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Numerical Modeling and Clinical Evaluation of Pulsed Dye Laser and Copper Vapor Laser in Skin Vascular Lesions Treatment

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Abstract

Introduction: Different yellow lasers have been successfully used for the treatment of vascular lesions. This study is aimed to ascertain the role and efficiency of copper vapor lasers (CVLs) and pulsed dye lasers (PDLs) for the treatment of vascular lesions using numerical modeling and to compare results with our clinical experience. In this study we aimed to develop criteria for the choice of more efficient laser exposure mode, investigate more relevant modes of laser irradiation to ensure selective photothermolysis of target vessels, and compare the CVL and PDL efficiency in the course of patients with skin vascular lesions (SVL) treatment.

Methods: We performed numerical simulation of the processes of heating a vessel with CVL and PDL to temperatures at which its coagulation could occur. Calculated fluencies were compared with clinical results of laser therapy performed on 1242 patients with skin hemangiomas and vascular malformations (SHVM), including 635 patients treated with CVL and 607 patients treated with PDL. PDL and CVL provided excellent results in 40 and ten days after treatment. The treatment was not painful. Patients did not need anesthesia. Postoperative crusts were greater with PDL than with CVL.

Results: Results of computer simulation of a selective vessel heating using PDL and CVL radiation are presented. By results obtained, depth of the location and sizes of vessels that could be selectively heated to more than 75°C are determined.

Conclusion: Based on calculated and clinical data, the heating mode for dysplastic vessels using a series of CVL micropulses could be regarded to be safer and more efficient than the mode of a PDL short, powerful pulse.

Keywords: Copper vapor laser; Pulse dye laser; Micropulse mode, Vascular malformations; Laser treatment; Selective photothermolysis; Port wine spots; Telangiectasia

Introduction

Development of various laser systems for the treatment of skin hemangiomas and vascular malformations (SHVM) allowed achieving important milestones in modern cosmetology and dermatology.[1-3] Nevertheless, accepted as a gold standard in the SVL treatment the pulsed dye lasers (PDLs) were reported to fail to provide desirable results in the capillary malformations therapy with a majority of patients both due to incomplete SVL bleaching and patients widespread complaints of purpura.[4,5] The advanced efficiency of SVL treatment is based on the pathogenetic complete and selective photothermal obstruction of dysplastic vessels.[6] Thermal response of skin vessels exposed to laser irradiation was reported to be varying because of dilation, blood clot formation followed by a decline in the vascular lumen, extravascular blood cell transfer to the vascular wall, disruption and denaturation of dermis proteins along with increasing the laser light irradiation power.[7] On the other hand, the thermal response of a skin vessel is determined by both optic features of laser light and skin blood vessel interaction, and such spatial peculiarities of the skin vascular bed as vessel diameter and its location.[8,9] Up to now the application of modern computer technologies provides the possibility to compare the optic and thermal laser and skin blood vessel interaction. The challenge of the relevant mode of the SVL laser treatment could rely upon data obtained from numerical simulation of the skin blood vessels photothermal response to irradiation originating from different laser systems.[10] Such approach

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should provide appropriate options for the elaboration of a laser treatment protocol for the complete laser obstruction of the various diameter dysplastic vessels at specific depths without certain side effects on extravascular skin components.

The objective of the study was a clinical evaluation of different modes of laser therapy adjusted accordingly to data obtained as a result of numerical simulation of the photothermic response of skin vessels treated with PDL or copper vapor laser (CVL).

Methods

Numerical Simulation of Heating Vessels Exposed to CVL and PDL Radiation

Numerical simulation of skin vascular lesions (SVLs) exposure to various modes of laser treatment was implemented according to the solution of both thermal conductivity and diffusion equations.[11,12]

Numerical simulation considered optical and physical properties of skin containing different chromophores. The skin was assumed to have a multilayer plane-parallel structure of finite width and infinitely extended along the skin surface.[13] The skin structure was considered to consist of the epidermis including a basal layer (stratum basale) containing melanin, as the skin chromophore, and dermis composed of discrete blood vessels keeping oxyhemoglobin, as the most potent chromophore. Epidermis including the basal layer of 15 μm was assumed to have the thickness of 70 μm. Values of optical characteristics of melanin, oxyhemoglobin and extravascular dermal components as absorption coefficient, scattering coefficient, anisotropy index for the CVL and PDL wavelength and thermal characteristics of skin components - thermal conductivity and specific heat were taken from.[14,15]

Blood vessels were considered to have diameters ranging from 30 to 300 μm and located at a distance from skin surface varying from 100 to 300 μm. Vessels were presented in the form of a cylinder of the infinite length located parallel to the surface of the tissue. Optical properties of all considered skin structures were assumed to be both dependent on the wavelength and homogeneous. This model did not take into account changes in the skin sections optical and physical properties due to vessel obstruction or temperature changes. Calculations were implemented using the FEMLAB/COMSOL Multiphysics software (Table 1).

Table 1. Parameters of PDL and CVL Used for the Calculation

Laser System Settings	Laser System	
	CVL	PDL
Wavelength, nm	578	585
Mode	Pulse	Pulse
Fluence	5-20 J/cm^2	3-8 J/cm^2
Spot diameter, mm	1	5
Exposure duration, ms	30-200	0.45
Pulse width, t_p Interpulse interval, t_{pause}	t_p=15 ns, t_{pause}=60 μs	t_p=0.45 mc
Number of laser pulses during exposure duration	3332	1

Clinical Evaluation of the CVL and PDL Treatment Efficiency and Safety

The efficacy of laser treatment was evaluated with 1242 SHVM patients including 842 women and 400 men aged from 8 to 72 years. All patients were of Caucasian origin (I-II skin type according to Fitzpatrick). 635 cases treated with CVL included 168 patients with telangiectasia, 162 - angiomatous nevus, 132 - strawberry nevus, 63 - angiokeratoma, 48 - nevus flammeus, 34 presented telangiectatic nevi and 28 had Unna's nevus. PDL treatment was used in 607 cases including 158 cases with an angiomatous nevus, 157 – telangiectasia, 142 - strawberry nevus, 73 - angiokeratoma, 32 - nevus flammeus, 23 - telangiectatic nevi and 22 - Unna's nevus.

Laser Exposure Settings for the Treatment of Skin Vascular Lesions

Laser treatment of SVLs was performed using the CVL system (Yakhroma-Med, Russian Federation) with the following parameters (578 nm wavelength, 15 nanoseconds pulse width and 16.6 kHz repetition rate). The CVL output irradiation was delivered via the quartz optical fiber with a diameter of 600 microns and focused by a lensed handpiece in 1 mm spot on the skin. The CVL average power for treatment was set in the range of 0.50 to 0.65 W. To dose the effect on the skin, the laser was equipped with an electronic shutter opening for 0.1-0.2 seconds.

The SPTL-1 laser settings were as follows: 585 nm wavelength and 0.45 milliseconds fixed pulse width. The PDL was providing a light spot of 3 mm or 5 mm in diameter. The energy density could be varying from 3 to 8.5 J/cm^2. 10%-15% was overlapping the treated skin areas. Posttreatment skin care included the application of a thin layer of antibacterial gel several times a day until achieving complete recovery.

After treatment, patients were asked to evaluate their opinion on the treatment outcome.

The efficiency of laser therapy was estimated as the therapeutic response graded on a scale of 3 - 0, where the score was assumed to be of 3 with patients with >75 % improvements, 2 in cases with 50% to 75% improvements, 1 - patients with 50 % or less improvements and 0 - patients without improvements in the SVL treatment. We took into consideration side effects evaluated on the basis of the patients' attitude to the laser therapy mode using questionnaires.

Data on the evaluation of the treatment efficiency using CVL and PDL systems is presented in Table 2. The $\chi 2$ criterion assessed the reliability of differences in the

Table 2. CVL and PDL Treatment Efficiency in SHVM Cases

Treatment Results	Mode of Laser Treatment			
	CVL (n=635)		PDL (n=607)	
	No.	%	No.	%
Excellent	130	20.5	33	5.4
Good	375	59.0	229	37.8
Satisfactory	114	17.9	296	48.7
Unsatisfactory	16	2.6	49	8.1
The average score of the treatment efficiency	1.97		1.41	

efficacy of treatment with different lasers.

With the CVL treated patients, the relevant clinical recovery was achieved in 20.5 % cases that were 4 times more than in cases with patients, who received the PDL treatment. The number of CVL treated cases showed significant (excellent and good) improvements (79.5%) and were almost twofold, if compared with the PDL treated patients (43.2%). These results show the therapeutic efficiency of the SHVM CVL treatment, which was notably higher than in cases of the PDL treatment ($\chi 2 = 11.345$, $P < 0.01$).

Evaluation of the results and quality of treatment and a study on the reaction, and the attitude of patients to the use of laser therapy were carried out using questionnaires. The method of questioning consisted in the self-filling of a simple questionnaire, which made it possible to assess the compliance of patients and the further prospects of laser treatment with the SHVM patients. One CVL treated and nine PDL treated patients reported significant pain after the treatment procedure. Data about the safety of treating the SHVM patients with different laser systems is presented in Table 3.

With the CVL treated patients, the most frequent side effects were mild light linear crusts, which appeared on the third day and disappeared by the seventh day after treatment, edematous areas sized 1 mm in diameter, and hyperemia. With all the PDL irradiated patients, soon after the laser procedure there appeared purpuric spots replaced by dark crusts persisting for up to 10 days and disappearing by the 14th day. The other most frequent side effects with the PDL treated patients were depigmentation or hyperpigmentation, which was diminishing after six weeks and completely disappeared 6 months later, followed by crusts, edema, and hyperemia. The total prevalence of side effects with the CVL treated patients was almost three times less than in the PDL irradiated cases ($\chi^2 = 15.086$ for $P < 0.01$). 81% of patients with such capillary malformations as port-wine stains and 78% of cases with telangiectasias evaluated the results of treatment as positive and believed their appearance was improved. Thus, the recovery with the CVL treated patients took twice less time than in the case of PDL treatment.

Table 3. Prevalence of Side Effects After Treatment With CVL and PDL Systems

Clinical Symptom	Observation Groups			
	CVL (n = 635)		PDL (n = 607)	
	No.	%	No.	%
Crusts	32	5.1	49	8.1
Edema, Hyperemia	32	5.1	49	8.1
Vesicular rashes, Wetting		-	33	5.4
Depigmentation, Hyperpigmentation		-	66	10.8
Peeling	17	2.6	16	2.7
Telangiectasia			16	2.7
Total		12.8		37.8

Results

Numerical Simulation of the Photothermic Response of Skin Vessels Exposed to CVL and PDL Treatment

In Figure 1, we present the calculated temperature distribution for 3 depths (150, 300, and 500 mcm) and three vessel sizes (30, 100 and 300 mcm in diameter). We suggested that coagulation occurred at a maximum temperature of 75°C, and chose the maximum fluence value to reach this temperature for a vessel, and did not exceed this temperature for the basal layer and surrounding tissue.

Figure 1 shows the calculated temperature exposed to CVL and PDL radiation at maximum fluence values, at which the selective coagulation of the vessel could be achieved. Using the fluence values exceeding this limit, the "vessel heating" becomes nonselective; coagulation of the vessel, basal layer, and surrounding tissue is taking place (temperature exceeds 75°C).

The deeper vessels received less energy and were heated at the lower temperature. Our calculation indicates that the maximum heating temperature of a vessel and basal layer using CVL was lower than in the case of PDL. The vessel temperature after PDL exceeds 100°C.

If the vessel diameter is more than 100 mcm, it is difficult to reach the full volume heating because of the high magnitude of blood absorption at 585 nm (Figure 2). However, in 3 milliseconds after the end of PDL pulse, we could see temperature flattering along the entire volume of the vessel. We take into account this process during the determination of the PDL safe fluence range.

We calculated maximal depth at which the vessel could be selectively heated up to more than 75°C using PDL at 585 nm (pulse with 0.45 ms) and CVL at 578 nm (exposure duration 30-200 ms) (Figure 3).

As could be seen, limitation of the PDL technology is connected to the constant pulse duration. At the same time, we could change the CVL exposure time and adjust the vessel depth and location, which could be selectively heated (Figures 3 and 4).

Normal capillaries are approximately seven mcm in

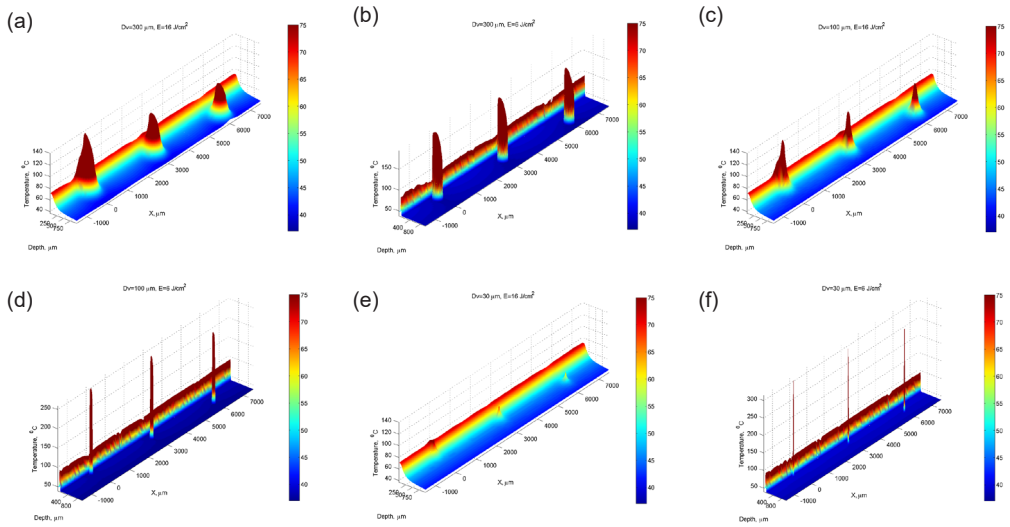

Figure 1. Calculated Temperature Distribution in the Tissue and Vessel According to the Depth and Transverse Coordinate. Vessel with a diameter of 30, 100 and 300 mcm is located at a depth of 150, 300 and 500 mcm for CVL (fluence of 16 J/cm^2) (a, c, e) and PDL (fluence of 6 J/cm^2) (b, d, f).

diameter. Normal capillaries could not be damaged by the CVL output with the treatment parameters that we calculated for the ectatic vessels. But the PDL output could overheat the normal capillaries to temperatures higher than 100°C.

Discussion

Laser irradiation of the skin vascular anomalies is widely accepted as the standard protocol in the SHVM patients' treatment. However, the SHVM therapeutic recalcitrance was reported to be registered with half of such patients.[16] The most promising strategy to overcome the SHVM therapeutic recalcitrance is believed to be introduction of the optimal models to ensure the highest efficiency and safety of the SHVM patients' laser treatment.[17] Histochemical studies of the post laser treatment skin vascular bed in cases with various outcomes of the laser treatment proved the complete obstruction of the dysplastic vessels to be the most necessary for the satisfactory results of the SHVM patients' laser therapy.[18] Relevant laser irradiation settings providing the appropriate heat transfer to dysplastic vessels for the complete obstruction could be determined with the numerical simulation of the photothermal response of skin blood vessels and extravascular components to the exposure to laser light with various wavelength and irradiation time modes.[15] So far, numerical simulation allows comparing features of heat transfer in the SHVM treatment using various laser systems and explaining the observed differences between them in terms of specific optical characteristics of main skin chromophores exposed to laser light irradiation of certain wavelengths and time periods.[19] The blood chromophores absorption of light with a 578 nm wavelength generated by CVL (354 cm^{-1}) appears to be almost twice higher, if compared to the absorption of light with a 585 nm wavelength

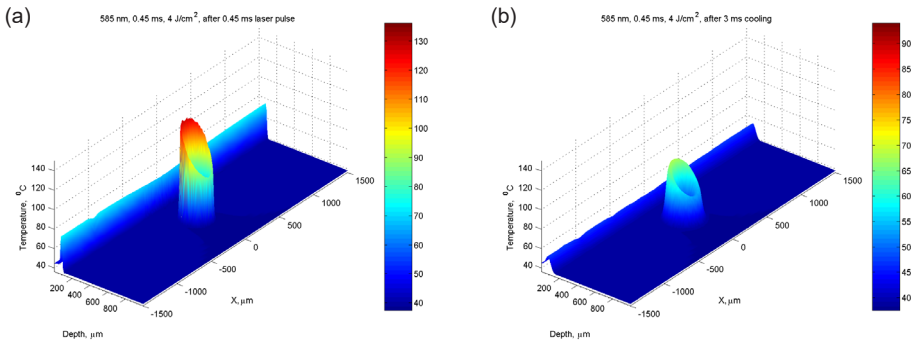

Figure 2. Calculated Temperature Distribution in the Tissue and Vessel According to the Depth and Transverse Coordinate. A vessel with a diameter of 300 mcm was assumed located at a depth of 500 mcm for PDL fluence of 4 J/cm^2 (a- maximum heating at the end of PDL pulse, b- 3 msec after the end of PDL pulse).

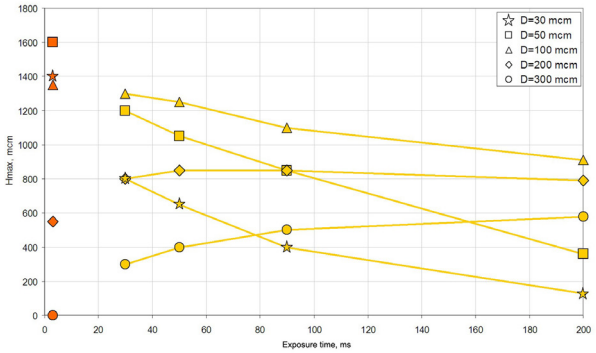

Figure 3. Calculated maximum depth, at which the vessel could be heated entirely up to 75°C using PDL at 585 nm (orange dots) and CVL at 578 nm(yellow dots).

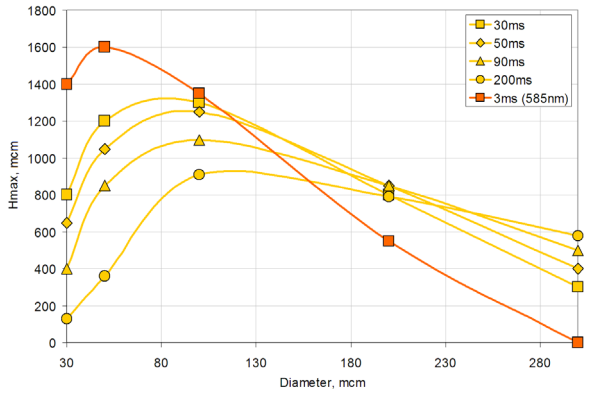

Figure 4. Calculated maximum depth, at which the vessels of different diameters could be heated entirely up to the temperatures higher than 75°C using PDL at 585 nm(orange line) and CVL at 578 nm(yellow line) with different exposure time.

(191 cm^{-1}) provided by PDL [14]. However, our data of numerical simulation of the blood vessels photothermal response showed PDL treatment to give rise in the more pronounced heating of blood vessels than CVL treatment of the same vessels matched in diameter and location (Figure 3).

Presented by us high-temperature values of blood vessels exposed to PDL are completely consistent with reports concerning numerical simulation of vascular photothermal responses to PDL exposure.[15] The different rate in the laser heating of the targeted vessel could explain the observed difference in photothermal response of blood vessels to CVL and PDL light exposure. The overheating of dysplastic vessels exposed to PDL irradiation demonstrated in our numerical simulation was consistent with our clinical data indicating the longer recovery time after PDL treatment. PDL treatment caused the development of purpura due to extravasation of overheated erythrocytes in the dermis and associated with side effects, such as crusts, edema, depigmentation or hyperpigmentation due to deterioration of skin extravasal components.[20]

Our data of the numerical simulation of the photothermal response of dysplastic vessels exposed to different laser irradiation showed the higher risk for the loss of selectivity in laser treatment with PDL irradiation to the smallest vessels due to the very high temperature of blood vessels.[21,22] It is of special value for the clinical application of PDL in the hemangioma infants treatment from the view of results of investigations performed in the framework of bench-bedside medicine. The elevated expression of proinflammatory vascular endothelial growth factor (VEGF) in hemangioma infants necessitates the gain in the vascular permeability due to disrupting interendothelial junctions.[23,24] So far, the preferable mode of the SHVM laser treatment should provide laser irradiation with both light wavelengths mostly absorbed by target blood chromophore and pulse pattern as a train of micropulses with exposure duration set according to the diameter and location features of dysplastic vessels with the use of modern imaging technologies.[25]

The results of our simulations for CVL were compared with the histochemical study by Neumann et al.[26] Our model is in excellent agreement with the experimental data and predicts the selective vascular heating with slight perivascular collagen damage.

According to classification of port-wine stains (https://birthmark.org/node/100), we are able to predict the optimal exposure time and laser type for different 4 grades of PWS by their degree of vascular ectasia (Table 4).

Conclusion

Numerical simulation of the photothermal skin vascular response to laser irradiation allows comparing the efficiency and safety of laser treatment of skin vessels exposed to different laser systems. The data on numerical simulation of skin vascular photothermal response of SHVM vessels indicated CVL to be considered to provide more safe laser treatment especially for skin vascular anomalies involving vessels of smaller diameter and located more close to the skin surface. The numerical simulation of the photothermal skin vascular response could be used for adjusting individual laser settings and considering the specific diameter and location of the involved dysplastic vessels typical for a personal clinical SHVM picture or determined by modern imaging

Table 4. Laser Types Predicted to Provide the Maximum Efficiency for Different Ranges of PWS Vessels

Grade of PWS	I	II	III	IV
Vessel diameter range, mcm	50-80	80-120	120-150	More than 150
Laser type	PDL	CVL, PDL	CVL, PDL	CVL

technologies.

Ethical Considerations

The authors certify that all the patients reported in the article have given the informed consent concerning the publication all information about their management and side effects of the treatment.

Conflict of Interests

The authors declare no conflict of interest.

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