Efficacy of a Picosecond and Nanosecond Dual Pulse Duration Q-switched Nd:YAG Laser Versus a Traditional Nanosecond Q-switched Laser for Tattoo Removal: A Comparison Study

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Objective: To assess the safety and efficacy of nanosecond and picosecond pulse durations of a dual wavelength—1064 nm and 532 nm—laser on tattoo clearance.

Materials and methods: Forty-two tattoos were enrolled in this multi-center prospective randomized split-tattoo clinical study. Subject tattoos were divided in two portions and randomly assigned treatment with a Nd:YAG laser with nanosecond and picosecond pulse durations (enlighten™, Cutera Inc., Brisbane, CA), or with a comparator traditional QS Nd:YAG with a fixed, six nanosecond pulse duration (Quanta Q-Plus, Solbiate Olona, Italy). Subject tattoos received two or three treatments with each system at six-week intervals. The fluence, total energy, spot size and repetition rate were all kept constant for both devices; the only variable was pulse duration. Primary efficacy assessments were performed through blinded physician review of standardized photographs of subject tattoos taken at baseline and six weeks after the final treatment. The treating investigator assessed safety at each visit, and via phone surveys conducted three and 14 days after each laser treatment.

Results: Blinded review of baseline and post-treatment photographs resulted in a clinically and statistically significant mean improvement of 2.54 (95% CI: 2.13-2.94) based on a 0 to 4 scale, where 0 indicated "no change" and 4 was "very significant clearing" at six weeks post final treatment for tattoos treated with enlighten. Tattoos treated with the comparator device demonstrated a mean improvement of 2.17 (95% CI: 1.77-2.57). The enlighten laser showed statistically significant higher clearance than the comparator device ($p<0.001$). No unexpected or serious adverse events were reported.

Conclusions: The enlighten laser with both nanosecond and picosecond pulse durations demonstrated substantial, statistically significant improvement in tattoos, as compared to the comparator device.

INTRODUCTION

The pervasiveness and popularity of tattoos today is without dispute. Tattoos are increasing in popularity across all socioeconomic and demographic groups and a recent survey reveals that 27% of US adults have at least one tattoo, a 6% increase from a 2012 Harris Poll (Tattoo Incidence Study, ORC International 2015; Americans with Tattoos Poll, Harris Interactive, 2012).[1,2] Concomitantly, more people are regretting their tattoos, mostly driven by a change in taste, lifestyle or fashion. Tattoo regret is driving removal demand. In fact, the demand for tattoo removal increased fivefold in the U.S. from 2004 to 2014.[3] And now one in four people with tattoos wishes to have one removed.

There are several methods to remove tattoos with varying levels of success and side effects. The two most common are surgical removal and laser tattoo removal (LTR). Because of scarring associated with surgical removal, LTR is the preferred method and is considered the gold standard; however, traditional laser technologies for LTR may require up to 20 treatments over a span of several years in order to achieve satisfactory clearance, and often a visual remnant of the tattoo can linger. Pier Luca Bencini, et al. reported that after ten treatments on black ink tattoos, fewer than 60% of patients observed clearance.[4] The ideal LTR solution would provide better results in fewer treatments.

BACKGROUND

For a laser to successfully remove tattoos, the laser light energy must be absorbed preferentially by the ink particles so as not to heat and damage the surrounding skin.[4] The energy absorbed by the ink causes the ink particles to undergo thermal expansion and break into smaller fragments; these smaller fragments are collected and removed by the lymphatic system, or removed via phagocytosis by other cells in the dermis.[6-10] In addition, some ink may also be removed through trans-epidermal elimination as ink particles are transported to the skin surface.

In order for laser light to fragment ink, the length of the laser pulse, known as pulse duration, must be equal to or less than the ink's thermal relaxation time (TRT). The ink's TRT is the time it takes for the ink particle to cool by half the maximum temperature reached after the laser light is absorbed.[11,12,13] Larger ink particles take longer to cool than smaller ink particles. Thus, it is axiomatic that larger particles will require longer pulse durations to fragment and smaller particles will require shorter pulse durations.

MATERIALS AND METHODS

This was an IRB approved, multicenter prospective, open-label, randomized, controlled clinical trial to compare safety and efficacy of two Nd:YAG lasers for tattoo removal. Subject tattoos were divided into 2 portions for random assignment into two arms: active control and treatment. Tattoo portions assigned to the treatment arm were treated with a nanosecond and picosecond pulse duration, dual wavelength 1064 nm Nd:YAG laser (enlighten™, Cutera Inc., Brisbane, CA), while the active control arm received treatment with a comparator fixed, six nanosecond pulse duration, dual wavelength QS 1064 nm Nd:YAG laser (Quanta Q-Plus, Solbiate Olona, Italy).

Subjects

Forty-two subjects from two research sites were enrolled. Eligible subjects

had a tattoo containing black or blue ink, alone or with other colors, between 2 and 12 in^2 in size, and at least one year old. Patients were excluded from the study if they had a history of prior tattoo removal treatment, presence of double tattoo in the treatment area, or a history of allergic reaction to local anesthetics, topical antibiotics or ink pigments. Additional exclusion criteria included history of photosensitivity disorders or taking prescription medications known to cause photosensitivity, history of keloid formation, abnormal wound healing or any skin disease involving the treatment area, or significant concurrent illness. Female patients who were pregnant or breastfeeding were not eligible for participation.

Twenty-four males (57%) and 18 females (43%), ranging in age from 20 to 51 years and mean age of 34, were treated in this study. Study subjects were mainly skin type II or III, 48% and 38% respectively. Fourteen percent of subjects had skin type IV or V. Subject tattoos were present in various body locations, but back and arm tattoos comprised 50% of the locations. Fifty-seven percent of subjects had professional tattoos, while 43% had amateur or homemade tattoos. Study tattoos ranged in age from one to 23 years, with an average tattoo age of nine years. The majority of subject tattoos (71%) consisted of only black ink. See Tables 1 and 2 below for full subject demographics and tattoo characteristics.

Investigational Laser Device: Cutera enlighten

The Cutera enlighten laser is a high power, dual-wavelength system which offers a 1064 nm Nd:YAG and frequency-doubled 532 nm KTP. Advanced technology provides the option to treat with pulse widths of 750 picoseconds or 2 nanoseconds, using a variety of spots sizes and fluences. The laser treatment parameters are selected using the touchscreen control panel.

Treatment Protocol

Subjects received up to three laser treatments spaced six weeks apart. Twenty-four subjects (57%) received two laser treatments and 17 subjects (41%) received three treatments. Split-tattoo treatment were performed according to randomization assignment. Investigators performed one pass treatment to each tattoo portion and selected treatment parameters based on subject skin type, observation of the clinical endpoint of whitening or frosting of the tattoo following irradiation, and the subject's reported discomfort. Both laser devices were used with a spot size of 16 mm^2. Fluences for both devices were comparable with 1064 nm delivered at 1.99 (±0.28) J/cm^2. When utilizing 532 nm, fluences were delivered at 0.87 (±0.15) J/cm^2 for the enlighten system and 0.85 (±0.28) J/cm^2 for the comparator device (Table 3). Pulse durations for the enlighten device were 750 ps and/or 2 ns for the 1064 nm wavelength, and 750 ps for the 532 nm wavelength. Pulse duration for the enlighten device was selected based on tattoo ink density and color. Dark, dense tattoo areas were treated with 2 ns pulses. Lighter tattoo areas, including areas of diffuse shading, were treated with 750 ps pulses. In addition, as subject tattoos demonstrated lightening at subsequent laser treatment visits, enlighten treatment were increasingly administered using the 750 ps pulse duration. For the comparator QS nanosecond device, the pulse duration was 6 ns for both wavelengths.

Pain levels (0–10 numeric rating scale) and adverse events were also recorded. Following laser treatment, standard wound care procedures were followed. Subjects were instructed to use SPF 50 in the treated area for the duration of the study.

Blinded Clinical Evaluation

Two independent board certified dermatologists performed a blinded evaluation of standardized subject photographs taken at baseline and 6 weeks post-final treatment. Degree of improvement (clearing) was assessed using a 0 to 4 scale (0=No Change, 1=Mild Clearing, 2=Moderate Clearing, 3=Significant Clearing, 4=Very Significant Clearing).

In addition, the blinded investigators compared the improvement to the active control by assessing if the split treatment showed similar clearing, more clearing or substantially more clearing between the segments.

Statistical Analysis

The difference in tattoo clearing for each arm, as assessed by blinded reviewers, was tested for statistical significance using the student's paired

Table 2. Baseline Characteristics of Subject Tattoos

Tattoo Type, n (%)	Professional	24 (57%)
	Amateur	18 (43%)
Tattoo Age (years)	Mean (± SD)	9 (± 6)
	Minimum	1
	Median	9
	Maximum	23
Tattoo Location, n (%)	Back	11 (26%)
	Arm	10 (24%)
	Chest	6 (14%)
	Neck	5 (12%)
	Hip	3 (7%)
	Hand	2 (5%)
	Shoulder	2 (5%)
	Behind Ear	1 (2%)
	Foot	1 (2%)
	Leg	1 (2%)
Tattoo Colors, n (%)	Black only	30 (71%)
	Black and Red	7 (17%)
	Black with other colors	3 (7%)
	Blue	1 (2%)
	Blue with other colors	1 (2%)

Table 1. Subject Demographics

Subjects (n)		42
Mean Age (Range)		34 (20 – 51)
Females, n (%)		18 (43%)
Males, n (%)		24 (57%)
Race, n (%)	White	0 (0%)
	Black or African American	1 (2%)
	Asian	0 (0%)
	American Indian or Alaska Native	0 (0%)
	Native Hawaiian or Pacific Islander	2 (5%)
	Mixed Race	15 (36%)
Ethnicity, n (%)	Hispanic or Latino	10 (24%)
	Not Hispanic or Latino	16 (38%)
	Declined to state	16 (38%)
Fitzpatrick Skin Type, n (%)	I	0 (0%)
	II	20 (48%)
	III	16 (38%)
	IV	3 (7%)
	V	3 (7%)

Table 3. Treatment Fluence

	Investigational QS Nd:YAG		Comparator QS Nd:YAG	
Wavelength	**532 nm**	**1064 nm**	**532 nm**	**1064 nm**
Fluence (J/cm²)				
Mean (± SD)	0.87 (± 0.15)	1.99 (±0.28)	0.85 (± 0.13)	1.99 (±0.28)
Minimum	0.7	1.5	0.7	1.5
Median	0.8	1.9	0.8	1.9
Maximum	1.1	2.4	1.1	2.4

sample test (1-sided test, alpha=0.05) Statistical analysis of the primary efficacy variable was performed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, North Carolina). Kappa analysis of blinded reviewer agreement was performed using the Minitab statistical package, version 16.2.2.0 (Minitab Inc., State College, Pennsylvania).

Results

Blinded Assessment

Blinded photographic assessments of treatment outcome found a clinically and statistically significant mean improvement of 2.54 (95% CI: 2.13 – 2.94) and 2.17 (95% CI 1.77 – 2.57) for the Cutera enlighten device and the comparator QS device, respectively, at 6 weeks post–final treatment (Figure 3).

2.94) and 2.17 (95% CI 1.77 – 2.57) for the Cutera enlighten device and the comparator QS device, respectively, at 6 weeks post–final treatment (Figure 3).

The mean difference in the blinded global assessment of the improvement scores between the enlighten and comparator devices was 0.37 (95% CI: 0.20 – 0.53) indicating the enlighten device resulted in more clearing that the comparator device at six weeks following two to three treatments (p<0.001).

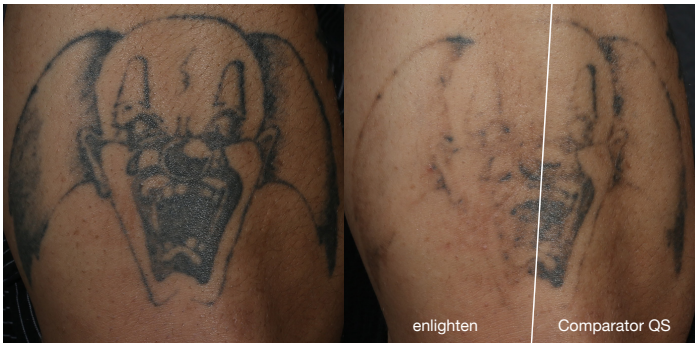
Sub-Group Analysis

Data was analyzed in the aggregate and according to three cohorts, to assess the impact of pulse duration treatment variations in tattoos treated with enlighten.

Subjects were divided into 3 cohorts: 1) subjects treated with enlighten using ps pulses only; 2) subjects treated with a combination of ps and ns pulses; and 3) subjects treated with using only the ns pulse durations.

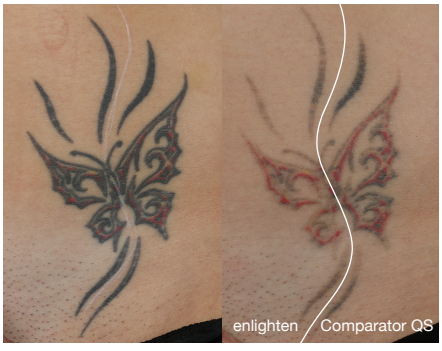
Blinded reviewer assessment of tattoo clearing at 6 weeks post-treatment demonstrated that for the subjects treated only with ps pulses (cohort 1) resulted in a clinically and statistically significant mean improvement score of 3.2 (95% CI: 2.54 – 3.86, p<0.001). Subjects treated with combination of ps and ns pulses (cohort 2) had a clinically and statistically significant mean improvement score of 2.77 (95% CI: 2.23 – 3.32, p<0.001). Subjects treated with ns pulses only (cohort 3) had a clinically and statistically significant mean improvement score of 2.3 (95% CI: 1.91 – 2.69, p<0.001). Mean and median improvement scores for each cohort (Figure 4). In all cohorts, enlighten showed a statistically significant higher clearance than the comparator device, with ps pulses only having the greatest difference [0.7 (95% CI: 0.22 – 1.18, p=0.01)], followed by ps and ns [0.46 (95% CI: 0.10 – 0.81, p=0.015)], and then ns pulses only [0.26 (95% CI: 0.05 – 0.47, p=0.018)].

Figure 1. Patient 01-05.
25-year-old male, FST IV with a 5-year old amateur tattoo located on the lower arm. Blinded reviewers rated post-treatment clearing on the enlighten side as "4=very significant clearing" and "3=significant clearing." Comparator QS was rated as "2=moderate clearing" by all reviewers. Treatment parameters used for this patient: enlighten (left): 750 ps, 1064 nm, 1.8 – 2.0 J/cm², 4 - 5 mm spot size; Comparator QS (right): 6 ns, 1064 nm, 1.8 - 2.0 J/cm², 4 - 5 mm spot size



Baseline 6 weeks post 3 txs

Figure 2. Patient 01-11.
26-year-old female, FST II with a 9-year old amateur tattoo located on the lower abdomen. Blinded reviewers rated post-treatment clearing on the enlighten side as "3=significant clearing" and "2=moderate clearing." Compartor QS side was rated as "2=moderate clearing" and "1=mild clearing" by physician reviewers. Treatment parameters used for this patient: enlighten (left): 2 ns for 1st tx, then 750 ps for 2nd and 3rd txs, 1064 nm, 1.7 - 2.4 J/cm², 4 - 5 mm spot size; Comparator QS (right): 6 ns, 1064 nm, 1.7 - 2.4 J/cm², 4 - 5 mm spot size. Red ink was not treated.



Baseline 6 weeks post 3 txs

Subject Satisfaction

The majority of the subjects were satisfied with the results, with higher subject satisfaction in the enlighten treatment arm. At six weeks post-final treatment, 97% percent of the subjects were willing to have enlighten laser treatment again and 89% would recommend it to others.

Side Effects

No significant adverse effects were reported for the enlighten device or the comparator device. As expected, subjects experienced erythema, edema and pin-point bleeding most frequently in both treatment arms. Treatments were tolerated well, and pain scores were consistent between both treatment arms.

Discussion

One of the primary challenges to successful LTR is the variance in size of ink particles. The smallest particles are the hardest to fragment and traditional Q-switched lasers only offer longer nanosecond pulse durations better suited for larger particle sizes. Tattoos comprised of larger ink particles generally respond to nanosecond pulse durations, but studies have shown that shorter picosecond pulse durations offer better clearance of smaller ink particles than nanosecond pulse durations.[10,12,13,14,15] The ideal laser for LTR should be able to target both large and small tattoo ink particles and therefore, be able to deliver both nanosecond and picosecond pulse durations.

This study, designed to assess the safety and efficacy of a dual wavelength, dual nanosecond-picosecond pulse duration laser on tattoo clearance, successfully demonstrated that enlighten is able to provide more tattoo clearance than a traditional QS laser with a longer 6 ns pulse duration. The fluence, total energy, spot size, and repetition rate were all kept constant for both devices; the only variable was pulse duration. In addition, enlighten outperformed the traditional QS with statistically significant results in all three pulse duration cohorts: 1) picosecond alone, 2) picosecond plus nanosecond, and 3) nanosecond alone.

Conclusion

The dual wavelength, 1064 nm and 532 nm, enlighten laser, with both nanosecond and picosecond pulse durations, resulted in significant tattoo clearing six weeks following two to three treatment sessions. Furthermore, subjects treated with only picosecond pulse durations for all laser treatment sessions demonstrated more clearing over the entire study population. Subjects tolerated the enlighten treatment well and post-treatment adverse effects were consistent with the comparator device and traditional QS laser treatments. The novel enlighten laser system was found to be a safe and effective treatment for tattoo removal.

Figure 3.

Boxplot of blinded reviewer assessment for each treatment arm.

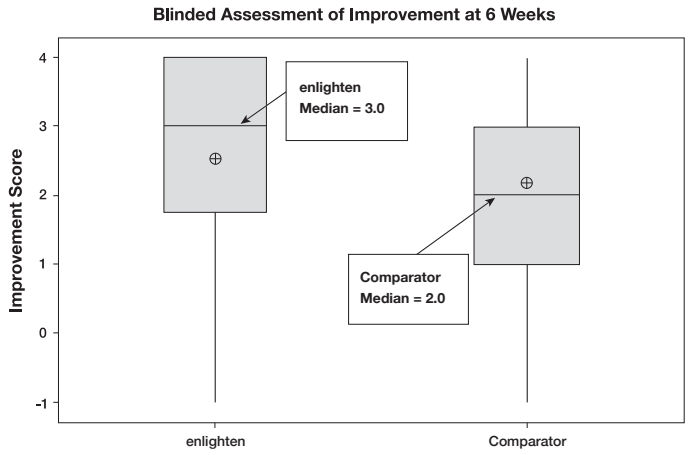
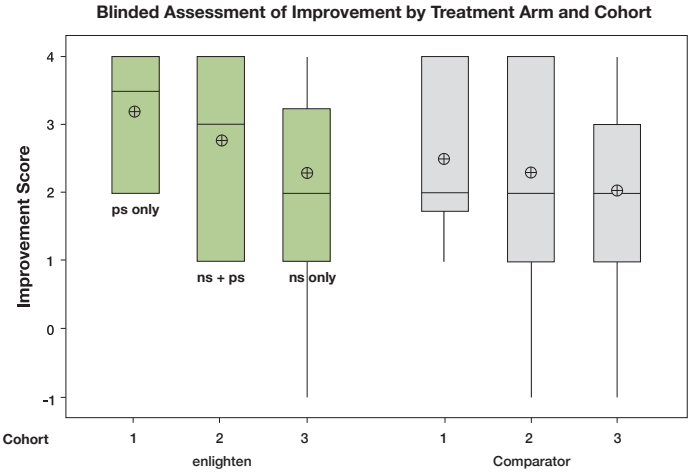


Figure 4.

Boxplot of blinded reviewer assessment for each treatment arm.



References

1. Tattoo Incidence Study, ORC International (Commissioned by CUTERA) 06/15
2. Harris Interactive, 2012
3. Tattoo Removal Practitioners Market Research Report. IBIS World, 2014.
4. Bencini PL, Cazzaniga S, Tourlaki A, Galimberti MG, Naldi L. Removal of tattoos by q-switched laser: variables influencing outcome and sequelae in a large cohort of treated patients. Arch Dermatol. 2012 Dec;148(12):1364-1369.
5. Ara, G., et al., Irradiation of Pigmented Melanoma Cells With High Intensity Pulsed Radiation Generates Acoustic Waves and Kills Cells. Lasers Surg Med, 1990. 10(1):52-59.
6. Ho, D.D., et al., Laser-tattoo removal--a study of the mechanism and the optimal treatment strategy via computer simulations. Lasers Surg Med, 2002. 30(5):389-397.
7. Ferguson, J.E., et al., The Q-switched neodymium:YAG laser and tattoos: a microscopic analysis of laser-tattoo interactions. Br J Dermatol, 1997. 137(3):405-410.
8. Hu, X.H., et al., In vivo study of intradermal focusing for tattoo removal. Lasers Med Sci, 2002. 17(3):154-164.
9. Kent, K.M. and E.M. Graber, Laser tattoo removal: a review. Dermatol Surg, 2012. 38(1):1-13.
10. Herd, R.M., et al., A Clinical and Histologic Prospective Controlled Comparative Study Of The Picosecond Titanium Sapphire (795nm) Laser Versus the Q-switched Alexandrite (752 nm) Laser For Removing Tattoo Pigment. Journal of the American Academy of Dermatology, 1999(40):603-606.
11. Choudhary, S., et al., Lasers for tattoo removal: a review. Lasers Med Sci, 2010. 25(5):619-627.
12. Izikson, L., et al., Safety and effectiveness of black tattoo clearance in a pig model after a single treatment with a novel 758 nm 500 picosecond laser: a pilot study. Lasers Surg Med, 2010. 42(7):640-646.
13. Saedi, N., et al., Treatment of Tattoos With a Picosecond Alexandrite Laser: A Prospective Trial. Arch Dermatol, 2012:1-4.
14. Ross, V., et al., Comparison of Responses of Tattoos to Picosecond and Nanosecond Q-switched Neodynium-YAG lasers. Arch Dermatol, 1998(134):167-171.
15. Brauer, J.A., et al., Successful and rapid treatment of blue and green tattoo pigment with a novel picosecond laser. Arch Dermatol, 2012. 148(7):820-823.