

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

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Background: Optimal selective photothermolysis of a pigment particle requires pulse durations equal to or less than the particle's thermal relaxation time ($t_{\frac{1}{2}}$). Since tattoo particles in skin range in diameter from 40 to 300 nm, picosecond pulses would approximate $t_{\frac{1}{2}}$ more closely and, therefore, might be more effective at tattoo particle fragmentation.

Materials and Methods: India Ink (carbon) or iron oxide tattoos were placed on the back of a Yorkshire pig. Six weeks later, each tattoo was treated with either a 758 nm 500 picosecond laser (Cynosure), a 755 nm 30–50 nanoseconds laser, or left untreated. After 4 weeks, clinical responses were evaluated by three dermatologists based on pre- and post-treatment photographs; histopathologic findings were evaluated by a dermatopathologist; and electron microscopic findings were analyzed for treated and non-treated carbon tattoos.

Results: After a single treatment, picosecond-domain pulses at 758 nm produced a significantly greater degree of carbon tattoo clearance compared to nanosecond-domain pulses at 755 nm. For iron oxide tattoos, both modalities produced minimal-to-poor clearance that was generally comparable. Neither modality resulted in scarring, textural changes, or hypopigmentation, and there was no histopathologic evidence of scarring. Electron micrographs revealed the presence of amorphous material (treated pigment) in picosecond and nanosecond laser-treated tattoos, consistent with effective targeting of India Ink pigment.

Conclusions: The 758 nm 500 picosecond laser is more effective at carbon tattoo clearance after one session in a porcine model than the 30–50 nanosecond laser emitting at a similar wavelength. Both lasers cleared carbon tattoos more effectively than iron oxide tattoos. Both lasers have a comparable safety profile, and neither produced clinical or histopathologic scarring. Further studies in humans are necessary to evaluate whether repeated treatments with picosecond versus nanosecond domain modalities might yield superior tattoo pigment clearance with a comparable safety profile. *Lasers Surg. Med.* 42:640–646, 2010.

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Key words: tattoo; removal; laser; nanosecond; picosecond; pigment; porcine; carbon; iron oxide

INTRODUCTION

Approximately one quarter of all Americans 18–50 years old have tattoos [1], and women comprise 45–65% of the tattooed population [2]. While the overwhelming majority are pleased with their tattoos, 17–20% of the tattooed population is dissatisfied, and 6% actually seek tattoo removal [2].

Currently, laser tattoo removal is accomplished with nanosecond domain lasers that emit at wavelengths designed to target specific chromophores within a tattoo. Tattoo removal is challenging for several reasons. According to the theory of selective photothermolysis [3], optimal targeting of a particle, leading to its fragmentation, is accomplished with pulse durations at or slightly lower than the particle's thermal relaxation time and at a wavelength absorbed by the particle. As the origin and chemical structure of tattoo compounds used by tattoo artists are unknown, and most tattoos contain more than one compound, one wavelength may not target effectively all the resident pigment particles. Additionally, nanosecond-domain pulses may be too long for most effective targeting of tattoo particles, most of which range in size from 40 to 300 nm in vivo [4,5]. Thus, most particles would have thermal relaxation times in the picosecond range.

The precise mechanisms responsible for tattoo particle clearance are poorly understood. However, laser energy produces several effects that likely contribute to particle lightening and fragmentation (summarized by Bäuml et al. [5]). The photoacoustic/photomechanical effect is due to a shock wave generated into a particle from ultrashort heating of the particle shell, which shatters the particle and disrupts the surrounding cellular structures. The photothermal effect is due to conversion of absorbed energy into heat and heat-induced pigment modification. The photochemical effect is due to breakage of chemical bonds within

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pigment particles by absorbed energy. Finally, the steam-carbon reaction for carbon-containing tattoos is due to steam-induced conversion of carbon to an electron-lucent structure. All of these likely result from a single laser pulse [5]. Thus, as a result of laser energy, larger aggregates break down into smaller crystals, particles pulverize and form a solution of pigment molecules, and molecules themselves may break up, leading to structural change and decomposition products. The lymphatics subsequently remove smaller particles, newly generated compounds, and decomposition products [5].

When Ho et al. [6] modeled the process of graphite tattoo removal in a computer simulation using 755 and 1,064 nm, and a sample 50 nm particle, they observed that strong acoustic waves can be generated if laser pulses is sufficiently short. These waves have tensile strengths greater than the fracture threshold for graphite. Indeed, shorter pulse durations generated stronger waves. Additionally, while smaller particles required weaker waves, larger particles could reach higher temperatures and generate larger cavitation bubbles. Finally, laser energy density decreased rapidly with particle depth (only 25% and 10% of 1,064 nm light could penetrate to 2 and 3 mm, respectively). Accordingly, they concluded that energy confinement time increases with particle diameter (so it is optimally 10–100 picoseconds for 50 nm particles, and optimally longer for larger aggregates). Because particles never reached the graphite melting point temperature, they argued against the “photothermal effect” as one of the mechanisms for tattoo lightening [6]. On the basis of these findings, the goal of tattoo removal is to generate enough tensile stress with a laser pulse to fragment the particle, without creating excessive collateral damage due to absorbed energy.

Picosecond pulses have the potential to produce more specific and confined pigment disruption at lower fluences. This has been demonstrated by Herd et al. [7], in carbon tattoos in guinea pigs; and by Ross et al. [4], in black tattoos on patients. While neither group observed clinical evidence of scarring, Herd et al. [7] found some evidence of fibroplasia in picosecond-treated specimens. Notably, neither study evaluated the differential effects of the 758 nm wavelength picosecond laser at high fluences on carbon and iron oxide tattoos in a pig model. Both carbon and iron oxide make black tattoos, but only carbon can undergo combustion. Therefore, we decided to compare them directly.

Because clinical tattoos comprise mainly 40–300 nm particles, along with some larger aggregates of pigment, most such particles can be disrupted by 500 picosecond pulses. In this study, we evaluated the effectiveness and safety of a single treatment with a 758 nm 500 picosecond laser at three different fluences for carbon and iron oxide tattoo removal in a Yorkshire pig model, and compared it with a widely used and commercially available Q-switched 755 nm Alexandrite laser at 30–50 nanoseconds.

MATERIALS AND METHODS

All of the protocols were evaluated and approved by the MGH Animal Research Subcommittee.

Animals: Two adult female non-pregnant Yorkshire pigs (30–50 kg). **Housing:** MGH Large animal housing facility and MGH animal farm.

Before each procedure, Buprenorphine HCL, Buprenex[®], 0.010 mg/kg IM was injected in full recommended dose and then another dose was given 3–4 hours after the first one, for analgesia. Each pig’s flanks and back were cleansed with Hibiclens and saline, hair shaved, cleansed again, dried with a towel. After each procedure, the animals were observed by Dr. Izikson and Mr. Farinelli, as well as the MGH veterinary staff, for 3 days post-procedure, with a clinical examination.

Each procedure was performed in the MGH large animal OR. The pigs were anesthetized using Telazol/Xylazine 4.4 mg/kg IM + 2.2 mg/kg IM and inhalant anesthetics (halothane or isoflurane (1.5–3.0%)) with oxygen (3.0 L/min) delivered by mask and filtered with an F-Air canister only if the injectable anesthetics did not provide enough somatic analgesia. The level of somatic analgesia was monitored every 15 minutes by evaluation of heart rate and pulse oximetry. Also, an increase of more than 15% of heart rate led to further adjustment of the somatic analgesia.

Each pig’s flanks and back were divided into 10 mm diameter square areas for tattoo placement with a tattoo gun (Spaulding and Rogers, Voorheesville, NY). Each test spot was randomly chosen for tattooing with either carbon (India Ink) (carbon) (MGH Pharmacy, Boston, MA); or iron oxide—midnight brown/black tattoo pigment (Silver Needle, Pompano Beach, FL). Sites were cleaned with sterile saline and dressed with Neosporin. The animals spent the next 6 weeks recovering at the MGH animal farm.

Since tattoo particles range in size from 40 to 300 nm in vivo [4,5], their thermal relaxation times are mostly in the picosecond range. The thermal relaxation times for tattoo particles were calculated using a formula for thermal relaxation time of carbon particles as described by Ho et al. [6], who specifically modeled this for laser tattoo removal, $t_{\frac{1}{2}} = (r^2) \times \rho \ (2.25 \text{ g/cm}^3) \times C_v \ (1.7 \text{ J/g K}) \times 1/K \ (0.8 \text{ W/cm}^2)$; and a range of thermal relaxation times is listed below for each diameter: 40 nm—19.12 picoseconds, 60 nm—43.03 picoseconds, 80 nm—76.5 picoseconds, 100 nm—119.5 picoseconds, 150 nm—268.9 picoseconds, 200 nm—478 picoseconds, 250 nm—747 picoseconds, 300 nm—1,060 picoseconds.

Six weeks after tattooing, each spot was examined, photographed with a digital camera (Nikon D80 digital camera, with a Nikon 60 mm Marco lens, and a Canfield flash system (which is a Nikon speed light SB-600), and cross-polarizers (Nikon, Inc., Melville, NY)), and randomly chosen for treatment with either with the 755 nm 30–50 nanoseconds laser (Q-switched Alexandrite laser, Candela, Wayland, MA) (setting: 3 mm spot, 8 J/cm², endpoint: pigment whitening and punctate hemorrhage), or the 758 nm 500 picosecond laser (Cynosure, Westford, MA) (spot and fluence settings: HIGH—1.3 mm spot, 13–16 J/cm²; MEDIUM—1.9 mm spot, 6–7.5 J/cm²; LOW—2.9 mm spot, 2.5–3.9 J/cm²; endpoint: pigment whitening and punctuate hemorrhage), or no treatment at all (control). Great care was taken not to double pulse any treated area.

The spot size and fluence of the 755 nm nanosecond Alexandrite laser represent the commonly used parameters in clinical practice. As spot size determines the depth of penetration, the smaller spot sizes of the picosecond laser would be expected to have more limited depths of penetration compared to the nanosecond laser.

Fourteen and 28 days after treatment, one of the animals was examined clinically, and photography of treated sites was obtained in the OR after skin was cleaned and hair shaved. Each tattooed site, and some areas of normal untreated skin, was biopsied with a 4 mm punch. Specimens were fixed in 10% buffered formalin, and processed for hematoxylin and eosin (H + E) staining. Several specimens were also fixed in Karnofsky's medium, and processed for electron microscopic (EM) examination. After specimen collection, each animal was euthanized with IV Pentobarbital.

Clinical photographs were examined by three dermatologists blinded to the study design and execution. They were asked to rate the degree of lightening using a scale from 0 (no improvement) to 10 (complete clearance), as below:

Score	Degree of lightening (%)
0–1 (none)	0–9
2–3 (poor)	10–34
4–7 (fair)	35–69
8–9 (good)	70–90
10 (excellent)	> 90

The responses for the treatment groups were analyzed using the 2-tailed Student's *t*-test with a 95% confidence interval. An ANOVA analysis was also performed (results not shown), revealing that there was statistically significant variability amongst the various groups in each series, the carbon and the iron oxide tattoos.

Histopathologic H + E sections were examined by a dermatologist (LI), who performed the study; and a dermatopathologist (ZT) who was blinded to the study design and execution. The EM specimens were processed, evaluated, and photographed by the EM specialist in the Wellman EM core facility (Ms. Margaret Sherwood), as previously described [4].

RESULTS

Clinical Safety

Clinical evaluation of tattooed sites at 6 weeks, performed by a dermatologist (LI) and research scientist (WF), showed no evidence of clinical scarring in any tattooed sites. Some of the sites had a remaining slight scab on their surface. This was easily debrided with saline-soaked gauze, and did not reveal any underlying scarring.

Clinical evaluation of tattoos at 2 and 4 weeks after treatment (with the 500 picosecond laser at three different fluences, with the Q-switched Alexandrite laser at a single fluence, and untreated sites), performed by a dermatologist (LI) and research scientist (WF), as well as photographic evaluation of same sites by three dermatologists blinded to the study design and execution, revealed no evidence of clinical scarring at 2 and 4 weeks after treatment and no pigment darkening. Of note, treatment with either laser modality at all of the settings produced the same clinical endpoint: pigment whitening with punctate hemorrhages. This is analogous to the clinical treatment endpoint achieved when treating tattoos on human skin in clinical practice.

Histopathologic examination of skin specimens (tattoos treated with the 500 picosecond laser at three different fluences, with the Q-switched Alexandrite laser at a single fluence, untreated tattoo specimens, and normal skin),

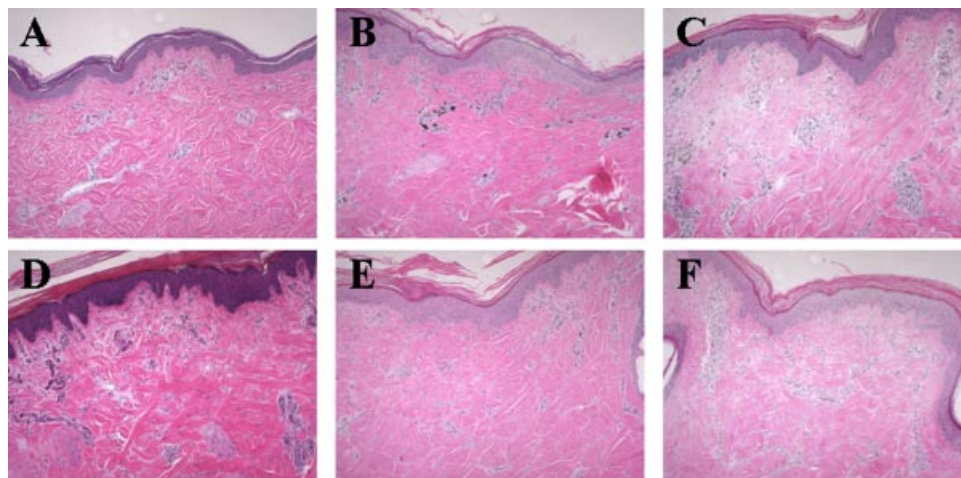


Fig. 1. India Ink Tattoos 1 month after treatment with lasers. (A) Non-treated normal skin, (B) tattoo, non-treated, (C) tattoo treated with the Q-switched 755 nm laser (3 mm, 8 J/cm²), (D) tattoo treated with the picosecond 758 nm laser (1.3 mm, 13–16 J/cm²), (E) tattoo treated with the picosecond 758 nm laser (1.9 mm, 6–7.5 J/cm²), (F) tattoo treated with the picosecond 758 nm laser (2.9 mm, 2.5–3.9 J/cm²). None of the treated areas showed evidence of fibrosis or scarring.

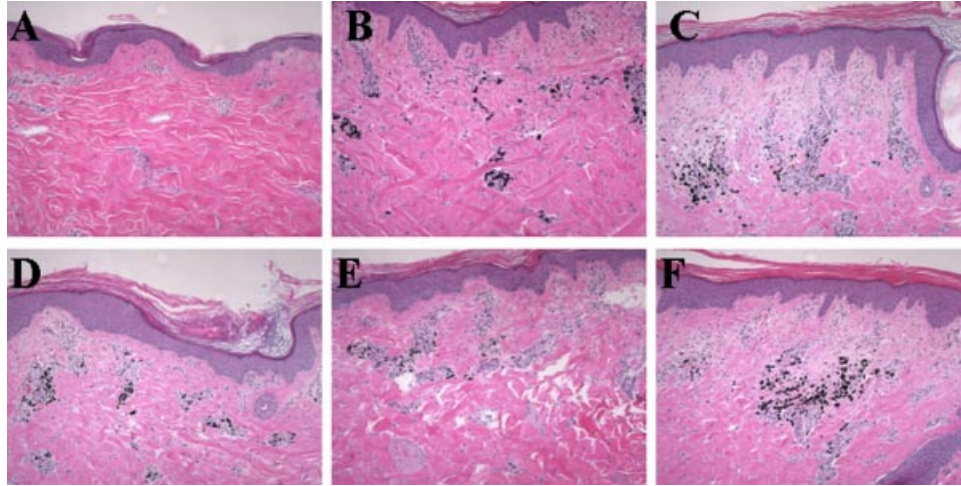


Fig. 2. Iron Oxide Tattoos 4 weeks after treatment with lasers. (A) Non-treated normal skin, (B) tattoo, non-treated, (C) tattoo treated with the Q-switched 755 nm laser (3 mm, 8 J/cm²), (D) tattoo treated with the picosecond 758 nm laser (1.3 mm, 13–16 J/cm²), (E) tattoo treated with the picosecond 758 nm laser (1.9 mm, 6–7.5 J/cm²), (F) tattoo treated with the picosecond 758 nm laser (2.9 mm, 2.5–3.9 J/cm²). None of the treated areas showed evidence of fibrosis or scarring.

performed by a dermatologist (LI), and a dermatopathologist blinded to the study design and execution (ZT), revealed no histopathologic evidence of fibrosis at 2 and 4 weeks after treatment. In several specimens treated with the 500 picosecond and the Q-switched Alexandrite laser, there was some evidence of fibroplasia. Representative photos are shown in Figures 1 and 2.

Clinical Effectiveness

In clinical practice, the effectiveness of tattoo pigment lightening is generally evaluated at 4 weeks after treatment. Therefore, this was the time point at which the degree of pigment lightening was evaluated by three dermatologists blinded to the study design and execution based on post-treatment photographs.

Clinical evaluation of pre- and post-treatment photographs of carbon (India Ink) tattoos revealed significant

lightening of all laser-treated sites compared to untreated controls (results summarized in Table 1). Sites treated with the picosecond laser at either the high, medium, or low fluence setting, showed a greater degree of pigment lightening compared to those treated with the Q-switched Alexandrite laser (these values were statistically significant). There was no statistically significant difference in the degree of pigment lightening between the different settings of the picosecond laser. Representative photos are shown in Figure 3.

Clinical evaluation based on pre- and post-treatment photographs of iron oxide tattoos revealed statistically significant lightening of all laser-treated sites compared to untreated controls (results summarized in Table 2), though the overall degree of lightening was markedly lower than that observed for carbon tattoos. Sites treated with the picosecond laser at either the medium or low fluence setting

TABLE 1. Blinded Observer (Three Dermatologists) Photographic Evaluation of Treated Tattoos: Carbon (India Ink)

	No. of sites	Mean	Median	SD	P: C vs. X	P: A vs. X	P: H vs. M	P: H vs. L	P: M vs. L
Control (untreated)	12	1.72	1	1.32					
Alexandrite	6	6.44	6.5	1.65	<0.001				
HIGH—picosecond 1.3 mm, 13–16 J/cm ²	18	7.57	8	1.91	<0.001	0.028	0.56	0.43	
MED—picosecond 1.9 mm, 6–7.5 J/cm ²	18	7.81	8	2.08	<0.001	0.014	0.56		0.96
LOW—picosecond 2.9 mm, 2.5–3.9 J/cm ²	18	7.83	8	1.5	<0.001	0.0015		0.43	0.96

t-test, evaluating the degree of improvement (0—none; 10—cleared) based on scoring by three independent observers (C, control, A, Alexandrite nanosecond laser, H, high fluence setting of the picosecond laser, M, medium fluence setting of the picosecond laser, and L, low fluence setting of the picosecond laser).

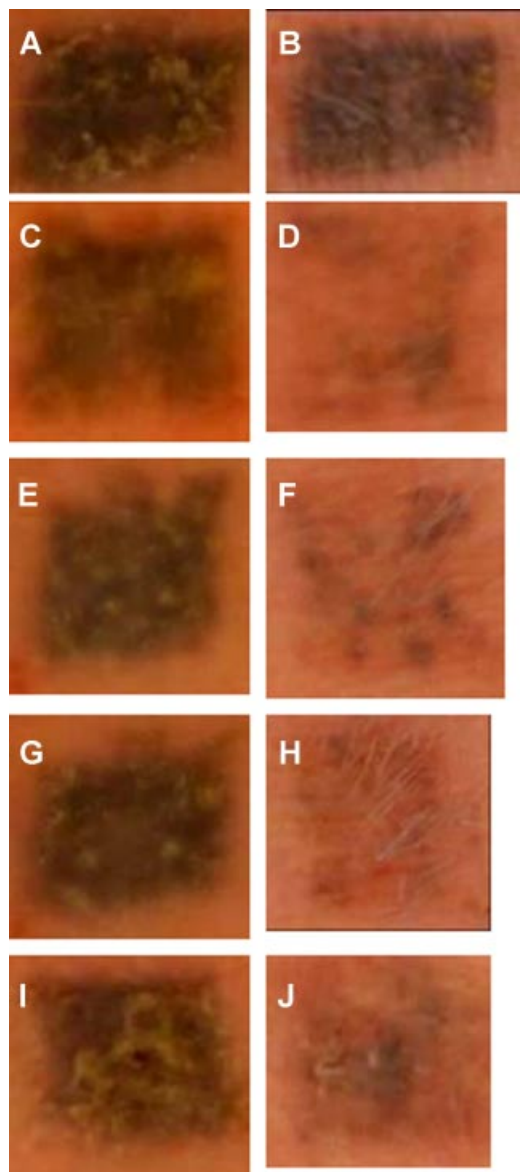


Fig. 3. India Ink Tattoos before treatment (A,C,E,G,I), and 4 weeks after no treatment (B) or treatment with lasers: (D) tattoo treated with the picosecond 758 nm laser (1.3 mm, 13–16 J/cm²), (F) tattoo treated with the picosecond 758 nm laser (1.9 mm, 6–7.5 J/cm²), (H) tattoo treated with the picosecond 758 nm laser (2.9 mm, 2.5–3.9 J/cm²), (J) tattoo treated with the Q-switched 755 nm laser (3 mm, 8 J/cm²). None of the treated areas showed evidence of fibrosis or scarring.

showed a similar degree of pigment lightening compared to the Q-switched Alexandrite laser. However, the picosecond laser at the high fluence setting was inferior to either the medium or low fluence setting, or to the Q-switched Alexandrite laser, producing a statistically significantly lesser degree of lightening. There was no statistically significant difference in the degree of pigment lightening between the medium and low fluence settings of the picosecond laser.

Electron Microscopic Studies

EM evaluation of carbon tattoos treated with the picosecond laser or with the Q-switched Alexandrite laser at 4 weeks after treatment showed the presence of amorphous light material and some electron-dense particles within cellular organelles (lysosomes) consistent with pigment disruption. This was comparable in picosecond and Q-switched Alexandrite-treated tattoos. In contrast, untreated cells contained electron-dense particles only. Representative photos are shown in Figure 4.

DISCUSSION

In sum, the 758 nm 500 picosecond laser is both safe and effective in the treatment of black carbon tattoos, and demonstrates similar clinical safety to the commercially available and widely used Q-switched Alexandrite laser. Both, the 758 nm picosecond and 755 nm nanosecond laser treatments that achieved the same clinical treatment endpoint, produced greater lightening of black carbon tattoos compared to black iron oxide tattoos after a single treatment in a pig model. Neither modality produced clinical or histopathologic evidence of scarring after a single treatment. The 758 nm 500 picosecond laser at all three fluences produced a significantly greater degree of carbon tattoo lightening after a single treatment compared to the Q-switched Alexandrite laser.

The mechanisms of laser-induced tattoo clearance remain poorly understood. They include the photoacoustic effect; photothermal effect; generation of plasma [8–11] that could amplify at ultrafast pulse durations [12] and modify surrounding pigment [13]; steam-carbon reaction for carbon tattoos; cellular disruption, leading to clearance of spilled particles via lymphatics; or a combination of these events. Nonetheless, the initial event is confinement of delivered laser energy to the pigment particle. Most precise confinement occurs at pulse durations that are equal to or lesser than the particle's thermal relaxation time. Accordingly, a picosecond-domain pulse would allow better confinement of laser energy to 40–300 nm tattoo particles in vivo. The greater degree of carbon tattoo lightening after a picosecond laser treatment compared to a nanosecond laser treatment found in this study supports the idea that more precise confinement of laser energy to a pigment particle generates more effective particle lightening, even as the downstream mechanistic events that are ultimately responsible for this lightening remain to be elucidated further.

While at a high fluence, the picosecond laser was inferior to the Q-switched Alexandrite laser for clearance of iron oxide pigment, the degree of lightening produced by either modality was minimal (with “poor” being the most successful treatment outcome). This may be due to several factors: (a) the generation of some amount of ferrous oxide species after laser treatment (e.g., laser-induced reduction of ferric oxide) [14], along with concomitant destruction and clearance of ferric oxide particles from the skin; (b) the differential effects of laser energy on covalent CC bonds in carbon particles compared to ionic FeO bonds of iron oxide

TABLE 2. Blinded Observer (Three Dermatologists) Photographic Evaluation of Treated Tattoos: Iron Oxide

	No. of sites	Mean	Median	SD	P: C vs. X	P: A vs. X	P: H vs. M	P: H vs. L	P: M vs. L
Control (untreated)	12	0.583	0	1.02					
Alexandrite	12	2.64	2	1.93	<0.001				
HIGH—picosecond 1.3 mm, 13–16 J/cm ²	12	1.08	1	0.94	0.034	<0.001	0.0037	0.0019	
MED—picosecond 1.9 mm, 6–7.5 J/cm ²	12	2.08	2	1.76	<0.001	0.21	0.0037		0.59
LOW—picosecond 2.9 mm, 2.5–3.9 J/cm ²	12	2.33	2	2.12	<0.001	0.53		0.0019	0.59

t-test, evaluating the degree of improvement (0—none; 10—cleared) based on scoring by three independent observers (C, control, A, Alexandrite nanosecond laser, H, high fluence setting of the picosecond laser, M, medium fluence setting of the picosecond laser, and L, low fluence setting of the picosecond laser).

particles; or (c) the lack of “steam-carbon” reactions induced by laser pulses in the iron oxide particles. However, it remains to be determined whether repeated treatments with the picosecond laser might more effectively lighten

iron oxide pigment compared to the Q-switched lasers in commercial use today.

For optimal pigment disruption, high-energy picosecond pulses delivered with larger spot sizes to limit scattering losses would be required. This would improve the depth of tissue penetration and produce greater pigment disruption, while at the same time maintaining improved energy efficiency of the pulses. Indeed, higher energy picosecond pulses would also generate more plasma (optical breakdown). Plasma would consume greater amounts of energy from subsequent pulses that are intended for deeper tattoo particles [4], and would behave somewhat unpredictably in vivo. Nonetheless, plasma itself could have beneficial effects for tattoo clearance via plasma-generated stress-waves in tissue [13], or via production of a pinpoint surface defect that could result in greater dermal inflammation and transdermal/transepidermal pigment elimination.

Both nano- and picosecond lasers produce plasma [15,16], which raises a theoretical concern for mutagenicity of treated tissues. However, the clinical risk of mutagenicity is very low, since intermittent, limited, and very low dose exposures would not be expected to produce a significant impact on treated tissue. There was no clinical or histopathologic evidence of radiation dermatitis in our study. In ophthalmology, nanosecond laser-induced plasma is used routinely for posterior capsulotomy after lens extractions [17]. The intraocular radiation emitted from these plasmas has been deemed at a safe exposure level. To date, there is no evidence that laser-treated tattoos or tissues treated with picosecond lasers have a greater propensity for malignant transformation. At the same time, it is well documented that some tattoo pigments are carcinogenic [18]. Hence, placement of such chemicals into skin or their manipulation by lasers represents a more relevant concern for the development of subsequent cutaneous or other malignancy in affected individuals.

One limitation of this study is the use of only one commercially available nanosecond laser for positive control. We did not compare the effectiveness of the picosecond laser to those of shorter nanosecond lasers. Indeed, other commercially available nanosecond Nd:YAG lasers with shorter pulse durations (5–10 nanoseconds) have been used successfully to treat black tattoos [4], and

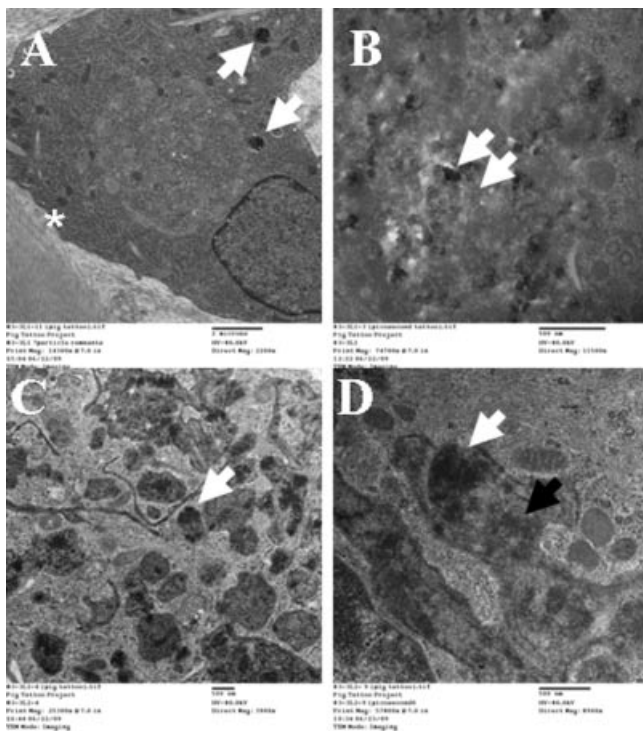


Fig. 4. Transmission electron microscopy: India Ink Tattoos 10 weeks after tattooing. Pigment clumps and granules (white arrows) in lysosomes of dermal fibroblasts and macrophages (white star) (A,B—untreated India Ink Tattoo). India Ink Tattoo 4 weeks after treatment with the picosecond 758 nm laser (1.3 mm, 13–16 J/cm²). Residual pigment clumps (white arrows) and disrupted pigment clumps (black arrow) in lysosomes of dermal fibroblasts and macrophages (C,D). Note the amorphous material signifying disrupted pigment (black arrow). Magnifications, 2,200 \times , 11,500 \times , 3,900 \times , and 8,900 \times , respectively.

may offer a reasonable alternative to the longer pulsed nanosecond lasers in certain clinical situations. This possibility needs to be evaluated experimentally in order to define the subset of tattoos best responsive to each modality.

Based on the results in this study, the 758 nm 500 picosecond laser represents a safe and effective therapeutic intervention for tattoo removal. Further studies of multiple sequential treatments of black tattoos of various chemical compositions with pico- and nanosecond lasers in humans are necessary to determine the most effective and safe modality in the clinical setting. Due to more efficient targeting of smaller pigment particles, picosecond-domain lasers might be more efficacious for the treatment of resistant tattoos than available technologies. Future studies should examine the effects produced by different wavelength picosecond lasers on tattoo pigments of various colors and made up of various chemical compositions.

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