LASER TREATMENT OF SCARS IN DARK SKIN AND WARTS

Summary of Ph.D. dissertation

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2011

Szeged, Hungary

1. INTRODUCTION

1.1. Laser treatment of scars

The use of lasers to treat atrophic scarring conditions in darker skin types presents a significant challenge to laser practitioners.

Treatment options are limited due to increased risks of pigmentary complications including hypo- and hyper-pigmentation. This is especially true when attempting to treat large areas with atrophic scarring.

Post chickenpox scars are usually more common in adults and its treatment represents a major challenge for cosmetic dermatologists. Current methods of treating scarring include traditional fully ablative erbium and carbon dioxide (CO_2) treatments as well as non-ablative and ablative fractional resurfacing with CO_2, erbium:yttrium-aluminum-garnet (Er:YAG), and erbium:yttrium-scandium-galium-garnet (Er:YSGG) lasers. These options can be challenging for skin type IV patients and not feasible for patients with skin types V and VI without significant pre- and post-treatment skin conditioning and a hyper-pigmentation risk. With traditional fully ablative CO_2 resurfacing, studies showed hyper-pigmentation rates of 20% to 30% in Fitzpatrick skin type III and nearly 100% in skin type IV if treatment is performed without pre-treatment prophylaxis. Further, 19% of traditional resurfacing patients experience some form of hypo-pigmentation. A recent study on the treatment of acne scarring with fractionated Er:YAG laser reported a Post inflammatory Hyperpigmentation (PIH) incidence of 50% in 15 subjects with skin types IV-VI.

When the 1064 nm neodymium-doped yttrium aluminum garnet (Nd:YAG) laser with the option of sub-millisecond pulse width is used with 300-500 micro second pulse durations, a 5 mm spot size and repetition rates of 5-10 Hz, it offers the ability to focus heat in the papillary and upper reticular dermis. The sub-millisecond 1064 nm Nd:YAG laser has been proven to stimulate new collagen synthesis. It is therefore feasible that deliberate sub-millisecond 1064 nm Nd:YAG laser treatments could result in substantial reduction in scarring by stimulating collagen formation resulting in smoothing of the skin.

1.2. Laser treatment of warts

Warts are benign epithelial neoplasm of the skin and mucosa resulting from human papilloma virus infection. They are a common dermatologic complaint, with an estimated incidence of 10% in children and young adults.

Verruca plana (flat warts) are less exophytic than common warts, frequently presenting as several or dozen of subtle papules 2–6 mm in diameter elevated above the surface less than a millimetre or so. These can be quite subtle, and may be missed by a casual observer. Pigmentary disturbances may be the most disturbing part of the flat wart infection to the patient. These lesions are frequently a problem on the face and the glabrous skin of non-immunocompromised individuals. At present, therapies aim to remove the lesion rather than specifically target human papillomavirus infection.

The four morphologic types of genital warts are condylomata acuminata, which have a cauliflowerlike appearance; papular warts, which are fleshcolored, dome-shaped papules, usually 1–4 mm in diameter; keratotic warts, which have a thick, crust-like layer and may resemble common skin warts or seborrheic keratosis; and flat-topped papules, which appear macular to slightly raised.

In general, condylomata are most frequently detected on moist, partially keratinized epithelium, papular and keratotic warts on fully keratinized epithelium, and flat papular warts on either partially or fully keratinized epithelium. Treatment of warts can be difficult, with most approaches relying on physical destruction of infected keratinocytes. Common therapeutic approaches include liquid nitrogen, cryotherapy, topically applied acids, electro surgery, cantharidin application, bleomycin injection. Genital wart therapies

are classified as patient-applied or provider-administered. Patient-applied treatments include podofilox solution and gel, and imiquimod cream. To self-treat, patients must be able to identify and reach the warts and to follow the treatment application instructions. The provider-administered treatments include topical treatments (cryotherapy, podophyllin resin, trichloroacetic acid, bichloroacetic acid, and external application and intraurethral instillation of bacillus Calmette–Guerin); excisional treatments (curettage, electrosurgery, scissors excision, cryosurgery and laser therapy); or injectable treatments (interferon or 5-fluorouracil/epinephrine gel implant). Many types of lasers have been used for the management of warts. Carbon dioxyde laser vaporization for infected tissue was used. Tuncel et al. used the pulsed dye laser (PDL) for treatment of perianal warts in children. They found the pulsed dye laser to be effective and less traumatic compared with other treatment options. To date, there have been no trial evaluating the efficacy of long pulsed Nd-YAG laser in the treatment of common warts.

2. AIMS

The primary objective of our retrospective study was to determine the safety and efficacy of the unique pulse modality of submillisecond to reduce the signs of atrophic scarring, texture and PIH secondary to the acne condition in darker skin types. The secondary objective is to assess the incidence of PIH resulting from the laser treatments. As the post chickenpox scars are representing a clinical and therapeutic challange specially in dark skin so we also wanted to evaluate the safety and efficacy of using Microdermabrasion (MDA) and the sub-millisecond 1064 nm Nd:YAG laser in facial chickenpox scarring cases in adult men with skin type IV and V. Our further aim was to determine the safety and efficacy of the flashlamp pumped pulsed dye laser for the treatment of uncomplicated genital warts in adult males and the safety and efficacy of Nd:YAG laser in treatment of plane warts.

3. PATIENTS AND METHODS

3.1. Treatments of scars

3.1.1. Scar treatment in dark skin

STUDY DESIGN AND METHODS:

This is a retrospective study evaluating the safety and efficacy of a sub-millisecond 1064 nm Nd:YAG laser. Treatments were conducted at the National Institute of Laser Enhanced Sciences, Dermatology Unit, at Cairo University, Egypt and at Saheroun Hospital, Khartoum, Sudan on 22 patients with Fitzpatrick skin types III (n = 2), IV (n = 4), V (n = 14), VI (n = 2) who had atrophic scarring such as acne scarring. All patients who were treated over a six month period between February and July of 2008 were included in the study.

Treatments were performed using 300-500 μs pulse duration, 14-16 J/cm^2 and 5-7 Hz repetition rate. The hand piece was held 1-2 cm off the surface of the skin (about the width of an index finger) during delivery. Treatments were performed without topical anesthesia. No prophylactic therapy was used before or after treatment to control PIH resulting from laser treatments. On average, each patient received 6 treatments (minimum 5, maximum 7). The average interval between treatments was 24.5 days with a range from 18.7 to 33.0 days. Follow-up photographs were taken, on average, 9 months (range of 3 to 10 months) after the final treatment. Patient ages ranged from 18 – 47 years with a mean of 28.6 years. The average number of pulses per procedure was 11,700 pulses ranging from 8,000 to 13,900 pulses. The patient to patient variation in the number of pulses was associated with the size of the surface area treated, not

with the treatment indication. Treatment parameters used on each patient are listed in Table 1.

Table 1. Treatment Parameters and Follow-up Times

Patient	Age	# of Pulses per Treatment	# of Treatments	# of Days Between Treatments	Follow-up Post Final Treatment (months)
1	25	10,000	6	20.2	9
2	22	11,500	5	21	3
3	36	12,400	7	22.5	9
4	26	11,800	7	31	9
5	29	13,400	7	23	8
6	42	10,000	5	24.2	9
7	24	10,400	7	23.2	8
8	27	12,000	7	26.8	9
9	22	13,700	6	18.7	10
10	29	11,800	6	22	10
11	23	12,000	6	23.1	9
12	40	10,200	5	29	10
13	28	15,000	6	22.6	9
14	18	12,500	6	20.6	9
15	21	12,000	6	22.2	10
16	25	13,800	7	27.3	9
17	30	13,900	5	21.7	9
18	26	8,600	6	28.6	9
19	31	9,700	5	21	10
20	27	12,400	5	26.7	10
21	32	12,300	6	30.7	9
22	47	8,000	6	33	9
AVERAGE	**28.64**	**11,700**	**6**	**24.5**	**9**

To optimize laser results, the skin was treated with microdermabrasion (MDA) throughout the sub-millisecond 1064 nm Nd:YAG laser treatment series. Ten sessions of MDA were administered with an interval of 7 to 10 days between each session. A minimum of 3 days was allowed between MDA and laser treatments.

Following the MDA treatment, the whole face was treated with the sub-millisecond 1064 nm Nd:YAG laser. No additional passes were applied on the areas of atrophic scarring. The hand piece was held 1-2 cm off the face with continuous motion to build heat and erythema in the treatment area prior to moving to an adjacent part of the face. The surface area for each treatment region was approximately 5 cm x 5 cm. The total and average number of pulses per treatment, and the total number of treatments per patient are also shown in Table 1. Three independent physician reviewers (two dermatologists and one plastic surgeon) were asked to identify the before and after treatment photos which were presented to the physicians for assessment in random order. After selecting the before and after image, reviewers were asked to rank the degree of improvement in scarring, texture and PIH using a four-point scale (0 = < 25%, 1 = 25-50%, 2 = 51-75%, 3 = 76-100%). Any indication which did not apply to a patient was marked as N/A. The median improvement score was calculated based on scores from all three reviewers. When the before photo was incorrectly selected as the after photo (1 case only), the negative value of the improvement score was used in calculating the median score taking into account the magnitude of deterioration as assessed by the reviewer. This was done instead of excluding this case to avoid any bias in the data analysis. Patients were evaluated for erythema, edema, purpura, blistering, crusting, hypo- and hyper-pigmentation, and scarring. Patients were also asked if they observed any adverse reaction of the above or any other skin reaction they consider adverse between visits.

Statistical Analysis

Statistical analysis was performed using Minitab statistical package, version 15.1.20.0 (Minitab Inc., State College, Pennsylvania). For statistical testing, two-sided one-sample Wilcoxon signed rank test was used, and *P* values less than .05 were considered statistically significant. Additionally, the medians and spread of the data were displayed in box plot graph. Kappa agreement analysis was performed to measure the inter-reviewer reliability of before and after photos assessments and the kappa coefficient was reported.

3.1.2. Post chickenpox scars treatment

Regarding the Post-chickenpox scar group, Fifteen male patients aged 35 to 48 years (mean, 42 years) with Fitzpatrick skin type IV and V presented with a history of chickenpox infection 3 months earlier which left numerous scars over the face and forehead (Figure 9 1a, 1c, and 2a). All patients reported the occurrence of skin lesions few days after the onset of the fever. This was followed by scab formation over the skin lesions which started to fall off within 10 days of the onset of their appearance which resulted in scars. Gentian violet lotion or topical antibiotic ointment was applied topically over the skin lesions and antibiotic was administered orally for 1 week. No other intervention had been administered before the patients presented to us. Exclusion criteria included any prior trial for treatment of the scars, any concomitant systemic disease, and any active skin infection.

Patients were referred to our clinic seeking treatment for their facial scars. Treatments were performed without topical anesthesia. No prophylactic therapy was used before or after treatment to control postinflammatory hyperpigmentation (PIH) resulting from laser treatments.

The treatment regimen was started with MDA utilizing aluminum oxide crystals, followed by the session with the sub-millisecond 1064-nm Nd:YAG laser. The MDA sessions were repeated every 7 days for 8 sessions and the laser session was repeated every 3-4 weeks for 5-6 sessions. A minimum of 3 days was allowed between MDA and laser treatments. Treatment was performed without topical anesthesia and no prophylactic therapy was administered before or after treatment to control post inflammatory hyperpigmentation (PIH) resulting from laser treatments. Treatment was performed over 6 months.

The following parameters used during laser treatments: 5-mm spot size, 14 J/cm^2, and 0.4-millisecond pulse width with a repetition rate of 5 Hz. The face was divided into squares of 5 x 5 cm and laser pulses were delivered with a continuous motion. The hand piece was moved to the adjacent treatment area when erythema developed. Erythema was seen after an average of 500 pulses per treatment square. The laser treatment was conducted with no pre- or post-cooling of the skin while defocusing the hand piece 1 to 2 cm above the skin using multiple passes of the treatment area.

The patients were followed up for a period ranging between 3 and 12 months after the last laser session. There was no downtime or any incidence of adverse effects such as pigmentary changes or scab formation after the procedure. The post treatment erythema persisted for 20 to 30 minutes immediately after each laser session and completely faded away afterwards. The patients were asked to utilize sun block with at least SPF 30 in between the sessions. A questionnaire was administered to all participants 4 weeks after the last laser session regarding changes in scarring and skin texture as well as PIH. These 3 parameters were graded on a 4-point scale (2=marked improvement; 1=mild improvement; 0=no change; -1=worsening). The same questionnaire also was administered to the treating physicians to grade changes observed in each participant. Photographs were taken before treatment and 3 months (or more) after the last laser session. Blinded assessments were performed by 3

independent physicians using before and after photographs (unlabeled) that were not arranged in chronologic order. Reviewers were asked to identify the before and after photographs and evaluate the degree of improvement or worsening observed in scarring, skin texture, and PIH using a 4-point scale (2=marked improvement; 1=mild improvement; 0=no change; -1=worsening). No statistical analysis was performed.
Adverse effects were evaluated immediately after each laser treatment and 2 and 4 weeks after each laser session.

3.2. Treatment of warts

3.2.1. Treatments of genital warts

General examination for the whole body, including the oral mucosa, was done for signs of sexually transmitted diseases (STDs) (for example, vesicles, ulcers, warts, mucous patches, lymph node enlargement).
Local genital examination was done while the patients were completely uncovered from the umbilicus down to the knee. The skin of the lower abdomen, penis, scrotum, perineum, perianal area, upper thighs, and the urethral meatus were inspected under good illumination for the presence of warts and other STDs. In all settings, patients with genital warts were examined and treated for other STDs. Whenever possible, their wives or current sexual partners were also offered examinations and treatments for macroscopically visible warts and other STDs. Examination of the anogenital warts was done and the following data were recorded: site, number, type, area, presence of complications such as ulcerations or bleeding. The wart area was estimated as follows: the two largest perpendicular diameters were measured, and the wart area was defined as the product of the two measurements.
Finally, a total of 174 adult males with 550 uncomplicated anogenital warts and with no history of topical or systemic therapy for warts during the last 2 months were included and treated by pulsed dye laser. A pulsed dye laser (585 nm, 450 μs pulse duration; Cynosure, USA) was used with the following parameters: spot size 5–7 mm according to the size of the lesions, and fluence 9–10 J/cm^2. Overlapping pulses were done, up to three to four pulses, until the appearance of grayish discoloration of the lesions which was an end point for lesion coagulation.
Treatments were repeated every 2 weeks with a maximum of three sessions. Topical antibiotic ointments were prescribed between the sessions to be used for a period of 7–10 days following every session. The number of warts, and the area of warts at presentation and at the end of treatment was recorded. Any adverse reactions were also recorded. Patients were followed-up for at least 4 months after the warts had cleared.

3.2.2. Treatments of plane warts

Fifty patients with a total of 326 verrucae were enrolled in the study over 8 months period. They were 23 males and 27 females, with a mean age of 26.5 (12–41) years old. All patients were complaining of flat warts mainly on the forehead, cheeks, chin, neck, arms and the dorsum of the hands. Inclusion criteria included no treatment of lesions within the past month, and no history of constitutional or iatrogenic immunosuppression. All patients gave informed consent. The study was completed by 42 patients, which completion defined as clearance of all visible warts or a maximum of 3 treatment sessions on the same lesion.
Treatment sessions consisted of treatment with the long pulsed Nd-YAG laser (1064 nm, Coolglide, Cutera, RIT 220 Excl.) with 20–30 msec pulse duration and fluence between 95–110 J/cm^2, with 5,7 mm spot size according to the size of the lesion, applying double or triple overlapping pulses. Our endpoint was light greyish discoloration of the lesion.

Following treatment, there was slight peri-lesional erythema. Very minimal heat sensation or sometimes slight burning pain was experienced especially in children. Topical anaesthetic cream of 5 % lidocaine and 3.5 % prilocaine was used only in cases of children or with patients of low pain threshold. Treatment sessions were carried every 2 weeks with a maximum of 3 sessions on the same lesion. All patients and health care providers wore protective eyewear and micropore laser masks. A smoke evacuator was used as a precaution against potential aerosolised viral particles. Photographs were obtained at the initial visit and at 3 months follow up after the last treatment session.

4. RESULTS

4.1. Treatments of scars

4.1.1. Treatment of scars in dark skin types

Blinded Photo Assessments

Two reviewers correctly identified all photos (22/22). The third reviewer incorrectly labeled one pair of before and after images and was not able to identify another pair of photos due to insufficient image quality (20/22). The reviewers were highly consistent (inter-reviewer reliability, kappa of 0.88) in identification of before and after photos (kappa coefficient: poor < 0.20, fair 0.21-0.40, moderate 0.41-0.60, good 0.61-0.80, and very good 0.81-1.00).

Of the sixty-six possible image reviews for each category (22 images each reviewed by 3 physicians), one was determined by one reviewer as insufficient quality to grade before and after. Additionally, 4 images were excluded from scarring analysis, 4 were excluded from texture analysis and 5 were excluded from pigment analysis. Images were excluded due to insufficient focus, color balance and or lighting.

The results of the blinded photo assessments indicated clinically and statistically median improvement of 2 in scarring, 2.3 in texture and 2 in PIH ($P < 0.001$). Figure 1 displays the median improvement scores and the variability of data for all three conditions (scale of 0-3).

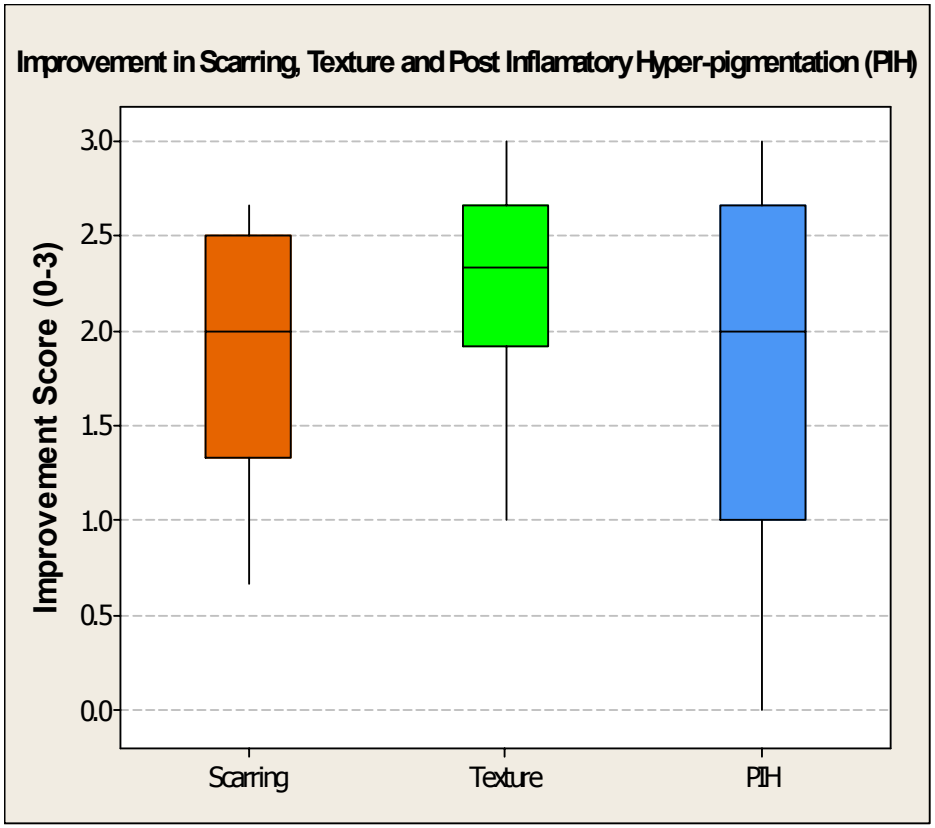

Figure 1. Median improvement of 2 in scarring, 2.3 in texture and 2 in pigment based on blinded photo assessments by three reviewers. The box illustrates the 25th percentile to the 75th percentile with a line placed at the median (50% percentile). The bottom and top ends of whiskers show the minimum and maximum respectively.

Transient mild edema and erythema were observed in all patients and resolved within 2 hours after treatment. No transient or permanent complications such as blistering, crusting, purpura, scarring, transient or permanent hyper- or hypo-pigmentation were noted. There was no single patient who reported any adverse effects during or after the treatment sessions till the end of the follow up period in this study.

4.1.2. Treatment of chickenpox scars

All 15 participants were included in the analysis. The mean length of follow-up after the final laser session was 9.1 months. Questionnaire results demonstrated marked improvement in scarring, skin texture, and PIH as observed by participant and physician evaluation. Results of the participant assessment revealed mean scores in scarring, skin texture, and PIH of 1.8, 1.9, and 1.8, respectively. Physician evaluation of improvement revealed mean scores of 1.9, 1.9, and 1.8, respectively (2=marked improvement; 1=mild improvement). Participant and physician evaluation did not reveal scores of no change or worsening for the 3 parameters.

For the blinded photographic assessments, all 3 reviewers correctly identified the chronology of 13 participant photographs (13/15). Of the 90 possible photograph reviews for each category (15 before and 15 after photographs reviewed by 3 physicians), 2 were determined by 1 reviewer as insufficient quality to judge before and after photographs. Additionally, 4 photographs were excluded from skin texture analysis and 5 were excluded from PIH analysis. Photographs were excluded due to insufficient focus, color balance, or lighting. The results of the blinded photographic assessments indicated clinically significant improvements in scarring, skin texture, and PIH, with mean scores (based on all 3 reviewers) of 1.9, 1.8, and 1.8, respectively (2=marked improvement; 1=mild improvement). None of the reviewers scored these parameters as no change or worsening.

Transient mild edema and erythema were observed in all participants and resolved within a maximum of 2 hours after treatment. No transient or permanent complications such as blistering, crusting, purpura, scarring, or transient or permanent hyperpigmentation or hypopigmentation were noted at 2 or 4 weeks. None of the participants reported any adverse effects during or after the treatment sessions through the end of the follow-up period.

4.2. Treatments of warts

4.2.1. Treatments of genital warts

The mean age of patients included was 31.33 $\pm$ 4.7 years (range from 22 to 49). The mean duration of lesions was 4.29 $\pm$ 3.15 months (range from 1 to 48). The number of warts ranged from one to 14 per patient (average 3.82 + 4.33). Warts were frequently present with more than one lesion on one anatomical site. Warts were also present more frequently on different genital sites (104 patients, 59.78%) and on one genital site in 70 patients (40.22%). Among those latter patients, lesions were present on the penis in 39 (22.41%), on the scrotum in 11 (6.32%), on the urethral meatus in four (2.29%), and on the Peri-anal area in 16 (9.2%). The mean area of lesions was 26.9 mm^2 and the area varied from 6 mm^2 to 64 mm^2. With regard to the morphological type of warts detected, it was predominantly condylomatous in 129 patients, papular in 31, keratotic in nine, and flat-topped papules in five patients.

Complete clearance of 528 anogenital warts (96%) treated by pulsed dye laser occurred after one to three sessions. A few small warts of short duration occurring on one anatomical site cleared significantly after fewer sessions and resulted in earlier clearance. Patients with fewer than three and with an area less than 20 mm2 cleared most frequently after one session. Other factors such as a patient's age and the morphological type did not affect the treatment results. Overlapping pulses (three to four) revealed better clearance of warts than single and even double pulsing. Side effects were infrequent

and transient, mostly in the form of mild pain at treatment and transient hypopigmentation after treatment. Patients were followed-up for at least 4 months (up to 9 months in some cases).
Complete resolution and healing of skin without scaring or texture changes were found in the majority of cases. Lesion recurrence rate was 5%. Recurrence was defined as a new wart at the same site detected within the 4-month follow-up period after clearance of lesions.

4.2.2. Treatments of plane warts

Of the 50 patients initially enrolled, 42 patients with a total of 256 warts completed the study. The 8 patients who withdrew, were for reasons unrelated to treatment. In the evaluation of treatment response, complete response was defined as complete absence of clinically apparent warts without any textural changes such as fibrosis or scar formation. Partial response was defined as greater than 50% reduction in wart size or number.
Complete response was observed in 35 patients (83.3 %), while partial response was observed in 7 patients (16.7 %). No case showed no response to the lesion treatment. The mean number of treatments to achieve complete response was 2.00, while the mean number of treatments to achieve partial response was 2.65. Postoperative complications such as transient post inflammatory hypopigmentation was observed only in 4 cases and only 1 case experienced transient post inflammatory hyperpigmentation and was given hydroquinone 4% cream. The recurrence of warts during follow up period was reported only in 2 cases. As regards patient satisfaction, ninety two percent of all patients even those who experienced partial response were satisfied with the treatment they were given.

5. DISCUSSION

5.1. Laser treatment of scars

Retrospective photographic analysis of 22 cases of scars in our study and 15 cases of post chickenpox scars indeed shows that sub-millisecond 1064 nm Nd:YAG laser may be a viable treatment modality capable of generating improvement in texture, scarring and PIH secondary to the acne condition in darker skin types. Blinded photo assessments by three independent physicians indicated that six treatments performed, on average, 24.5 days apart resulted in clinically and statistically significant improvement in atrophic scarring, texture and PIH in patients with skin types III-VI. High consistency between reviewers was observed in identifying before and after photos.
It is noteworthy to state that The non-invasive treatments with the sub-millisecond 1064 nm Nd:YAG laser: (1) Improved the existing PIH from acne scarring; (2) Did not induce additional PIH; (3) Did not require pre- or post-treatment agents to control PIH in dark skin patients; (4) Did not require anesthetic.
The percentage of subjects with skin types IV and V included in studies for the treatment of atrophic scarring are very limited compared to lighter skin types due to pigmentation concerns. Even with the use of hydroquinone pre- and post-treatment, a recently published prospective study of 15 subjects with skin types IV-VI and acne scarring using Er:YAG laser showed a 50% rate of the PIH. In the same study, the pain levels were reported to increase as the skin type went from IV to VI and as the number of passes went from 1 to 8.
One challenge faced in this retrospective study was not all patient photos had sufficient image quality. As a result, a couple of photos were excluded from the data analysis. The second challenge was the data only captured an overall percentage improvement without assessments of severity and types of scars at baseline and follow-up.

This was due to the lack of high resolution standardized photos. In future studies, high resolution photos of scarring (using macro lens settings without flash or a three-dimensional optical profiling system) should be used for objective assessment of scar severity and type. Lastly, it would be beneficial to collect data on patient satisfaction in addition to physician assessments.

The theory behind combining MDA treatments with laser treatments was to reduce the thickness of the stratum corneum thereby allowing greater light penetration to the papillary dermis. Thus, MDA treatments performed before the laser treatments were mild in intensity to prevent discomfort or complications from deep dermal abrasions. The conservative MDA settings used in this study were not considered effective to treat acne scarring and PIH and were unlikely to have had an effect on the observed improvement. Nonetheless, randomized split face studies would be required to definitely determine whether MDA is necessary or has an additional benefit when used in combination with laser treatments.

In previous studies, the sub-millisecond 1064 nm Nd:YAG laser therapy has been shown to stimulate collagen and to improve scar severity. However, no assessment has been performed on secondary improvement to texture and pigment. We hypothesize that the sub-millisecond Nd:YAG laser works through two parallel actions to safely stimulate collagen and improve discoloration. The first mechanism involves discrete cellular damage caused by direct absorption in hemoglobin, melanin and water during each pulse and bulk heating from cumulative pulsing in a region. As a result, damage created through direct absorption and through sustained time at elevated temperature initiates a healing response, prompting collagen stimulation.

Nd:YAG is absorbed by melanin and hemoglobin and is subsequently used for vascular and hair reduction treatments. Pulse durations in these treatments are in the 10-100ms range, roughly 30-300 times longer than the pulse durations used in this study. The short pulse durations used in sub-millisecond treatment does not change the characteristics of chromophore absorption. At these short pulse durations, the laser energy is heating fine structures during each pulse, thus more selectively targeting the microvasculature in the papillary dermis and melanocytes within the epidermis without actually damaging the epidermis or larger vessels in the dermis.

The second mechanism of action occurs through bulk heating. The laser uses a 5 mm spot pulsing at 5-10 Hz to deliver large amounts of energy in relatively short bursts to a finite area of tissue. Heat conducts to surrounding tissue over time to create bulk heating in each treatment. The degree of bulk heating is a function of total energy delivered per unit area per unit time. The goal during treatment is to deliver energy to an area of tissue faster than the body can extract the heat. For this reason, skin cooling is not desired during treatment. This bulk heating occurs gradually and non-selectively through heat conduction, so no structures are specifically targeted. This allows for safe treatment, even on type VI skin.

5.2. Laser treatment of warts

Management of genital warts presents a problem of increasing magnitude to genitourinary medicine and Dermatology specialists. Choice of treatment is guided by patient preference, with consideration given to the patient's age and ability to comply with moderately complicated directions, to the location and number of warts, and to the clinician's training. Many conventional lines of therapy are used, the aim of which is to destroy the infected tissue; however, none are consistently effective, making genital warts a therapeutic challenge.

Laser therapy had been used for the treatment of genital warts since the 1970s. CO_2, argon, Nd:YAG and Er:YAG lasers have been used, especially for refractory genital warts, giant condyloma acuminatum

or Buschke–Lowenstein tumor, with variable degrees of safety and efficacy.

The pulsed dye laser was used initially for selective photothermolysis of vascular lesions, whereby the wavelength is selectively absorbed by the oxyhemoglobin, leading to destruction of the vascular component of the tissue. It was also used in the management of other non-vascular lesions, depending on the photothermal effect of laser on the cutaneous tissue ± its selective photothermolysis effect. The pulsed dye laser was used for the management of simple and recalcitrant verrucae vulgaris on different sites of the body using fluencies ranging from 6 to 9 J/cm^2. Other studies reported higher fluencies of 9.4 J/cm^2 giving variable clearance rates.

Tuncel et al. used the pulsed dye laser for the management of perianal warts in children with a fluence of 7.5 J/cm^2. In our study, we used higher fluencies of 9–10 J/cm^2, which ensured greater destruction of the vascular component of the lesions.

The overlapping pulses increased the photothermal effect of the laser radiation leading to coagulation of the lesions and immediate graying of the warty tissue. The technique was done as an outpatient procedure and did not require any infiltration anesthesia as in electrocautery or surgery, which is another advantage of the pulsed dye laser in the treatment of genital warts. It is safe in comparison to the toxicity of podophyllotoxins, which are continuously investigated in an attempt to increase efficacy and decrease toxicity. In the light of results from our study, in which there was a significant number of patients presenting with multiple and/or large size 5 lesions, complete resolution and healing of skin without scaring or texture changes were found in the majority of cases. This is in contrast with what is usually found with other traditional treatments such as electrocautery, surgical excision, cryotherapy or CO2 laser. Lesion clearance rate in our study was 96%, which is superior to that achieved by the more widely used treatment modalities (32–88%). Better results (smaller number of sessions and earlier clearance) were observed with lesions of short duration and in cases with a small number of warts occurring on one anatomical site. On the other hand, failure of treatment that occurred only in 4% of cases was observed in highly recalcitrant lesions with a large number of warts, which might be attributed to increased fibrosis and hyperkeratosis due to previous attempts of treatment. Lesion recurrence rate (5%) was also less than reported with other treatment modalities (8–22%). Post-treatment recurrence rates are not well defined in most studies because in most cases either too few subjects have been studied or follow-up protocols had not been standardized. Common warts are hyperkeratotic papulonodules most often seen on the hand, arms and legs, but can seen anywhere on the glabrous skin. Common verrucae represent the most frequent clinical lesions produced by human papillomavirus. Verruca plana (flat warts) are less exophytic than common warts, frequently presenting as several or dozen of subtle papules 2–6 mm in diameter elevated above the surface less than a millimetre or so. These can be quite subtle, and may be missed by a casual observer. Pigmentary disturbances may be the most disturbing part of the flat wart infection to the patient. These lesions are frequently a problem on the face and the glabrous skin of non-immunocompromised individuals. At present, therapies aim to remove the lesion rather than specifically target human papillomavirus infection. Many different types of therapy have been used in treatment of verrucae. Commonly used methods of physical destruction include: electrodessication, cryosurgery and laser therapy. Chemical destruction is induced with salicylic acid, cantharidin, among others. Chemotherapeutic agents include podophillin resin and 5-fluorouracil. More recently immunomodulators such as interferon, systemic retinoids have been used.

Many types of lasers have been used for the management of warts. Carbon dioxyde laser vaporization for infected tissue was used. Results were not superior than the ordinary electrocautery which remove blindly the infected tissue as well and may sometimes lead to textural changes. Several investigators have demonstrated the efficacy of 585 nm pulsed dye laser in treating warts. The mechanism of action may be a result of intense heating of dermal vessels with collateral damage of virally infected keratinocytes. This theory is based on the presence of dilated and congested vessels at the base of most of verrucae and the mechanism of selective photothermolysis that result in targeting of haemoglobin by pulsed dye laser. To our knowledge, one report used KTP laser at 532 nm wavelength for treatment of recalcitrant pigmented warts, through selective photothermolysis and propagation of photoacoustic waves. Nd-YAG laser hyperthermia proved to be effective in treatment of resistant warts with significant clearance of the lesions and absence of viral particles, but it cannot be performed on very sensitive areas for example lesions on the face, neck or cheeks. Patients will not tolerate the procedure since it is done without anaesthesia and needs laser exposure time of 1-2 min in comparison to the pulsed lasers with micro and milliseconds pulse durations. Thus laser hyperthermia is not practical for large number of lesions.

The Nd-YAG laser is one of the most versatile and interesting lasers in dermatological laser medicine. Almost no other laser has such a wide spectrum of applications. Depending on wavelength (1064 nm) and mode (continuous, Q-switched, long pulsed), it is applied on benign pigmented, vascular lesions and permanent hair reduction, due to the fact that 1064nm is absorbed by all the skin chromophores.

Reports using long pulsed Nd-YAG laser as an effective line of treatment for vascular lesions such as telengietasia and venous lakes, encouraged us to use this laser system for thermal destruction of resistant flat warts. With its deeper penetration and lower absorption coefficient for melanin, there is less concern for collateral epidermal damage.

Unlike ablative treatment modalities, with long pulsed Nd-YAG laser therapy, no wound was created, especially if the lesions were on exposed parts of the body mostly head and neck as in our study, thus avoiding prolonged post operative pain, crusting, scarring or downtime.

Applying the pulsed mode of laser system, made the technique tolerable by the patients, most of whom returned to work or normal activities immediately postoperatively. There was no need for local infiltration anaesthesia (only topical anaesthetic cream was used for selected cases) was another advantage. The limited number of sessions up to three sessions in our protocol was to be comparable to other treatment modalities such as topical retinoids, chemical cautery also for the cost benefit wise. Most of the patients who experienced partial response was due to their large number of warty lesions, most of the lesions were not de novo, they were being treated before and lasted for more than six months. The risk of high incidence of post inflammatory hyperpigmentation is minimized by preferentially sparing epidermal pigment. The procedure proved to be acceptable and effective by the patients. Our results are comparable to pulsed dye laser treatment modalities which was another positive point, with an advantage over the pulsed dye laser of having no post laser purpura and no consumables such as dye kit.

6. SUMMARY AND NEW FINDINGS

Preliminary data collected in our retrospective study suggest that sub-millisecond 1064 nm Nd:YAG laser treatments are safe and effective for treating atrophic scarring in patients with darker skin types, delivering clinically and statistically significant results with reduced risk of pigment complications. This offers a new standard of care or first treatment option for patients with a high risk of

pigmentary complications. Prospective studies with the sub-millisecond Nd:YAG laser alone are required to further assess treatment outcomes considering the effect of number treatments as well as to determine targeted treatment parameters for improved effects on scars of various severity and type. Further, randomized split face studies are needed to show the treatment effect and the incidence of PIH compared to non-treated and treated controls with alternative treatments.

A further study was conducted to evaluate the safety and efficacy of the combination of the MDA and the sub-millisecond 1064-nm Nd:YAG laser in treatment of the post chickenpox scars in dark skin patients and the result of our study poved our treatment protocol to be safe and effective treatment modality for the postchickenpox scarring and inflammation induced hyperpigmentation in all skin types. In our study of genital warts in males, the pulsed dye laser has been found to be a safe, effective, and satisfactory treatment for genital warts. It is capable of selectively destroying warts without damaging the surrounding skin. Regarding the plane warts, we concluded that Long Pulsed Nd-YAG laser can be added to the long list of traditional treatment of plane warts as an effective, safe and well tolerated method with minimal complications. We recommend the following inclusion criteria for long pulsed Nd-YAG laser treatment of plane warts: limited numbers of warty lesions, especially on very sensitive areas, lasted for less than six months with no previous attempt of treatment. In Patients with previous criteria, long pulsed Nd-YAG laser would be significantly more costly effective than other treatment modalities.

List of publications

Publications related to the subject of the dissertation

1. **Badawi A**, Tome MA, MD, Ayse N Turley AN, Kemény L Successful treatment of post chickenpox scars with microdermabrasion and sub-millisecond Nd:YAG (1064 nm) laser. Cosmetic Dermatology 2011; 24:389-94.
2. **Badawi A**, Tome MA, Atteya A, Sami N, Morsy IA. Retrospective analysis of non-ablative scar treatment in dark skin types using the sub-millisecond Nd:YAG 1,064□nm laser. Lasers Surg Med. 2011; 43:130-6. **IF: 2,605**
3. **Badawi A**, Shokeir HA, Salem AM, Soliman M, Fawzy S, Samy N, Salah M. Treatment of genital warts in males by pulsed dye laser. J Cosmet Laser Ther. 2006; 8:92-5.
4. Samy N, Salah M, Soliman M, **Badawi A**: Plane warts can be managed successfully using long pulsed Nd-YAG laser. Kosmetische Medizin 2008; 1:14-8.

Publications indirectly related to the subject of the dissertation

1. **Badawi A**, Soliman M, Sobhi R, Fawzy S, Shokeir H, Salem AM: Microdermabrasion in Cosmetic Dermatology: A Clinical Study. Cosmetic Dermatology. 2006;19:191-6.
2. Sami NA, Attia AT, **Badawi A**: Phototherapy in the treatment of acne vulgaris. J Drugs Dermatol. 2008;7:627-32.
3. Salem AM, Shokeir H, **Badawi A**, ElMorsy I: Effective Reduction of Fine and Coarse Hair in Patients with Skin Types III-V by Long-Pulsed Alexandrite Laser at 5- & 20-Millisecond Pulse Durations. Cosmetic Dermatology 2003;16:39-42.

ACKNOWLEDGEMENTS

I believe finishing this work, is the best opportunity to express my deepest gratitude and appreciation to Professor Lajos Kemény, Professor of Dermatology, and Head of the Department of Dermatology and Allergology, Albert Szent-Györgyi Medical Center University of Szeged for his continuous teaching, encouragement, and constructive criticism. Profesor Kemény's role in my clinical and academic progress is unforgettable. Many thanks for his advice and generous supervision during this work.

I also would like to express my heartfelt thanks and sincere gratitude to Prof. Dr. Hisham Shokeir, Professor of Dermatology, and Dean of the National Institute of Laser Enhanced Sciences, Cairo University for whom I'm greatly indebted for his valuable guidance, creative ideas during the studies we conducted along my clinical career. As a matter of fact, without the efforts of Prof. Shokeir, this work would have never been complete.

Today, I can not forget to thank all my colleagues in the Dermatology unit, National Institute of Laser Enhanced Sciences, Cairo University, especially Prof. Dr. Mona Soliman, Dr. Manal Salah, Dr. Nevine Samy, Dr Abeer Atteya, and Dr. Mohamed Tome, Al Rebat University, Khartoum, Sudan, from whom I have learned alot in the field of Laser applications in Dermatology.