Real-time Photothermal Imaging and Response in Pulsed Dye Laser Treatment for Port Wine Stain Patients

Cheng-Jen Chang[1], De-Yi Yu[2], Shu-Ying Chang[1], Yen-Chang Hsiao[1], Kuen Ting[3], Kuen-Tsann Chen[4], Kuang-Hua Hou[5]

Background: This study was performed to assess the photothermal response of highly focused laser energy using infrared thermal imaging instrument to detect and assess the actual temperature distribution during flash lamp pumped pulsed dye laser (FLPPDL) treatment for port wine stain (PWS) patients and avoiding its complications.

Methods: A retrospective review of 40 patients with PWS birthmark treated with FLPPDL (l = 585 nm, tp = 1500 ms, 7 mm spot) was conducted over a 2-year period. Subjects' ages ranged between 28 and 46 years (mean 29 years); there were 24 females and 16 males. Twenty patients received non-cooling laser treatment (NC-LT) using light dosages of 5–12 J/cm^2. Another 20 patients received cryogen spray cooling laser treatment (CSC-LT) using light dosages of 5–12 J/cm^2. A real-time infrared thermal imaging and the thermal wave equation were used for assessment. The results of temperature distributions related to the energy change were analyzed.

Results: Proper temperature measurement using infrared thermal imaging instrument and thermal wave equation in non-cooled PWS patients showed that the energy density of pulsed dye laser (PDL) higher than 7 J/cm^2 can reach >44°C and result in burn injury. However, when energy densities beyond 10 J/cm^2 were administered, along with using CSC, thermal damage was could still be minimized without the risk of damage to the treated area.

Conclusion: Using infrared thermal imaging instrument and thermal wave equation, we can predict the skin temperature distribution in FLPPDL for PWS patients during the treatment. In conjunction with CSC, the complications can be minimized.

(*Biomed J 2015;38:342-349*)

Key words: Flash lamp pumped pulsed dye laser, infrared thermal imaging, port wine stain, thermal wave equation

At a Glance Commentary

Scientific background of the subject

Laser treatment involves high stability and low diffusivity, which generates an influx of high energy in a short period of time. Pulse dye laser has become the standard procedure for port wine stain (PWS) treatment. However, more information on the thermal response and temperature distribution during laser treatment is needed for avoiding complications.

What this study adds to the field

The use of cryogen spray cooling in conjunction with pulsed dye laser treatment for PWS is capable of preventing complications and producing excellent clinical results. Using an infrared thermal image instrument and with the thermal changes obtained using thermal wave equations, the reliability of the analytic solution can be ensured.

From the [1]Department of Plastic Surgery, Chang Gung Memorial Hospital at Taipei, Chang Gung University College of Medicine, Taoyuan, Taiwan; [2]Department of Plastic Surgery, Chang Gung Memorial Hospital at Chiayi, Chang Gung University College of Medicine, Taoyuan, Taiwan; [3]Department of Mechanical Engineering, Lunghwa University of Science and Technology, Taoyuan, Taiwan; [4]Department of Applied Mathematics, National Chung Hsing University, Taichung, Taiwan; [5]Department of Mechanical Engineering, Chang Gung University, Taoyuan, Taiwan

Received: Mar. 10, 2014; Accepted: Dec. 17, 2014

Correspondence to: Dr. Cheng-Jen Chang, Department of Plastic Surgery, Chang Gung Memorial Hospital at Taipei. 199, Tung-Hua North Rd., Taipei 105, Taiwan (R.O.C.). Tel: 886-2-27135211 ext. 3502; Fax: 886-2-25140600; E-mail: chengjen@adm.cgmh.org.tw

DOI: 10.4103/2319-4170.148903

Laser treatment involves high stability and low diffusivity, which generates an influx of high energy in a short period of time and, therefore, holds a highly important position in studies requiring constancy and precision.[1-5] The increasingly rapid development and progress of laser techniques have been successfully and broadly applied to cutaneous surgery. However, skin or biological tissues react differently to the absorption and scattering of different light waves, and each wavelength of a laser beam can be used to treat different pathological changes.

Port wine stain (PWS) is a congenital, progressive vascular malformation of the dermis.[6-8] Since two-thirds of these malformations occur on the face, PWS is a clinically significant problem. PWS should not be considered a cosmetic problem, but a disease with potentially devastating psychological and physical complications. Personality development is adversely influenced in virtually all patients by the negative reaction of others to a "marked" person.[9-11] PWS lesions are faint pink macules at birth, but can potentially darken progressively to reddish-purple color.[12] Subsequent hypertrophy of the soft tissue and the underlying bone can also further disfigure the facial features of many patients. Histopathological studies of PWS show a normal epidermis overlying an abnormal plexus of subsurface blood vessels located in the upper dermis.[13] The development of lasers and their ability to damage selective PWS blood vessels has offered a new approach to the clinical management of these patients. To date, multiple laser devices have been utilized for the treatment of PWS birthmarks, but it is the flash lamp pumped pulsed dye laser (FLPPDL) that has produced the best clinical results with the lowest incidence of adverse effects.[14-16] The yellow light produced by the FLPPDL under a wavelength of 585 nm and at a duration within the thermal relaxation time of the ectatic vessel can be preferentially absorbed by hemoglobin, thus allowing selective destruction of the dilated ectatic capillaries in the upper dermis.

Selective photothermolysis has shown to be effectively helpful when used for the inner target tissues in skin or biological tissues and can display the absorption of thermal energy while conducting laser illumination with appropriate wavelength [Figure 1].[17] Because the time period of laser illumination can be abrupt, these target tissues exhibit photothermal phenomena by absorbing the high energy of a laser beam nearly instantaneously, where the surrounding tissue is narrowly affected. Therefore, the energy is capable of damaging the target tissues and not injuring the surrounding skin, a concept closely related to the knowledge of heat transfer. Such an understanding of the temperature distribution on the skin surface will contribute to effective laser surgery and will result in the prediction of skin temperature distribution and the study of skin burn injury, thus becoming important issues in laser surgery today.[18,19]

Current methods that have become standard procedural applications for more than a decade include the use of cryogen spray cooling (CSC). 1,1,1,2-Tetraflouroethane (R134a, BP = −26.2°C) (ICE KLEA, Wilmington, DE, USA), an environmentally compatible, non-toxic, non-flammable refrigerant, was used as the cryogen. Such coolant material is capable of preventing epidermal injury when used in conjunction with pulsed dye laser (PDL) treatment and, thus, when and how administration of the material takes place will be discussed in this stu dy.[15,20-24] However, more information on the thermal response and temperature distribution during laser treatment is needed for avoiding complications.

In regards to the measurement of skin temperature in laser cutaneous surgery, an infrared thermal image instrument was used in this study. The main objective of this study is the analysis and evaluation of skin temperature during laser application which will, in turn, assist medical practitioners in assessing and treating the reaction of skin to laser energy.[25] A heat transfer analysis using the thermal wave equation helps us to learn the importance of the thermal wave theory of photothermal effect. Using an infrared thermal image instrument and with the thermal changes obtained using thermal wave equations, the reliability of th e analytic solution can be ensured. Further discussion of FLPPDL used in cutaneous laser surgery will be presented to improve knowledge of the temperature changes of patients' skin during laser treatment. With this, more accurate predictions of skin surface temperature can be achieved, which could serve as treatment references for researchers and clinicians.

METHODS

This was a retrospective review of 40 subjects (24 females and 16 males) with PWS birthmarks of face

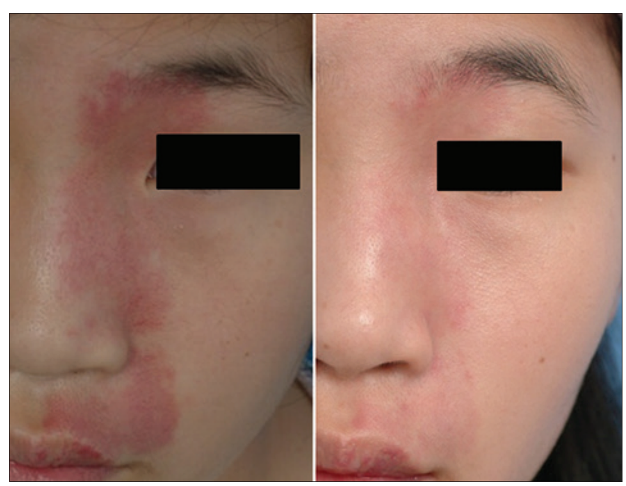

Figure 1: Eleven-year-old female with PWS of the left face: (Left) prior to laser therapy; and (Right) Two year after three treatments with CSC-LT (585 nm) using an energy density of 9 J/cm^2. Results were evaluated as an excellent blanching response.

treated with the FLPPDL over the preceding period from January 2010 to December 2011. Patients' ages ranged between 28 and 46 years (mean 29 years). Information regarding the following variables was extracted from charts: Age, sex, PWS severity grade prior to laser treatment, number of treatments, duration of follow-up, and result following laser therapy. The PWS severity was based on clinical description as follows. Skin with faint, barely discernible borders, plus well-defined borders with areas of normal skin interspersed within the lesion was given score 1. Skin with well-defined borders, uniform lesion with no areas of normal skin, plus raised or thickened lesion, plus nodularity or hypertrophy of involved anatomic structure was given score 2. The study protocol was approved by the Institutional Review Board (IRB) at Chang Gung Memorial Hospital, Taipei, Taiwan. The following were the inclusion criteria of the study: (1) PWS suitable for comparison testing; (2) PWS greater than 20 cm^2; and (3) apparent good health as documented by medical history. The following were the exclusion criteria: (1) Inability to commit to a 3-month follow-up period; (2) pregnancy; (3) history of photodermatoses or skin cancer; (4) concurrent use of known photosensitizing drugs; and (5) any therapy within the previous 2 months to the proposed PWS test sites.

Upon enrollment, 32 test sites were prospectively identified on each patient for treatment assignments to the following regimens: (A) PDL treatment with CSC (CSC-LT); (B) non-cooling PDL treatment alone (NC-LT); (C) CSC alone; and (D) control. Sites were assigned to the treatment regimens by randomization. Every effort was made to place the test sites on optically uniform areas of the PWS. This was done to ensure that clinically relevant PWS characteristics and geometry (i.e. epidermal melanin concentration, blood vessel size, and depth) did not substantially vary between each of the test sites on an individual patient basis. Photographs were taken of the test sites after assignment of treatment regimen and at follow-up visit.

FLPPDL test sites received a single treatment using the ScleroPLUS® (Candela, Wayland, MA, USA) laser (585 nm wavelength; 1.5 ms pulse duration) at energy densities of 5, 6, 7, 8, 9, 10, and 12 J/cm^2, with and without CSC. Patients ($n = 20$) received NC-LT using light dosages of 5–10 J/cm^2. Another group of patients ($n = 20$) received CSC-LT using light dosages of 5–12 J/cm^2. Laser energy was delivered to the skin through an optical fiber and lens which focused the beam onto a 7-mm spot on the PWS. For the CSC-LT group, 1,1,1,2 tetrafluoroethane [C2H2F4 (R134a, cryogen's name in accordance with the National Institute of Standards and Technology); BP = −26.2°C; an environmentally compatible, non-toxic, non-flammable Freon substitute] was used as the test cryogen (ICE KLEA). Cryogen spurt was sprayed for duration of 30 ms onto the PWS through an electronically controlled solenoid valve positioned approximately 10 mm from the skin surface, and covered a nearly circular 10-mm-diameter area. Duration of the cryogen spurt and timing between cryogen delivery and laser irradiation (20 ms) were controlled with a programmable digital delay generator (DG535, Stanford Research Systems, Sunnyvale, CA, USA).

The imaging and changes of skin temperature were measured in real time using an infrared thermal image instrument (ThermaCAM™S60; FLIR System, Danderyd, Sweden). The results of temperature distributions related to the energy change were analyzed. Data of the skin surface temperatures measured by infrared thermal image instrument was put into the analytic solutions of the thermal wave equation with comparisons made between the results calculated. The thermal wave equation can be expressed as:

$$\frac{\partial^2 T}{\partial x^2} - \frac{\rho C \tau}{K}\frac{\partial^2 T}{\partial t^2} - \frac{\rho C + \tau W_b C_b}{K}\frac{\partial T}{\partial t} +$$

$$\frac{W_b C_b}{K}(T_b - T) + \frac{Q}{K} = 0, Q = Q_m + Q_r + \left(\frac{\partial Q_m}{\partial t} + \frac{\partial Q_r}{\partial t}\right)$$

$$Q = Q_m + Q_r + \left(\frac{\partial Q_m}{\partial t} + \frac{\partial Q_r}{\partial t}\right)$$

Here, K is presumed as a constant, Q represents the changes of tissues in terms of the heat source (including the metabolic rate of tissue), Q_m is the thermal energy transformed from chemical energy caused by partial metabolism, $[W_b C_b (T_b - T)]$ is the blood flow (the thermal energy transmitted from in/out controlled volume blood), Q_r shows the volumetric heating, K [W/(m^2•k)] is the thermal conductivity, W_b [kg/(m^3•s)] is the blood perfusion rate, C_b and C [J/(kg•k)] are the specific heats of blood and tissue, respectively, T_b and T (°C) are the temperatures of blood and tissue, respectively, Q_m (W/m^3) is the metabolic rate of tissue, Q_r (W/m^3) is the volumetric heating rate, and τ (kg/m^3) is the density of tissue.[26]

The blenching/dyspigmentation was assessed by a DermoSpectrometer (Cortex Tech., Hadsund, Denmark)[27,28] to calculate the hemoglobin/melanin index at follow-up visit for each of the treatment regimens. The device emits light from diode sources at three defined wavelengths. The amount of light backscattered from the skin is then used to determine the indices for hemoglobin/melanin. Therefore, care was taken to make each measurement with the device in contact with the skin, but without the application of pressure to the test site. Differences between the responses after NC-LT and CSC-LT treatment were then determined and analyzed. Patients were also closely monitored for any adverse effects. Safety was evaluated by examining each of the test sites for any abnormal wound healing (blistering, scabbing, erosion, scarring). The primary efficacy measure was the quantitative assessment of NC-LT PWS as compared to CSC-LT PWS. Differences between the temperatures measured mean blanching/depigmentation response scores for both groups were then determined and a Chi-square analysis was performed.

RESULTS

Based on a multivariate analysis of variance (MANOVA), there were no statistically significant differences between the two groups based on age, sex, PWS severity score prior to laser treatment, and the number of PDL treatments ($p > 0.05$) [Table 1]. Using the one-dimensional equation with fixed surface illumination time and different laser energy densities of 5, 6, 7, 8, 9, 10, 11, and 12 J/cm^2, the initial temperature of the tissue inside the body was set at 37°C.[29] To measure the changes in PWS patients' superficial skin temperature during PDL treatment with the energy density of 7 J/cm^2, an infrared thermal image instrument was used [Table 2]. The baseline skin surface temperature was 32.4 ± 0.2°C. Over the time span of 15 s, the changes in temperature without CSC were recorded to assume proper care following treatment. Temperatures in treated areas were observed to have risen sharply within 5 s, "T-jump" in response to laser exposure, and then immediately began to taper out and decrease gradually afterward.

Thermal wave equation showed the relationship between the light dosage and temperature of the PDL illumination with and without CSC of the skin surface [Table 3]. Without CSC, when the energy density of PDL was higher than 7 J/cm^2, burning injury resulted (i.e. the temperature was higher than 44°C). In other words, the energy density should be lower than 7 J/cm^2 if the PDL is applied to the treatment of skin pathological changes and there is no cooling procedure involved [Figure 2]. The prediction of the skin surface temperature was made from the condition of a high heat flux for a very short time. The thermal wave equation showed that the tissue temperature inside the body was undisturbed at the initial stage of heating and then took an instantaneous jump. This can be viewed as a wave front resulting from a stepwise change in temperature at the skin surface.[30]

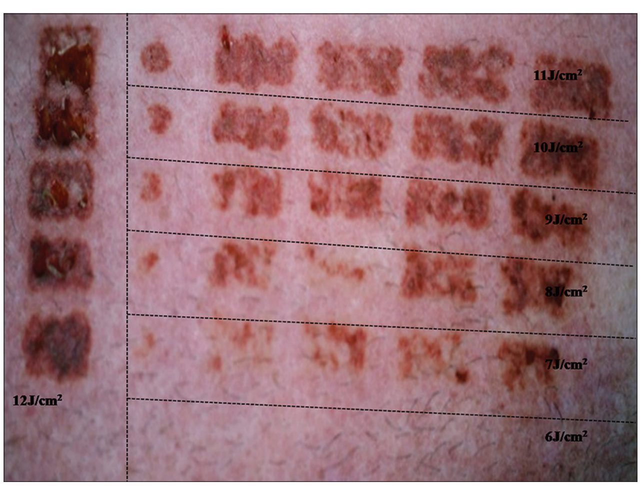

Figure 2: Without CSC, when the energy density of pulsed dye laser was higher than 7 J/cm^2, burning injury resulted.

Temperatures within the therapeutic dosages analyzed by thermal wave equation were observed to be acceptable when CSC was administered to ensure effective results with PWS treatment and prevent the occurrence of thermal damage to the treated area. However, in the instance where the energy density exceeded 10 J/cm^2 with CSC application, it is suggested that careful observation of treated area be conducted, as the risk of thermal injury may increase. On the other hand, based on what was observed in treated

Table 1: Information of PWS patients treated by pulsed dye laser

	NC-LT (*n*=20)	CSC-LT (*n*=20)
Mean age, years	29.4	28.6
Sex (male: female)	18:22	17:23
Mean severity score	1.55	1.54
Mean number of PDL treatments	3.33	3.35

P>0.05. Abbreviations: PWS: Port wine stain; PDL: Pulsed dye laser; NC-LT: Non-cooling laser treatment; CSC-LT: Cryogen spray cooling laser treatment

Table 2: Temperature determination of superficial skin with infrared thermal image instrument for the PDL treatment of the PWS patients

Time (s)	1	2	3	4	5
Temperature (°C)	42.7±0.1	42.9±0.3	43.2±0.2	43.6±0.3	44.2±0.2
Time (s)	6	7	8	9	10
Temperature (°C)	43.6±0.1	41.9±0.1	38.1±0.3	36.5±0.2	35.9±0.4
Time (s)	11	12	13	14	15
Temperature (°C)	34.6±0.3	34.2±0.3	33.5±0.2	33.1±0.1	32.6±0.2
Baseline skin surface temperature: 32.4±0.2°C					
NC-LT energy density: 7 J/cm^2					

Abbreviations: PWS: Port wine stain; PDL: Pulsed dye laser; NCLT: Non-cooling laser treatment; CSC-LT: Cryogen spray cooling laser treatment

Table 3: Skin surface temperatures assessed by thermal wave equation for pulsed dye laser illuminations for different light dosages

Light dosage (J/cm^2)	Skin surface temperature (°C)†	
	NCLT	CSC-LT
5	42.1±0.3	15.9±0.2
6	42.7±0.5	16.5±0.4
7	44.2±0.3	18.0±0.2
8	57.3±0.2	21.1±0.6
9	65.6±0.4	39.4±0.5
10	70.1±0.2	43.9±0.3
11	73.0±0.6	46.8±0.4
12	80.1±0.4	53.9±0.3

†Control skin surface temperature: 32.4±0.2°C. Abbreviations: PDL: Pulsed dye laser; NCLT: Non-cooling laser treatment; CSC-LT: Cryogen spray cooling laser treatment

superficial skin areas, it was determined that when energy densities beyond 10 J/cm^2 were administered, along with the use of CSC, thermal damage was acutely minimized. Higher laser temperatures observed within the therapeutic dosages analyzed by the thermal wave equation were applied with the use of coolant to ensure effective results with PWS treatment without the risk of damage to the treated area.

Infrared images were taken and graphs of patients' temperature were drawn, and the temperatures of both normal skin and skin with PWS were measur ed. The images and graphs represent a patient's reaction time of skin to a PDL energy density of 10 J/cm^{2,} without receiving CSC, and the resulting temperature spurt of super ficial skin without the presence of coolant is apparent. Other images and graphs were also taken of this patient to display the different reaction times of superficial skin after laser treatment with the use of CSC [Figure 3], and these temperature averages clearly show that over the course of 10, 20, 30, and 40 s, injury due to laser illumination can be minimized while using optimum, higher laser temperatures to treat PWS [Figure 4].

In our follow-up period of 1, 3, 6, and 12 months, the blenching/dyspigmentation was assessed by a DermoSpectrometer to calculate the hemoglobin/melanin index for each of the treatment regimens [Table 4]. Permanent scarring was not observed in both NC-LT and CSC-LT sites. Hyperpigmentation was noted in 45% (n = 9) and 25% (n = 5) of patients in the NC-LT and CSC-LT groups, respectively. However, in both groups, the hyperpigmentation was noted to be transient and it resolved spontaneously without medical intervention in all patients. Two patients (10%) in the NC-LT group developed delayed permanent hypopigmentation. Permanent hypopigmentation was not observed in the CSC-LT sites. Based on Chi-square analysis, the CSC-LT procedure was found to be safe, despite the higher light dosages used, since neither permanent scarring nor permanent dyspigmentation was observed ($p < 0.001$).

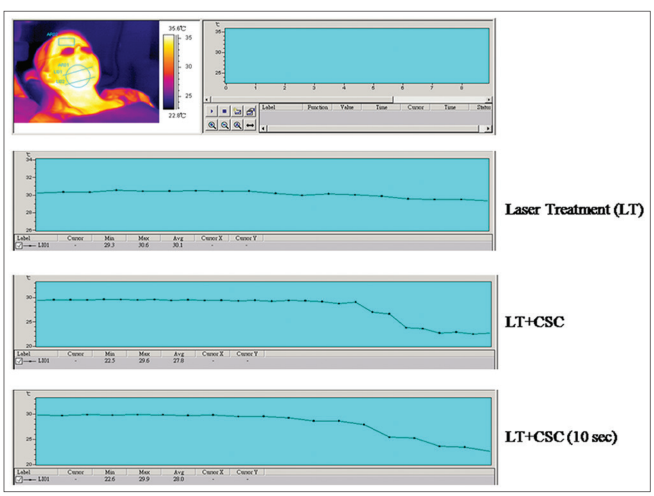

Figure 3: A patient's reaction time of skin, with a PDL energy density of 10 J/cm^2, whom did not receive CSC and the resulting temperature spurt of superficial skin without presence of coolant is apparent. Other images and graphs were also taken of this patient to display the different reaction times of superficial skin after laser treatment with the use of CSC.

DISCUSSION

Cutaneous laser surgery involves the heat transfer behavior of short-term heating in biological tissues, particularly in hypervascular lesions such as PWS. When the surface of living tissues is heated, causing a temperature change, a series of complex changes in their biophysics and biochemistry occur.[29,31] For example, the blood circulation system of biological bodies will not only make heat transfer more complex but also make it difficult to set up any accurate heat transfer analysis model. It is common to use the Pennes equation in predicting how temperature distributes in tissues in bioheat transfer studies.[32] However, some researchers have discovered that the behavior of waves has to be taken into account in bioheat transfer studies under the circumstances of fast heating or cooling.[33-35] This has led to the proposal of the thermal wave theory and thermal wave equation.

Because the thermal wave equation is hyperbolic, it is common to use numerical analysis instead of an analytic solution. Furthermore, owing to the large temperature gradient observed in a thermal energy input spot on the skin surface when the laser is heating the tissue for a short time, we can neglect temperature diffusion on the skin surface. Consequently, this matter will be simplified as a one-dimen-

Table 4: Mean hemoglobin indices of blanching responses by pulsed dye laser treatment

	NCLT (n=20)	CSC-LT (n=20)
Pre-PDL	29.17±5.93	29.17±5.93
1 month	12.42±2.74*	7.58±1.13
3 months	13.87±2.45*	8.97±1.25
6 months	15.646±2.97*	9.62±1.47
12 months	17.69±2.57*	9.86±1.35

*P<0.05. Abbreviations: PDL: Pulsed dye laser; NCLT: Non-cooling laser treatment; CSC-LT: Cryogen spray cooling laser treatment

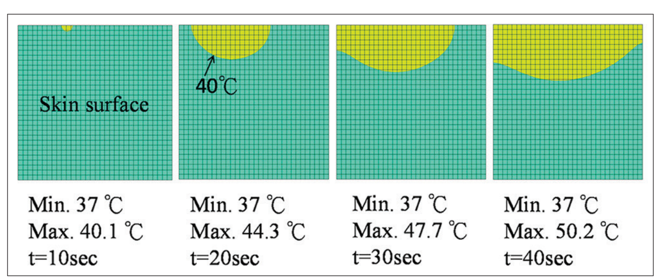

Figure 4: Temperature averages show over the course of 10, 20, 30, and 40 seconds injury due to laser illumination.

sional heat transfer equation applied to the finite difference method to find solutions to the thermal wave equation and to discuss burning injury caused by heating.[30,36] The other studies that also simulated heat transfer in biological tissues by the boundary element method applied the finite difference method to solve the thermal wave equation, in order to understand how the temperature distributes in biological tissues.[37,38] They found that temperature decreases when the thickness of tissue increases and the effect of blood perfusion rate on the tissue attenuates.

For example, human skin tissue contains three layers: Epidermis (thickness is 0.00008 m), dermis (thickness is 0.002 m), and hypodermis (thickness is 0.01 m). Therefore, the thickness of human tissue would be 0.01208 m.[39] It is necessary to consider burning injury when the skin temperature is 44°C.[40] Second- or third-degree burn of the skin will result if the temperature increases. Therefore, it is necessary to carefully control the skin surface temperature in cutaneous laser surgery. Because of the close relationship between the temperature of the skin surface and the energy density of laser illumination, it is important to avoid burning injury when using lasers of different energy densities within certain times and areas.

On the other hand, τ is defined as the characteristic time needed for accumulating the thermal energy required for propagative transfer to the nearest element within nonhomogeneous inner structures in biological tissues. That is, it is the time needed for the temperature of objects to drop by half from the warmest temperature, after being irradiated with a laser. For general homogeneous materials, τ is defined as the thermal relaxation time. The effect of the thermal relaxation time (τ) should be taken into account when applying the thermal wave equation. Usually the thermal relaxation time τ for general homogeneous materials is very low, i.e. between 10^8 and 10^{14} s.[34] Thermal waves show no clear effect during heat transfer, except when there is a marked change in heat flux rate. τ in biological systems has been predicted to be 20–30 s.[33,35] In 1995, researchers, like Mitra *et al*., conducted experiments on processed meat and obtained the following result: τ is 16 s.[41] Currently most studies of biological tissues use a τ of 20 s. Therefore, τ in this study also was set at 20 s.[36] It is very important for the laser surgeons to choose the correct τ for the treatment of vascular lesions.

Due to the instance of laser illumination requiring an extremely short time and its heat flux being tremendously high, the thermal wave effect is very clear during heat transfer, and therefore, our study has conducted an analysis with the thermal wave equation to be able to discuss skin heat transfer. Currently the most common lasers used in cutaneous surgery for PWS are the PDLs in conjunction with the CSC system. The wavelength of the dye laser is 585 nm and the heat flux is 90 kW/m^2. Regarding the input of laser energy, the use of a fixed pulse duration (1.5 ms) on a surface as a boundary condition must also be considered.

When the skin surface temperature exceeds 70°C immediately after pulsed laser exposure (<1 ms), the result is epidermal necrosis.[15] With an ambient skin temperature of 30°C, to ensure that the epidermal temperature does not exceed 70°C after pulsed laser exposure, the highest permissible "T-jump" (ΔT_{LASER}) is 40°C. If a preliminary subtherapeutic diagnostic laser pulse, D_0, produces a T-jump (because incident light dosage is directly proportional to ΔT_{LASER}), then the threshold for epidermal damage (D_E) is

$$D_E = 40D_0/\Delta T_{LASER}$$

When the skin surface is precooled with a cryogen spurt that reduces the epidermal temperature by an amount ΔT_{CSC} immediately prior to pulsed laser exposure, then the maximum permissible epidermal T-jump increases to $40 + \Delta T_{CSC}$, and therefore, the maximum incident light dosage for PWS laser treatment in conjunction with CSC without exceeding the threshold for epidermal damage ($D_{E\text{-}CSC}$) increases to

$$D_{E\text{-}CSC} = (40+ \Delta T_{CSC})\ D_0/\Delta T_{LASER}$$

Consider a simple example to illustrate the principle in a patient with the normal skin surface temperature of 30°C. One joule of laser energy delivered to the skin produces a T-jump of 8°C. Therefore, in order to keep the T-jump after laser illumination at less than 40°C, such that the epidermal temperature does not exceed 70°C. Therefore, in order to obtain attainable results, the boundary condition should be divided in terms of the light dosage of input energy. As to the analytic solution, the separation variable method and superposition principle theory can be used to obtain results. This will make the discussion of skin heat transfer easier and more precise.

In our study, real-time monitoring photothermal images and the prediction of temperature using the thermal wave equation were more reliable. We were able to clearly observe the temperature distribution of heat transfer and the features of the thermal wave phenomenon in laser treatment. Keeping the pulse duration of PDL (τ_p = 1500 μs) on the skin surface fixed, prediction of the skin surface temperature was more accurately analyzed and was devisable by use of the one-dimensional equation. Our study also showed different predictions of PDL illumination for different energy densities. Results show that the effective energy density of lasers should be lower than 7 J/cm^2 based on the thermal wave equation, if the PDL is applied to the treatment of skin pathological changes and if there is no CSC procedure involved. However, when energy densities beyond 10 J/cm^2 were administered, along with the use of CSC, thermal damage to the treated area was acutely minimized. This result is helpful for doctors in determining the optimum laser energy density while simultaneously minimizing damage to the surrounding tissue. Nevertheless, when addressing PWS with definitive treatment, in this case, exact thermal equations, proper procedural analysis of patient, and careful consideration of age, skin type, and area in-line for treatment all must be done for a successful clinical application.

Conclusion

Laser illumination requires an extremely short time and its heat flux is extremely high in cutaneous laser surgery. For prevention of complications, it is necessary to take the thermal wave effect into account. Real-time photothermal imaging and prediction of temperature response on the lesion site, as derived from this study, are helpful for determining the energy density for laser treatment of PWS patients. Energy density higher than 7 J/cm^2 can reach >44°C and result in burn injury. However, when energy densities beyond 10 J/cm^2 are used, along with the use of CSC, thermal damage can still be minimized without the risk of damage to the treated area. This study provides for increased and improved safety of laser surgery patients and establishes the research foundation of other laser treatments.

Acknowledgments

Our research has been supported by the grants of the National Science Council in Taiwan (NMRPG340661, 340662, 376311, 376312), CMRP966, CMRPG32001, CMRPG3B0301, CMRPG3B0302 and CMRPG5D0051. The authors would like to express their sincere gratitude to Dr. J. Stuart Nelson, M.D., Ph.D, Professor of Surgery at Beckman Laser Institute and Medical Clinic at the University of California at Irvine for providing his theoretical perspective and medical expertise to assist in the research.

REFERENCES

1. Stoll AM, Greene LC. Relationship between pain and tissue damage due to thermal radiation. J Appl Physiol 1959;14:373-82.
2. Lecarpentier GL, Motamedi M, Mcmath LP, Rastegar S, Welch AJ. Continuous wave laser ablation of tissue: Analysis of thermal and mechanical events. IEEE Trans Biomed Eng 1993;40:188-200.
3. Ogura M, Sato S, Kuroki M, Wakisaka H, Kawauchi S, Ishihara M, Kikuchi M, Yoshioka M, Ashida H, Obara M. Transdermal Delivery of Photosensitizer by the Laser-Induced Stress Wave in Combination with Skin Heating. Jpn J Appl Phys 2002;41:814-6.
4. Eto O, Tajima T, Zhang Y, Hirano T. Pulsed Homodyne Detection of Squeezed Light at Telecommunication Wavelength. Jpn J Appl Phys 2006;45:821-3.
5. Ozawa K, Okuzono T, Doi M. Simple model of skin formation caused by solvent evaporation in polymer solutions. Phys Rev Lett 2006;97:136103.
6. Pratt AG. Birthmarks in infants. Arch Dermatol Syphilol 1953;67:302-5.
7. Jacobs AH, Walton RG. The incidence of birthmarks in the neonate. Pediatr 1976;58:218-22.
8. Mulliken JB. Diagnosis and natural history of hemangiomas. In Vascular Birthmarks: Hemangiomas and Malformations. In: Mulliken JB, Young AE, editors. Philadelphia, Pa: W.B. Saunders; 1988.
9. Kalick SM. Toward an interdisciplinary psychology of appearances. Psychiatry 1978;41:249-54.
10. Heller A, Rafman S, Svagulis I, Pless IB. Birth defects and psychosocial adjustment. Am J Dis Child 1985;139:257-63.
11. Malm M, Calber NN. Port-wine stain-a surgical and psychological problem. Ann Plast Surg 1988;20:512-6.
12. Geronemus RG, Ashinoff R. The medical necessity of evaluation and treatment of port-wine stains. J Dermatol Surg Oncol 1991;17:76-9.
13. Barsky SH, Rosen S, Geer DE, Noe JM. The nature and evolution of port wine stains. a computer assisted study. J Invest Dermatol 1980;74:154-7.
14. Renfro L, Geronemus RG. Anatomical differences in the treatment of port wine stains with the pulsed dye laser. Arch Dermatol 1993;29:182-8.
15. Chang CJ, Nelson JS. Cryogen spray cooling and higher fluence pulsed dye laser treatment improve port wine stain clearance while minimizing epidermal damage. J Dermatol Surg 1999;25:767-72.
16. Geronemus R, Lou W, Quintana A, Kauvar A. High fluence modified pulsed dye laser photocoagulation with dynamic cooling for port wine stains in infancy. Arch Dermatol 2000;136:942-43.
17. Chang CJ, Kelly KM, van Gemert MJC, Nelson JS. Comparing the effectiveness of 585-nm versus 595-nm wavelength pulsed dye laser treatment of port-wine stains in conjunction with cryogen spray cooling during. Lasers Surg Med 2002;31:352-8.
18. Moritz AR, Henriques FC. Studies of thermal injury II. relative importance of time and surface temperature in the causation of cutaneous burns. Am J Pathol 1947;23:695-720.
19. Lawrence SB, Michael RT. Laser tissue welding. A comprehensive review of current and future. Lasers Surg Med 1995;17:315-49.
20. Chang CJ, Anvari B, Nelson JS. Cryogen spray cooling for spatially selective photocoagulation of hemangiomas-A new methodology with preliminary clinical reports. Plast Reconstr Surg 1998;102:459-63.
21. Chang CJ, Kelly KM, Nelson JS. Cryogen spray cooling and pulsed dye laser treatment of cutaneous hemangiomas. Ann Plast Surg 2001;46:577-83.
22. Huang PS, Chang CJ. Cryogen spray cooling in conjunction with pulse dye laser treatment of port wine stains of the head and neck. Chang Gung Med J 2001;24:469-75.
23. Chang CJ, Ma SF, Tzeng YF, Wei FC. Dynamic cooling for laser photocoagulation: *In vivo* and *ex vivo* studies. J Med Biol Eng 2002;22:25-32.
24. Chang CJ. Long Term Follow-up of Intralesional Laser Photocoagulation (ILP) for Hemangioma Patients. Laser Ther 2011;20:255-63.
25. Sun YS, Weng CI, Chen TC, Li WC. Estimation of Surface Absorptivity and Surface Temperature in Laser Surface Hardening Process. Jpn J Appl Phys 1996;35:3658-64.

26. Ting K, Chen KT, Cheng SF, Lin WS, Chang CJ. Prediction of Skin Temperature Distribution in Cosmetic Laser Surgery. Jpn J Appl Phys 2008;47:361-7.

27. Tejasvi T, Sharma VK, Kaur J. Determination of minimal erythemal dose for narrow band-ultraviolet B radiation in north Indian patients: Comparison of visual and Dermaspectrometer readings, Indian. J Dermatol Venereol Leprol 2007;73:97-9.

28. Ramsing DW, Agner T. Effect of glove occlusion on human skin. (I). short-term experimental exposure. Contact Dermatitis 1996;34:1-5.

29. Magaribuchi T, Ito Y, Kuriyama H. Effects of rapid cooling on the mechanical and electrical activities of smooth muscles of guinea pig stomach and taenia coli. J Gen Physiol 1973;61:323-41.

30. Liu J. Uncertainty analysis for temperature prediction of biological bodies subject to randomly spatial heating. J Biomech 2001;34:1637-42.

31. Alexander RR, Griffiths JM: Basic Biochemical Methods, 2nd ed. New York: Wiley-Liss, Inc.; 1993. p. 181.

32. Pennes HH. Analysis of tissue and arterial blood temperatures in the resting human forearm. J Appl Appysiol 1948;1:93-122.

33. Kaminski W. Hyperbolic Heat Conduction Equation for Materials with a Non-homogeneous Inner Structure. J Heat Trans 1990;112:555-60.

34. Diller KR, Hayes LJ. Analysis of tissue injury by burning: Comparison of *in situ* and skin flap models. Int J Heat Mass Transfer 1991;34:1393-406.

35. Liu J, Ren Z, Wang C. Interpretation of living tissue’s temperature oscillations by thermal wave theory. Chin Sci Bull 1995;40:1493.

36. Zhang XS, Zhu YS, Thakor NV, Wang ZM, Wang ZZ. Modeling the relationship between concurrent epicardial action potentials and bipolar electrograms. IEEE Trans Biomed Eng 1999;46:365-76.

37. Lu WQ, Liu J, Zeng Y. Simulation of the thermal wave propagation in biological tissues by the dual reciprocity boundary element method. Eng Anal Bound Elem 1998;22:167-74.

38. Nabil TM, Mona AA, Asma FE. Effects of microwave heating on the thermal states of biological tissues. Afr J Biotechnol 2003;2:453-9.

39. Cattaneo C. A Form of Heat Conduction Equation Which Eliminates the Paradox of Instantaneous Propagation. Compte Rendus 1958;247:431-3.

40. Torvi DA, Dale JD. A finite element model of skin subjected to a flash fire. J Biomech Eng 1994;116:250-5.

41. Mitra K, Kumar S, Vedavarz A, Moallemi MK. Experimental evidence of hyperbolic heat conduction in processes meat. ASME J Heat Transfer 1995;117:568-73.