Commentary on The Clinical and Histological Effect of a Low-Fluence Q-Switched 1,064-nm Neodymium:Yttrium-Aluminum-Garnet Laser for the Treatment of Melasma and Solar Lentigo in Asians

Melasma is a common, acquired disorder of skin pigmentation that occurs predominantly in women; it adversely affects quality of life indices and remains challenging to treat.[1] The report by Kaminaka and colleagues[2] "The clinical and histological effect of low fluence Q-switched 1,064 nm neodymium:yttrium-aluminum-garnet laser for the treatment of melasma and solar lentigo in Asians; Prospective, randomized, and split face comparative study" demonstrates the benefit of a series of low fluence (6 mm spot, 2.0–2.5 J/cm^2) Q-switched Nd:YAG laser (QSYL) treatments for melasma and solar lentigo. Kaminaka and colleagues provide insight into understanding of how melasma differs from solar lentigo and provides a basis for developing more effective therapies for these conditions.[2]

Melasma is often triggered by ultraviolet radiation, genetic susceptibility, hormonal changes, phototoxic medications, and high-energy laser treatments, but the pathogenesis remains unclear. Once triggered, lesional melanocytes remain highly metabolic and the condition is easily exacerbated by sun exposure, skin inflammation, and heat. Conventional treatments are primarily palliative, aimed at reducing excess pigment by exfoliation and inhibiting melanogenesis with topical agents and sunscreen. These therapies do not address the vascular or inflammatory component of melasma, nor do they target the free melanin and dermal melanophages that are present in almost all patients with melasma.

Histologic and immunohistochemical studies of melasma lesions by Kaminaka and colleagues confirmed previous findings of a thinned epidermis, increased solar elastosis, increased melanin in all layers of the epidermis, and increased free melanin and melanophages in the dermis. Lesional melasma skin also showed increased numbers of mast cells, blood vessels, and activated melanocytes. In Kaminaka's study, some melasma lesions had a thickened cornified layer and responded poorly to QSYL treatment.

Solar lentigo is another common, acquired disorder of skin pigmentation that occurs on sun-damaged skin. Unlike melasma, it responds well to high-energy ablative and pigment-specific lasers in lighter phototype skin, but these same treatments frequently produce postinflammatory hyperpigmentation in Asian populations. Histologic findings by Kaminaka and colleagues confirmed previous reports that there are 2 forms of solar lentigo: small plaque lesions with a thinned epidermis and basal layer melanosis, and large plaque lesions with epidermal hyperplasia, a thickened cornified layer, elongated rete ridges with increased melanophages. There are an increased number of activated melanocytes, mast cells, and blood vessels in solar lentigo. The authors found that low fluence QSYL effectively cleared small plaque solar lentigo without causing postinflammatory hyperpigmention. Large plaque solar lentigo with a thickened epidermis and stratum corneum responded poorly.

Frequent, often weekly, repetitive QSYL treatments have been used for almost a decade in Asia to treat pigment disorders. Protocols typically use high cumulative laser fluences—weekly treatments of up to 10 laser passes in the range of 3 to 4 J/cm^2 despite these procedures being described as "low fluence."[3] There is a low, but quantifiable incidence of postinflammatory hyperpigmentation after frequent, high-pass QSYL treatment protocols as well as permanent guttate

ISSN: 1076-0512 • Dermatol Surg 2017;0:1–3 • DOI: 10.1097/DSS.0000000000001164

leukoderma, presumably a result of chronic trauma to the melanocytes.[4] Ultrastructural studies in these patients demonstrate a patchy loss of melanin in basal keratinocytes as well as a decrease in the number of melanosomes and melanocytes.

Q-switched Nd:YAG lasers with nanosecond pulses shorter than the 1 microsecond thermal relaxation time of melanosomes provide deep tissue penetration and low absorption by melanin. They can be used at very low fluences ($\leq$2 J/cm^2) to fragment and disperse the melanin granules without causing melanocyte death, as demonstrated in ultrastructural studies by Mun and colleagues.[5] Kauvar[6] previously demonstrated in an open-label trial that infrequent (2–4 monthly), very low fluence QSYL treatments (2 laser passes at 1.6–2.0 J/cm^2) could effectively reduce melasma lesions without the risk of hyperpigmentation or leukoderma. Laser treatment was performed immediately after microdermabrasion to enhance laser penetration through a thickened startum corneum and used along with a daily topical regimen used to decrease melanogenesis (hydroquinone with tretinoin or vitamin C). Lesion clearance of greater than 75% was found in 81% of subjects with remissions lasting 6 months or longer, and no occurrence of postinflammatory hyperpigmentation or leukoderma.

Using QSYL monotherapy alone, Kaminaka and colleagues found that 50% of patients with melasma and 62.5% of patients with solar lentigo had greater than 50% clearance after the final treatment, and recurrence rates of 16.7% for melasma and 12.5% for solar lentigo at 6 months follow-up. They demonstrate that for both lesions there were reductions in epidermal and dermal pigmentation, activated melanocytes, number of mast cells, and number of blood vessels. There was no reduction in the melanin index in nonlesional laser-treated skin, and no cases of hyperpigmentation or hypopigmentation. The finding by Kaminaka and colleagues that melasma and solar lentigo lesions with a thicker stratum corneum were less responsive to low fluence QSYL is not surprising and illustrates the benefit of pretreating with microdermabrasion as described by Kauvar[6] to enhance laser light delivery to the dermis.

Melasma is a multifactorial disorder and there is a poor understanding of the interplay among the various etiologic events that cause or exacerbate the condition. Very low fluence QSYL has the advantage of selectively dispersing melanin granules in both the epidermis and dermis without inducing an inflammatory response that can lead to exacerbations, as is seen with high-energy laser treatments and deep chemical peels. Monotherapy with QSYL alone is insufficient and needs to be supplemented with exfoliation to reduce the stratum corneum for effective light penetration, melanogenesis suppressing topical therapy, and strict use of broad spectrum sunscreen because the activated melanocytes are reduced but not eliminated.

There is increasing evidence that inflammation and angiogenesis play an important role in the etiology of melasma and should also be addressed in the treatment design. Kim and colleagues[7] found that lesional melasma skin had a greater expression of vascular endothelial growth factor (VEGF) and numerous blood vessels. Mast cells can increase vessel proliferation through VEGF and transforming growth factor–beta, and human melanocytes express VEGF receptors. In Kaminaka's study, QSYL treatment of melasma resulted in decreased vascularity, mast cell number, and erythema index score. Topical and oral tranexamic acid have been shown to decrease both the melanin and erythema index in melasma lesions.[8] Tranexamic acid is a plasmin inhibitor that decreases angiogenesis and neovascularization. Recent reports indicate that vascular laser treatment can improve melasma.[9] There is increasing evidence that hyperpigmentation and neovascularization may be linked, and that endothelin 1 released by microvascular endothelial cells increases melanogenesis signaling.[10] Combination approaches targeting various abnormalities in melasma seem logical but are even more difficult to study, particularly in a disease that is characterized by exacerbations and remissions. Randomized, controlled trials with histologic and immunohistochemical correlation evaluating various interventions alone and in combination will help to further elucidate the etiology of melasma and optimize its treatment.

References

1. Sheth VM, Pandya AG. Melasma: a comprehensive update: part I. J Am Acad Dermatol 2011;65:689–97. quiz 698. Review.
2. Kaminaka C, Furukawa F, Yamamoto Y. The clinical and histological effect of low fluence Q-switched 1,064 nm neodymium:yttrium-aluminum-garnet laser for the treatment of melasma and solar lentigo in Asians; prospective, randomized and split face comparative study. Dermatol Surg 2017 [Epub ahead of print].
3. Kauvar AN. The evolution of melasma therapy: targeting melanosomes using low-fluence Q-switched neodymium-doped yttrium aluminium garnet lasers. Semin Cutan Med Surg 2012;31:126.
4. Kim T, Cho SB, Oh SH. Punctate leucoderma after 1,064-nm Q-switched neodymium-doped yttrium aluminum garnet laser with low-fluence therapy: is it melanocytopenic or melanopenic? Dermatol Surg 2010;36:1790–1.
5. Mun JY, Jeong SY, Kim JH, Han SS, et al. A low fluence Q-switched Nd:YAG laser modifies the 3D structure of melanocyte and ultrastructure of melanosome by subcellular-selective photothermolysis. J Electron Microsc (Tokyo) 2011;60:11–8.
6. Kauvar AN. Successful treatment of melasma using a combination of microdermabrasion and Q-switched Nd:YAG lasers. Lasers Surg Med 2012;44:117–24.
7. Kim MS, Bang SH, Kim JH, Shin HJ, et al. Tranexamic acid Diminishes laser-Induced melanogenesis. Ann Dermatol 2015;27:250–6.
8. Na JI, Choi SY, Yang SH, Choi HR, et al. Effect of tranexamic acid on melasma: a clinical trial with histological evaluation. J Eur Acad Dermatol Venereol 2013;27:1035–9.
9. Geddes ER, Stout AB, Friedman PM. Retrospective analysis of the treatment of melasma lesions exhibiting increased vascularity with the 595-nm pulsed dye laser combined with the 1927-nm fractional low-powered diode laser. Lasers Surg Med 2017;49:20–6.
10. Regazzetti C, De Donatis GM, Ghorbel HH, Cardot-Leccia N, et al. Endothelial cells Promote pigmentation through endothelin Receptor B activation. J Invest Dermatol 2015;135:3096–104.

Arielle N. B. Kauvar, MD
New York Laser & Skin Care
New York, New York

The author has indicated no significant interest with commercial supporters.