

CLINICAL DERMATOLOGY

Tweaks in intervals improve pulsed dye laser treatment of vascular lesions

Multi Passes

By CHERYL GUTTMAN STAFF CORRESPONDENT

Sacramento, Calif. — A multipass technique using a longer interval between pulses may offer new opportunities for therapeutic benefits when treating vascular lesions with a pulsed dye laser, Emil A. Tanghetti, M.D., said.

Dr. Tanghetti, clinical professor of dermatology, University of California

at Davis, and a private practitioner in Sacramento, reported the results of an experiment where he evaluated the skin effects resulting from pulsed dye laser treatment performed with a single pulse or dual pulses separated by variable interpulse intervals. Using a 595nm pulsed dye laser (V-Star) at a 1 Hz pulse

rate with adjunctive cooling (Smart-Cool), normal buttocks skin in five subjects was divided into five areas and treated to determine the purpuric threshold using a single pass or double passes spaced one, three, five, or 10 seconds apart.



Dr. Tanghetti

One side was treated with the pulse duration set at 0.5 msec and the contralateral side was treated with a pulse duration of 40 msec.

Clinical assessments were performed after 0.5 and 24 hours, and a biopsy was obtained at 24 hours for histological evaluation of the nature and extent of vascular damage.

The results showed purpura was less intense when treatment was delivered with a 40-msec versus 0.5-msec pulse duration and that the skin response was enhanced by double passing, especially in skin treated with the longer pulse duration. In addition, when a double-pass technique was used for the 40-msec treatments, the degree of vascular damage increased as the pulse interval was lengthened from one to 10 seconds, as demonstrated by the findings of increased histological depth of vascular damage and lowering of the purpuric threshold.

Further Proof

Dr. Tanghetti observed the latter findings corroborate results from an earlier study reported by Koster and colleagues [*Lasers Surg Med* 2001;28:176-181] who found pulsed dye laser treatment using overlapping pulses spaced three seconds apart could increase the depth of tissue injury relative to the effect of nonoverlapping pulses. However, the relationship between increased pulse interval and greater vascular damage is inconsistent with thermal diffusion theory, and so is likely accounted for by some yet to be explained biological phenomenon, he said.

"The mantra for using pulsed dye lasers is to perform only a single pass treatment in order to avoid complications," Dr. Tanghetti said. "However, our results, consistent with the earlier findings of Koster and colleagues, indicate there may be a role for multipassing and that by tweaking the interpulse interval correctly, we can achieve better results with pulsed dye laser treatment of vascular lesions."

He added that he has begun to apply that theory to develop new protocols for treating some resistant port-wine stains, and he reported anecdotally, multipassing with one- to 10-second pulse interval seems to be helpful for clearing those lesions by increasing the depth of injury.

"We believe, however, our study results contain a message about strategies for increasing depth of injury that might be applicable to all lasers," Dr. Tanghetti said.

In the experiment performed with the pulsed dye laser set at a 40 msec pulse duration, the purpuric threshold averaged almost 13 J/cm² for single-pulse treatments. That value was reduced significantly by nearly 3 J/cm² when two passes were applied one second apart, and there was a trend for the purpuric threshold to be even lower with a two-pass treatment performed with a 10-second interpulse interval.

"Our study only involved five subjects, which might account for our inability to detect a statistically significant difference," he said.

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Cutaneous Warts

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ing Medline, Embase, the Cochrane controlled trials register, and cited references. Dr. Gibbs and colleagues selected 50 trials for their systematic review of local treatments of extragenital warts. Criteria for trial selection included concealment of allocation, blinding of outcome evaluation, handling of patient withdrawals, dropouts, sample size, matching of treatment groups at baseline, data handling, and overall reporting.

"Most trials we looked at weren't clear about how randomization was being done," Dr. Gibbs said. "Many had a high dropout rate, the analysis was done only on patients who finished the trial, many were not properly blinded, and many were too small," Dr. Gibbs said. "We looked at other types of studies, but Cochrane dogma, which I happen to agree with, is that randomized trials are the only ones worth looking at."

Despite the heterogeneity of the trials, Dr. Gibbs and colleagues pooled some data and cautiously summarized their findings.

Salicylic Acid

Thirteen trials investigated the efficacy of topical salicylic acid at concentrations ranging from 16 percent to 60 percent. Some preparations contained lactic acid as well. Pooled data from six placebo-controlled trials showed a 75 percent cure rate compared to 48 percent in controls. In one trial, cellulitis was reported in one of 29 patients receiving 60 percent salicylic acid with monochloroacetic acid.

Cryotherapy

Sixteen trials evaluated cryotherapy. Four compared cryotherapy with placebo, no treatment, or salicylic acid and none found that cryotherapy was more effective. Pooled data from four other trials showed that "aggressive" cryotherapy was more effective than "gentle" cryother-

apy (52 percent vs. 31 percent cure rates, respectively). Blisters and pain were more frequent in the aggressive therapy and five of 100 patients withdrew from the aggressive treatment group because of these adverse effects.

Topical Immunotherapy with DNCB

Pooled data from two trials showed cure rates of 80 percent and 38 percent for DNCB and placebo, respectively. Neither trial provided precise data on adverse effects, although six of 20 patients treated with 2 percent DNCB became sensitized after only two treatments

therapy compared to 42 percent with placebo photodynamic therapy. All patients involved in this trial received topical salicylic acid in addition to acid photodynamic therapy. Two other photodynamic therapy trials reported adverse effects such as itching, burning, or severe pain during treatment with aminolevulinic acid photodynamic therapy. In one trial, all patients with plantar warts could walk after this treatment.

Other Treatments

Dr. Gibbs and colleagues found no randomized trials investigating the efficacy of CO₂ laser, cautery or curettage, surgical excision, formaldehyde, podophyllin, or podophyllotoxin.

"We had a lot of angry responses to our review, especially from dermatologists in the United States," Dr. Gibbs said. "But this is what the trials we looked at showed. It's a shame that so many trials were not done well because warts are very easy to do in randomized trials. The humble wart has defeated us."

Just Say No to Warts

Dr. Gibbs said that he tries not to treat warts and urges other dermatologists to do the same. "I encourage my patients to leave them and, at most, to put salicylic acid on them," he said. "If dermatologists are keen on other procedures, they should do a trial because there is no shortage of patients. We need better trials with cryotherapy if cryotherapy is to rescue itself as a respected treatment of warts."

According to Dr. Gibbs, his take-home message is not very palatable for dermatologists in private practice. "Doctors get paid for doing cryotherapy or lasers, but they won't get much of a fee for telling someone to buy some salicylic acid to paint on their warts," he said.

For more information

Gibbs S, Harvey I, Sterling J, et al. Local treatments for cutaneous warts: systematic review. *Br Med J* 2002;325:461-464.

"If dermatologists are keen on procedures [other than salicylic acid], they should do a trial because there is no shortage of patients."

in one trial. Treatment of these same six patients with 1 percent DNCB produced major local irritation.

Intralesional Bleomycin

Among five trials, cure rates ranged from 16 percent to 94 percent. In one trial, the cure rate with placebo exceeded the rate with bleomycin. No trial offered meaningful data on adverse effects, although two patients reported pain associated with the active treatment and two reported using local anesthetic before antibiotic injection.

Photodynamic Therapy

One 40-patient trial showed a 56 percent cure rate with aminolevulinic acid photodynamic

Laser Study Suggests New Strategy

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cant lowering of the purpuric threshold with lengthening of the interpulse interval. However, we can see from our data that the purpuric threshold was certainly not raised by spacing the pulses farther apart," Dr. Tanghetti said.

Greater Depths

Results from histological evaluation of biopsied tissue obtained 24 hours after laser treatment showed that when performing a double-pass treatment, whether using the 0.5-msec or the 40-msec pulse duration, average vasculitis depth increased as the interpulse interval was lengthened from one to 10 seconds. For skin treated with a pulse duration of 0.5 msec, average vasculitis depth was about 1.0 mm using a one-second interpulse interval compared with 1.3 mm using a 10-second interval. Corresponding average vasculitis depths for the 40-msec pulse duration at those two interpulse intervals were 0.8 mm and 1.2 mm, respectively.

Discussing the mechanism for the observed increase in vascular damage with lengthening of the interpulse interval, Dr. Tanghetti noted that, based on first-order thermodynamics and thermal diffusion theory, one would expect to achieve the reverse effect because the vessels would have more time to cool before being hit with the second pulse. In fact, in their landmark study investigating thermal relaxation of port-wine stain vessels, Christine C. Dierickx, M.D., and colleagues [*J Invest Dermatol* 1995;105:709-714] determined that the purpuric threshold increased with longer interpulse intervals. However, the early generation pulsed dye laser used

in that study had a much shorter pulse duration than current technology, only 300 microseconds, and the longer pulse width of present lasers along with their delivery of energy in several peaks might result in differences in tissue response, Dr. Tanghetti said.

Greater Susceptibility

He proposed that the relationship he found between lengthening interpulse interval and increased vascular damage might be accounted for by a biological change induced by the first laser pulse that alters the target for the follow-up pulse.

"Perhaps the first pulse partially damages the blood vessel and causes the endothelial cells to become anoxic. The degree of that anoxia might increase over the time interval — during which we varied pulse delivery. Thus, when the second laser pulse is applied later rather than sooner, the cells might be even more susceptible to damage," Dr. Tanghetti said.

His future plans are to continue studying the consequences of altering interpulse interval and the mechanism for the effects observed. In his next experiment, Dr. Tanghetti will lengthen the interpulse interval beyond 10 seconds, up to 30, and perhaps 60 seconds to examine if the target changes.

"If the findings of this initial study can be explained by increased susceptibility of an anoxic target, we are interested in finding out if there is a threshold for the interpulse interval beyond which the cells begin to recover and the effect of lengthening pulse duration is reversed," Dr. Tanghetti said.

The V-Star laser used in this study is a product of Cynosure. Dr. Tanghetti has no financial interest in the company.

CLINICAL BRIEFS

SKIN CRAFTING Use of laser-assisted autologous skin grafting for the treatment of vitiligo appears to achieve better results than does conventional grafting techniques, according to Dr. G.S. Pai and colleagues of Kasturba Medical College, Mangalore, India. The researchers used an erbium YAG laser on 16 of 20 subjects with stable vitiligo. They reported that more than three-quarters of the subjects who were punch grafted using a laser showed repigmentation of more than 75 percent. In contrast, only half of those who underwent conventional punch grafting showed such repigmentation.

DEFECTIVE GENE A University Hospitals of Cleveland dermatologist, who specializes in hair disorders, solved the mystery of why one patient didn't have body hair and had bumps all over his face. Paradi Mirmirani, M.D., diagnosed the rare genetic disorder as generalized atrichia with papules. When Dr. Mirmirani first laid eyes on the patient, she immediately suspected that a haywire hairless gene was the culprit. Blood tests results showed the hairless gene was fine, but another gene, the vitamin D receptor gene, was not. It will be years before a gene therapy is available to correct the condition. After she diagnosed her patient, Dr. Mirmirani discovered that doctors have linked the cases of three members of an Israeli family to faulty vitamin D receptor genes. Reports on her patient and the three Israelis likely will appear soon in a medical journal.

FDA APPROVAL The Food and Drug Administration approved GlaxoSmithKline's Zovirax (acyclovir) cream for the treatment of cold sores in patients 12 years and older. Approval was based on two Phase III trials that showed the active cream resulted in greater treatment benefit compared with vehicle. The product, for which Biovail Corp. has marketing rights, was deemed safe in the trials.

GRANTS AWARDED The National Rosacea Society (NRS) announced that five new studies of rosacea have been awarded funding. Because the etiology of rosacea is unknown, grants are given to studies relating to its pathogenesis, progression, mechanism of action, cell biology, and potential genetic factors. Researchers interested in applying for grants should call NRS at 888-662-5974. The deadline for proposals is July 15.

WART TREATMENT Silke Fuchs, M.D., and German colleagues at the Jena University Dermatology clinic reported that water-filtered infrared light is an effective and painless means of removal warts. Their study involved 80 patients and showed that when infrared radiation is conducted through water, its longwave parts are filtered out in favor of the shortwave IR-A band. This is said to result in reduced risk of superficial burns and a better penetration into tissues.