sloughed off after 4 months of LLLT, seen from a slightly different angle in Figure 5C. The clean wound margin at the top is seen, with healthy red granulation tissue extending over a large part of the still crater-like wound bed. The blackish object over the lower two-thirds of the wound is the sloughing eschar. After 5.5 months (Figure 5D) the wound bed is completely filled with really healthy well-vascularized granulation tissue, and in Figures 5E and 5F (7 and 8 months respectively of LLLT), the wound can be seen to close gradually, surrounded by normal-looking tissue. Treatment is still continuing, and the prognosis is excellent.

To summarize, in all three cases, we could find under LLLT for this extremely unmanageable condition: (1) Reduction of pain; (2) reduction of inflammation; (3) reduction of oedema; (4) fast demarcation of the necrotic area; (5) fast cleaning of the smudgy, purulent coats; (6) fast granulation of the ulcer ground; (7) wound healing with *restitutio ad optimum* (minimal scar); (8) in no case a change to the worse could be observed; (9) no amputation or reamputation was necessary; (10) treatment could be carried out in an outpatient setting.

The therapy of indolent ulcers caused by Buerger's disease is, due to the extremely disturbed microcirculation, very problematical. The great variety of conventional therapies necessary can be summarized as being required for the therapy of pain, to increase the blood flow, for antiinflammatory therapy and

to encourage fibroblast proliferation to achieve autoplasty for indolent ulcers. Also, all our patients had received conventional therapy before (sympathectomy, prostaglandin infusions, antiinflammatory therapy) without clear clinical improvement. With our IR-thermography equipment we could prove that LLLT induces, besides many other effects, a mean increase of skin temperature over a 'region of interest' of 0.9°C in relation to an increase of skin blood flow³¹⁻³³ (Table 1, Figures 2A and 2B). Thus, we could show objectively that LLLT increases the microcirculation in an ischaemic area. An increase in the efficiency of the microcirculation naturally leads to an increase in tissue metabolism, reduction of inflammation, oedema and due to all these factors, to a significant reduction of pain.

Some parameters in this chain have been proven already, others are still unknown. Buerger's disease, as said above, is rare, but the average age of our patients was 39.6 years, and amputation or reamputation would have led to a life-long invalidism in all cases, plus physical and psychical pain. With LLLT we were able to avoid this. With this clinical paper the authors would like to encourage other colleagues to think about LLLT as an alternative, if the clinical situation of a patient does not allow surgical intervention or if conventional therapy does not show clear clinical improvement.

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Figure 3. Case 1 patient. (A) Pretherapy condition of finger in case 1. (B) Same finger as in Figure 3A after 1 month of LLLT. (C) After 2 months, crust sloughed, healthy granulation seen. (D) 3 months, excellent final condition, LLLT stopped

Figure 4. Case 2 patient: 32-year-old male, mid-thigh amputation 2 years before. Ulcer started by ill-fitting prosthesis, uncontrolled increase. Enucleation of hip joint advised. Patient was a heavy smoker and, despite our advice, continued to smoke all through the treatment. (A) Pretherapy condition: severe ischaemic condition with extensive ulceration. (B) 3 months after first LLLT session, granulation appearing, inflammation down with healthier colour all over. (C) 8 months after first session: only small central area of granulation, surrounded by advancing healthy well-advanced wound healing. (D) 13 months of LLLT, wound completely healed

Table 1. Fibroblast number per treatment per time period (value $\pm$ standard error of mean [SEM])

Hours after plating	Sham	LA60	LA120	LB60	LB120
0	1000	1000	1000	1000	1000
24	3184 $\pm$ 35	4087 $\pm$ 134	3371 $\pm$ 72	2953 $\pm$ 44	2683 $\pm$ 53
48	3734 $\pm$ 89	4618 $\pm$ 100	4715 $\pm$ 145	4619 $\pm$ 286	3481 $\pm$ 122
72	4364 $\pm$ 277	5116 $\pm$ 151	4913 $\pm$ 74	4490 $\pm$ 98	3763 $\pm$ 76
96	4880 $\pm$ 147	6945 $\pm$ 180	8996 $\pm$ 623	6352 $\pm$ 342	5571 $\pm$ 318

Table 2. Results of the statistical analysis (Student's *t*-test) 96h post-plating

	Sham	LA60	LA120	LB60	LB120
LA60	$P < 0.05$	—	NS	NS	$P < 0.05$
LA120	$P < 0.05$	NS	—	NS	$P < 0.05$
LB60	NS	NS	NS	—	NS
LB120	NS	$P < 0.05$	$P < 0.05$	NS	—

NS = No statistical difference.

LA = 95% polarized lamp.

LB = 14% polarized lamp.

~ 60, ~120 = Irradiation time in s.

contrast, when the irradiation time with the 14% polarized light source was increased from 60 to 120 s, there was a decrease in fibroblast proliferation (Figure 3); it was, however, significantly greater than the sham-irradiated control cells.

Discussion

The results obtained suggest that the exposure of U-937 cells to polarized light is followed by the release of substances, presumably growth factors, which stimulate the proliferative activity of fibroblasts. Furthermore, the level of polarization affects

the level of stimulation. Of the two time periods examined, the best time for irradiation with the 95% polarized light was 120 s; with the 14% polarized light source it was 60 s. It has been suggested that the property of polarization induces a quantitative increase of negative surface charges on the irradiated cell surface of human embryo fibroblasts.¹³ In contrast, non-polarized light is responsible for many biological effects,¹⁴⁻²¹ its effects on the number of negatively charged binding sites on cells was only increased slightly compared to that of the sham irradiated cells in a recent study. This alteration of the plasma membrane induced by polarized light was significantly higher than that induced by non-polarized light.¹³ These observations suggest that the active participation of the cell membrane in the process of biostimulation by light is of significance. Evidence of increase in membrane permeability to calcium ions following the exposure of macrophage-like cells to low level laser therapy (LLLT) supports the view that membrane changes are of significance.⁷

Treatment of U-937 cells *in vitro* with polarized light appears to be an effective means of either (1) stimulating the release of fibroblast stimulating growth factor(s), or (2) modifying the irradiated culture medium in a stimulatory manner, or (3) a combination of both. Over-exposure to light

Figure 3. Graph plotting fibroblast cell number against time post-plating for each test group