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Neodymium-doped yttrium aluminium garnet (Nd:YAG) 1064-nm picosecond laser vs. Nd:YAG 1064-nm nanosecond laser in tattoo removal: a randomized controlled single-blind clinical trial

F. Pinto,[1] S. Große-Büning,[2] S. Karsai,[3,4] C. Weiß,[5] W. Bäumler,[6] S. Hammes,[2] M. Felcht[7] and C. Raulin[2]

[1]Pinto Medical Spa, Centro Laser Dermatologico Roma, Rome, Italy
[2]Laserklinik Karlsruhe und Medizinisches Versorgungszentrum, Karlsruhe, Germany
[3]Department of Dermatology, Klinikum Darmstadt, Darmstadt, Germany
[4]Department of Dermatology, University Hospital Greifswald, Ferdinand-Sauerbruchstraße, Greifswald, Germany
[5]Department of Medical Statistics, Biomathematics and Information Processing, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
[6]Department of Dermatology, Regensburg University Hospital, Regensburg, Germany
[7]Department of Dermatology, Venereology and Allergy, University Medical Centre Mannheim, Centre of Excellence of Dermatology of Baden-Wuerttemberg, Ruprecht-Karls-University of Heidelberg, Mannheim, Germany

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Summary

Background For decades, nanosecond lasers (NSLs) have been used to remove tattoos. Since 2012, pulses of picosecond lasers (PSLs) have been available for tattoo removal. Based on a few observational studies, the claim has been made that PSLs are considerably more effective while showing fewer side-effects in comparison with NSLs.
Objectives To compare the efficacy and side-effects of a PSL side by side with an NSL for tattoo removal.
Methods Twenty-one patients with 30 black tattoos were treated with PSL and NSL in a split-study design in two sessions at intervals of 6 weeks. The safety and efficacy of laser treatments were determined by blinded observers assessing randomized digital photographs in this prospective clinical study. The primary end point was the clearance of the tattoos ranging in quartiles from 0% to 100%; secondary end points were side-effects and pain.
Results The average clearance overall as evaluated showed no statistical difference between NSL and PSL ($P = 1{\cdot}00$). Using a visual analogue scale (0 = no pain, 10 = maximum pain), a value of $3{\cdot}8 \pm 1{\cdot}0$ was reported for the PSL, which was statistically different from NSL ($7{\cdot}9 \pm 1{\cdot}1$, $P < 0{\cdot}001$). Transient side-effects were observed, as well as hypo- and hyperpigmentation, but there was no statistically significant difference between PSL and NSL.
Conclusions After two treatments of black tattoos with a neodymium-doped yttrium aluminium garnet laser (1064 nm), the use of picosecond pulses does not provide better clearance than nanosecond pulses. However, pain is less severe when using a PSL.

Correspondence
Christian Raulin.
E-mail: info@raulin.de

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What's already known about this topic?

- Laser tattoo removal is increasing in proportion to the steadily growing incidence of tattoos.
- The industry and a few publications postulate that picosecond lasers are more efficacious in clearing tattoos and have fewer side-effects than nanosecond lasers.

What does this study add?

- This is the first randomized controlled trial to compare and analyse the clearance of tattoos.

- This study evaluates the side-effects of two commercially available nano- and picosecond lasers in a split-study design.
- Picosecond pulses do not provide better clearance than nanosecond pulses, but do result in less pain.

In Germany, some 9–12% of the general population has a tattoo.[1,2] In the younger population of 18–30 year olds the approximate incidence is higher, at 25%.[3,4] It is estimated that 6% of tattooed people want a professional removal 10–15 years after the tattooing.[3,5–7] The main reasons for removal are enhancement of self-esteem, and social, domestic and family reasons.[7] For the patient's safety, tattoos should not be removed by medical laypeople.[8,9]

The picosecond laser (PSL), which received approval from the US Food and Drug Administration for tattoo removal in 2012, was developed with the specific goal of abbreviating the overall duration of treatment, clearing tattoos that had previously resisted treatment with a nanosecond laser (NSL), and minimizing adverse effects. Treating cosmetic and traumatic tattoos is one of the primary indications for using the Q-switched (QS) 1064-nm neodymium-doped yttrium aluminium garnet (Nd:YAG) laser, which has pulse durations in the nanosecond range (approximately 5–20 ns). In addition to the QS ruby and QS alexandrite laser, it is considered the gold standard in removing tattoos. Theoretical calculations[10] indicate that a shorter pulse duration (in the picosecond range) effectively destroys smaller tattoo particles.

To date, there have been no randomized studies directly comparing currently approved NSLs and PSLs in human use. The question arises as to whether the PSL has a statistically significant and clinically relevant superiority to the much more cost-effective NSL. In this paper, two Nd:YAG lasers with pulse durations in the nano- and picosecond range are clinically evaluated in terms of their ability to remove tattoos in the course of a randomized and single-blind trial that featured a split-study design.

Patients and methods

Patients

The only tattoos included in the study were professionally applied black cosmetic tattoos. The exclusion criteria were increased sensitivity to light, scars or florid inflammation of the tattooed skin or area immediately surrounding it, pregnancy and unrealistic patient expectations. Prior to the first treatment, the patients were given verbal and written information about the course of the study, potential complications and therapeutic alternatives. The trial was conducted in accordance with the Declaration of Helsinki of 1964 in the revised edition of 1996 after receiving approval from the ethics committee of the University Medical Centre Mannheim, of the University of Heidelberg (verdict no. 5268; registration no. 2015-407M-MA-§23b MPG) and being registered in the German Clinical Trials Register (no. 00007709). A CONSORT flow diagram of the trial is given in Figure S1 (see Supporting Information).

Treatment

This study design was deliberately chosen to include tattoos with and without pretreatment, as more recent publications have stated that the PSL appears to be more effective than the NSL in pretreated tattoos.[11–16]

As approved by the ethics committee, only two treatments were performed, at an interval of 6 weeks, as prior publications have shown that good-to-excellent results have been attained after one to five sessions with PSLs.[13–16] The tattoos were divided into two halves of equal size: one half was treated with a QS 1064-nm Nd:YAG laser (MedLite®C6; Hoya-ConBio Inc., Fremont, CA, U.S.A.) at a pulse duration of 5 ns, and the other half with a 1064-nm Nd:YAG laser (Picoway®; Syneron Candela Corp., Wayland, MA, U.S.A.) at 450 ps. Table 1 lists details of the technical parameters of the lasers. Treatment was performed with fluences selected as high as possible and defensible, and the clinical threshold was defined as epidermal whitening and minimal pinpoint bleeding.

In all cases, the pulses were applied by the same operator using minimal overlapping. The operator did not take part in

Table 1 Medlite®C6 and Picoway® system parameters

	Medlite®C6 (NSL)	Picoway® (PSL)
System type	Nd:YAG	Nd:YAG
Wavelength	1064/532 nm	1064/532 nm
Pulse width	5 ns (= 5000 ps)	450 ps
Range of spot sizes	3–8 mm	2–10 mm
Maximum fluence per spot size	8 mm: 2·0 J cm^{-2} 6 mm: 3·5 J cm^{-2} 4 mm: 8·0 J cm^{-2} 3 mm: 12·0 J cm^{-2}	10 mm: 0·2–0·5 J cm^{-2} 9 mm: 0·25–0·65 J cm^{-2} 8 mm: 0·35–0·8 J cm^{-2} 7 mm: 0·45–1·0 J cm^{-2} 6 mm: 0·6–1·4 J cm^{-2} 5 mm: 0·9–2·0 J cm^{-2} 4 mm: 1·4–3·2 J cm^{-2} 3 mm: 2·5–5·5 J cm^{-2} 2 mm: 2·5–12·5 J cm^{-2}
Maximum repetition rate	10 Hz	10 Hz

PSL, picosecond laser; NSL, nanosecond laser; Nd:YAG, neodymium-doped yttrium aluminium garnet.

the assessment. The allocation of a tattoo half to a particular laser device was done on a randomized basis. Randomization was conducted by employees not otherwise involved in the trial (using www.random.org/lists).

During use of the laser, appropriate eye protection was worn, and the treated areas were subsequently gently cooled with cold packs for 10 min. If crusting occurred, patients were instructed to apply panthenol cream (Bepanthen®; Bayer GmbH, Leverkusen, Germany) three times a day until the crusts healed. The patients were also instructed about the importance of consistent ultraviolet protection.

Analysis

Photos of the tattoos were taken with the same digital camera (D50 with a 60-mm f/3.4 lens; Nikon, Tokyo, Japan) and under identical lighting conditions: (i) before beginning tattoo removal with MedLite C6® (before the beginning of the study); (ii) before the first split-treatment session began (Medlite C6® and Picoway®); (iii) 6 weeks after the first split-treatment session; and (iv) 6 weeks after the second and final split-treatment session.

Two investigators (C.R., S.G.B.) not involved in the treatment concurrently analysed the photos on a single-blind basis and in separate rooms. Tattoo clearance was defined in quartiles and based on a reduction of the colour intensity before the beginning of the split treatment (after any pretreatment) and after the second split treatment. Clearance was graded as follows: 1, no/minimal clearance (< 25% of the tattoo); 2, moderate/mild clearance (25–50%); 3, good clearance (51–75%); or 4, very good clearance (> 75%).

Selecting the study end points

Whenever present, several tattoos on the same patient were included in the study, as it can be assumed that there is an independent therapeutic effect of treatment at different points on the body. Tattoo clearance was selected as the primary end point. The secondary end points were defined as adverse effects (as determined by the treating physician) and pain (as determined by the patient). These end points were not changed after the trial began.

Adverse effects

Adverse effects were categorized as follows: (i) transient adverse effects such as blistering, crusting, swelling and bleeding and (ii) permanent adverse effects such as hypo- and hyperpigmentation and/or scars. The patients used a visual analogue scale (from 0 = no pain to 10 = maximum pain) to indicate painfulness immediately after the session.

Statistical analysis

Statistical calculations were done with the statistics program SAS version 9.3 (SAS Institute Inc., Cary, NC, U.S.A.). Mean values, SDs and minimum and maximum values were calculated for quantitative characteristics. The quartiles that quantified clearance were presented by their median values, while absolute and relative frequencies were determined for qualitative parameters. A Wilcoxon test for two-paired samples was used to compare clearance and painfulness between the two differently treated halves of the tattoos. The adverse effects were evaluated using a McNemar's test. A difference was deemed to be statistically significant if the P-value was $< 0{\cdot}05$.

Furthermore, the kappa value was determined to calculate inter-rater reliability, a measure of the correlation and thus the objectivity of clearance assessment (maximum kappa value of 1 = perfect agreement among two raters, kappa value of 0 = no agreement).

To estimate sample size, we wanted to test the null hypothesis that there was ≤ 10% difference in clearance between the two lasers. With a patient population of 30, a 30% difference between the two lasers would refute this hypothesis with a power of 80%. All statistical calculations were done using statistics software SAS version 9.3.

Results

Twenty-one patients (10 men and 11 women) took part in this study; they had a mean age of $33{\cdot}2 \pm 9{\cdot}3$ years (range 20–47) and a total of 30 professionally applied black tattoos (examples in Figs 1–4). The average size of the tattoo was $37{\cdot}8 \pm 47{\cdot}6$ cm^2 (range 2·25–160·0). On average, the tattoos had been present for $7{\cdot}6 \pm 6{\cdot}6$ years (range 1–20). Fourteen of the 30 tattoos were located on the upper extremities, six on the torso and five each on the head and lower extremities. A mean $4{\cdot}7 \pm 4{\cdot}1$ sessions (range 0–16) were held before the beginning of the trial (exclusively with the NSL MedLite®C6 as single-pass treatments), with clearance of 3 quartiles (median).

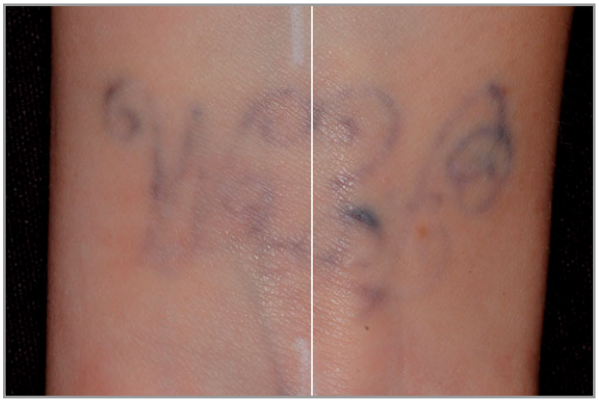

Fig 1. Digital image taken before split treatment. Tattoo 1, previously treated with the nanosecond laser 10 times. The left side of the tattoo was treated with the nanosecond laser and the right side with the picosecond laser.

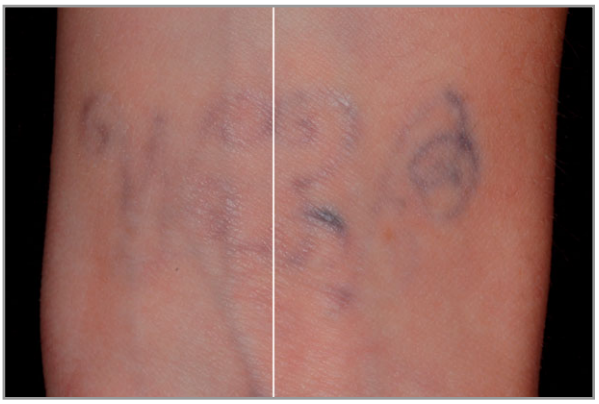

Fig 2. Digital image of tattoo 1, taken 6 weeks following the second and final treatment. The left side of the tattoo was treated with the nanosecond laser and the right side with the picosecond laser.

Fig 3. Digital image taken before split treatment. Tattoo 2, with no pretreatment. The left side of the tattoo was treated with the nanosecond laser and the right side with the picosecond laser.

Fig 4. Digital image of tattoo 2, taken 6 weeks following the second and final treatment. The left side of the tattoo was treated with the nanosecond laser and the right side with the picosecond laser.

Primary end point

After two sessions, both the PSL and NSL achieved a median clearance of 1 quartile (up to a maximum of 36% and 37%, respectively). Consequently, no difference could be determined between the PSL and NSL for all of the tattoos ($P = 1{\cdot}00$). Both pretreated (PSL and NSL median = 1, $P = 1{\cdot}00$) and untreated tattoos (PSL and NSL median = 1·5, $P = 0{\cdot}50$) showed no statistically significant difference in clearance between the lasers (Fig. 5).

With the NSL, the kappa value was 0·96, and it was 0·91 for the PSL, which corresponds to very high concurrence among both raters for both lasers.

Secondary end points

Statistically significant differences were found in painfulness. On a visual analogue scale (from 0 = no pain to 10 = maximum pain), participants reported $3{\cdot}8 \pm 1{\cdot}0$ points for the PSL and $7{\cdot}9 \pm 1{\cdot}0$ for the NSL ($P < 0{\cdot}001$), thus demonstrating a significantly lower degree of painfulness with the PSL.

There were no statistically significant differences with regard to the incidence of all of the adverse effects (bleeding, blisters, crusts, swelling, hypopigmentation, scars); there was only a slight advantage for the PSL in terms of bleeding ($P = 0{\cdot}083$).

On the side treated with PSL, there were a total of four cases of hypopigmentation, and one case each of hypo- or hyperpigmentation was reported on the side treated with the NSL. McNemar's test thus showed no statistically significant difference between the PSL and NSL as far as long-term adverse effects were concerned ($P = 0{\cdot}32$). Scarring did not occur in any case.

Discussion

Tattoos consist of water-insoluble pigment particles in the dermis. The disintegration of these particles via laser technology is based on photothermal or photoacoustic processes.[17] The exact underlying mechanism of these processes has still gone largely unexplored. Based on theoretical models of selective photothermolysis and countless clinical experiences, one can assume that a shorter pulse duration could destroy the particles more efficiently due to the greater intensity of the light.[10] This is why the pulse duration of lasers used to remove tattoos has gradually been lowered over the past several years from 50 to 5 ns and ultimately to 0·35 ns (= 350 ps).

This study is the first to make a clinical comparison of two currently available 1064-nm Nd:YAG lasers with pulse durations of 450 ps (PSL) and 5 ns (NSL). In terms of clearance, the trial shows equal results for both lasers. Both groups achieved a difference of 1 quartile (25%) in lightening (1 is the median of the difference). If there had been two or more additional sessions, the statistical analysis would have shown an improvement of 0·06 (PSL) vs. 0·06 (NSL). In other words, if more laser treatments had occurred, it is almost certain that no statistical differences between the two lasers would be observable, and only 6% of all patients would benefit from improvements. This is of course a purely mathematical model, and clinical experience tells us the lightening rates

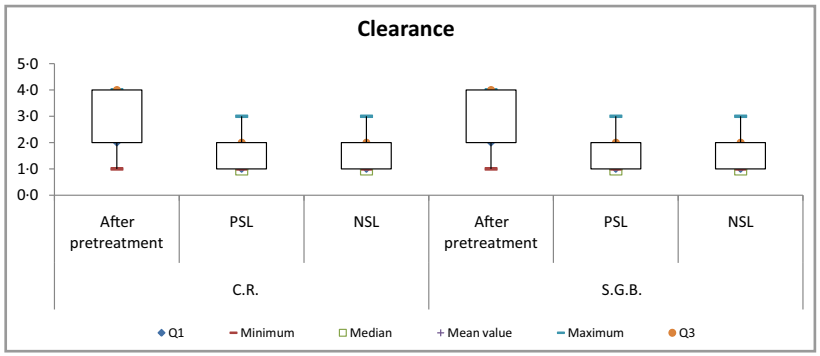

Fig 5. Clearance data for the two independent investigators (C.R. and S.G.B.). PSL, picosecond laser; NSL, nanosecond laser; Q1, 1st quartile; Q3, 3rd quartile.

Table 2 Treatment parameters after the first and second split treatments (Medlite, nanosecond laser; Picoway, picosecond laser)

Parameter	Picoway® 1st session	Picoway® 2nd session	Medlite® 1st session	Medlite® 2nd session
Fluence (J cm^{-2}), mean ± SD	2·53 ± 0·99	2·95 ± 0·88	7·68 ± 2·54	7·96 ± 2·39
Fluence range (J cm^{-2})	1·10–4·30	1·40–4·60	3·80–11·00	4·00–11·00
Spot size (mm), mean ± SD	4·57 ± 1·14	4·18 ± 0·90	4·04 ± 1·04	3·96 ± 1·07
Spot size range (mm)	3·0–7·0	3·0–6·0	3·0–6·0	3·0–6·0
No. of treated tattoos	30	30	30	30

are more likely to decrease over time. The significantly lower rate of pain during PSL treatment is probably due to the lower fluence (Table 2).

To date, three comparative studies on PSL and NSL have been published (Table 3).[11,12,18] Ross *et al.*[18] presented the comparison between a prototype PSL and an NSL (split treatment) in humans; here, two 1064-nm Nd:YAG lasers (35 ps and 10 ns) were compared on 16 tattoos with identical parameters in spot size and fluence (1·4 mm and 0·65 J cm^{-2}). The PSL achieved a statistically significantly greater improvement ($P < 0·02$) in lightening black tattoos in 12 of 16 patients. However, this difference could not be achieved in coloured tattoos ($P > 0·2$). It should be noted that the pulse duration of the PSL used by Ross *et al.* was shorter than the one we used by a factor of more than 10, which leads to the question of whether the pulse duration of 450 ps used with the PSL in our trial was clinically relevant to the purported enhanced effect described in the literature so far.

Herd *et al.*[12] showed slight superiority of the PSL (titanium–sapphire laser, 795 nm, 500 ps) compared with the QS alexandrite laser (752 nm, 50 ns) in a trial of 12 black tattoos in guinea pigs. However, the P-values were not cited, and the areas treated with the PSL had histological evidence of increased dermal fibrosis. Furthermore, this study prompts an important question about whether and to what extent differences in wavelengths might have affected the outcome, as the differently used (black) particle combinations have a particular absorption spectrum of wavelengths.[19]

Another experimental trial, by Izikson *et al.*,[11] compared one alexandrite laser each in a nanosecond (755 nm, 30–50 ns) and picosecond system (758 nm, 500 ps) in animals. The statistically significant superiority of the PSL was shown in tattooed domestic pigs. The factor separating the pulse durations was approximately 100 in the Izikson study, and in our study it was 11 (lower factor due to shorter NSL pulses). However, it must be taken into consideration that the tattoos on pig skin were only 6 weeks old at the time they were treated with the laser. Consequently, several pigment particles were still located in the upper dermal layers of the skin and were thus more easily accessible to laser light.[20,21] Tattoos on human skin have usually been present for several years prior to laser treatment,[3,6,7] which means the pigments are located deeper in the skin. The superiority of the PSL determined in animal experiments may have been artificially caused by this effect, which will greatly diminish the comparability of these studies with research in humans.

In some observational studies on the PSL (Table 4), cases were reported in which clearance sometimes occurred at a much higher rate after only a few sessions, especially in green- or blue-coloured tattoos. A case series by Brauer *et al.*[13] using an alexandrite PSL on blue and green tattoos showed clearance rates of 75–100% after one or two laser sessions, independently of the colour.

In a study by Alabdulrazzaq *et al.*,[15] yellow tattoos treated with a frequency-doubled Nd:YAG PSL achieved lightening of 100% in one patient after only one session, and lightening of at least 75% in five patients after two to four sessions. However, both hypopigmentation and scarring structures were visible in the 'after' pictures.

Bernstein *et al.*[16] showed a clearance of approximately 79% after 6·5 treatments of multicoloured tattoos (92% clearance in black tattoos) using a 532-nm/1064-nm Nd:YAG PSL (PicoWay®). This study disproved the hope of colour-independent tattoo removal via PSL. In one study with an NSL and

Table 3 Summary of comparative studies: picosecond laser (PSL) vs. nanosecond laser (NSL)

Study	Laser and specifications	Factor[a]	Results
Animals			
Izikson 2010[11]	PSL: alexandrite 758 nm, 500 ps NSL: alexandrite 755 nm, 30–50 ns	60–100	PSL significantly more efficacious in black ink, $P < 0{\cdot}001$
Herd 1999[12]	PSL: titanium–sapphire 795 nm, 500 ps NSL: alexandrite 752 nm, 50 ns	100	Slight superiority of PSL in black ink, without specification of P-value
Humans			
Ross 1998[18]	PSL: Nd:YAG 1064 nm, 35 ps NSL: Nd:YAG 1064 nm, 10 ns	285	PSL significantly more efficacious in black ink, $P < 0{\cdot}02$
This study 2016	PSL: Nd:YAG 1064 nm, 450 ps NSL: Nd:YAG 1064 nm, 5 ns	11	No difference in black ink between PSL and NSL, $P = 1{\cdot}00$

Nd:YAG, neodymium-doped yttrium aluminium garnet. [a]The factor is the ratio of pulse duration for NSL: PSL.

Table 4 Summary of noncomparative clinical trials in humans

Study[a]	Laser and wavelength	PD	Study design	No. of tattoos	No. of treatments	Colour	LA	Results
Brauer 2012[13]	Alexandrite 755 nm	750–900 ps	Single-pass sessions	12	1–2	Blue/green	Yes	≥ 75% clearance after 1–2 treatments
Saedi 2012[14]	Alexandrite 755 nm	500–900 ps	Single-pass sessions	12	2–10	Black/blue	No	≥ 75% clearance after an average of 4·25 treatments
Alabdulrazzaq 2015[15]	Nd:YAG 532 nm	450–500 ps	Single-pass sessions	6	1–5	Yellow	Yes	≥ 75% clearance after an average of 1–5 treatments
Bernstein 2015[16]	Nd:YAG 1064 nm and 532 nm	450 ps; 350 ps	Single-pass sessions	31	≤ 7	Multicolour	Yes	79% clearance with an average of 6·5 treatments

PD, pulse duration; LA, local anaesthesia; Nd:YAG, neodymium-doped yttrium aluminium garnet. [a]All four studies declared industrial sponsorship or support.

larger patient cohort, 75 black/grey tattoos had clearance rates of 80% after seven sessions with an Nd:YAG NSL, which is comparable with the results of previous studies.[22]

The objective of removing tattoos is to achieve lightening as quickly as possible without incurring hypo- or hyperpigmentation, changes in texture or scarring. A closer objective look at several photos published in PSL manuscripts reveals scarring and hypo- or hyperpigmentation.[13–16,18,23] A total of 18 before-and-after cases were presented in these six articles. In 10 of these 18 cases, scarring, changes in texture and/or hypo- or hyperpigmentation were visible. It is likely that in these PSL studies, the comparatively rapid clearance rates were achieved by using higher intensities, which is reflected in the higher rate of permanent adverse effects.

In our trial, treatment was performed using the MedLite C6®. Since the study was completed, a technically improved NSL model (Revlite®; Cynosure, Westford, MA, U.S.A.) has been released, which permits higher maximal fluences ($2{\cdot}5$ J cm^{-2} instead of $2{\cdot}0$ J cm^{-2}, maximum spot size 8 mm each) and could therefore potentially facilitate more rapid clearance times than the MedLite C6® device used here. Karsai *et al.* successfully demonstrated this context *in vivo* by comparing the previous model, the MedLite C3®, with the MedLite C6® at optimized parameters.[24] These clinical findings are corroborated in theoretical studies conducted by Humphries *et al.*,[25] which confirm positive effects of the fluence and spot diameter on clearance rates.

In trials published on PSLs to date,[13,15,16,18] theoretical hypotheses have been offered for their ostensibly superior clearance rate compared with NSLs, but this too has been the subject of critical discussion.[26] Up to 57% of the publications on randomized clinical trials in the field of dermatology[27] mention sponsorship, although this is no different from other branches of medicine.[28–30] As sponsoring can create a bias – even unintentionally – in study results, findings in laser tattoo removal should be evaluated in independent studies whenever possible.[31]

There is great need for further discussion here, which is why the assessment of our results below also includes theoretical aspects of tattoo removal.

Selective photothermolysis is the process of a target selectively absorbing the wavelengths of laser pulses. The damage of the target can be modulated by appropriate pulse duration. The pulse duration correlates to the thermal relaxation time,

which can be estimated when the size of the target is known. Tattoo pigment particles have small sizes, which require pulse durations of only a few nanoseconds to be destroyed. However, this estimation of pulse duration is based on a simplified model assuming linear optics and simple thermodynamics. In addition, the density of the heated particle is considered to be homogeneous, without changing its optical and thermal properties. With regard to the short laser pulse (10^{-9} to 10^{-12} s), the intensity of such laser pulses is high enough to permit nonlinear optical processes such as two-photon absorption. The key feature of two-photon absorption is the fact that in the presence of intense laser pulses, molecules can simultaneously absorb two or more photons, and the transition probability for absorption of two identical photons is proportional to I^2, where I is the intensity of the laser pulse. Numerous dye molecules show light absorption at half of the wavelength that is applied for excitation.[32,33]

Ho *et al.*[10] investigated via computer simulation the magnitude of the tensile stress generated inside graphite tattoo particles as functions of laser pulse length and particle size. The authors concluded that the break-up of tattoo particles is photoacoustic and the optimal pulse length is approximately 10–100 ps. However, these calculations are based on homogeneous graphite particles, which may not reflect the morphology of real black tattoo particles, and the respective values for density, specific heat and thermal conductivity being kept constant. By contrast, it was recently shown that the values for density and thermal conductivity of carbon black decrease and the value of specific heat increases with greater temperatures.[34]

The authors concluded that an increased spot diameter and beam fluence improve the lightening response of tattoos. Conversely, variations in the pulse width are known to have little influence on the fragmentation response.[25] Computer simulations are important on the one hand, but they might not reflect the reality of a laser pulse hitting tattoo particles of unknown origin and morphology. In view of all these unknown facts, shortening pulse duration might be an oversimplified recommendation.

In summary, we have determined that there is no statistically significant and no clinically relevant difference between the PSL and NSL in terms of the therapeutic outcome and our primary end point. With regard to the secondary end points, painfulness is significantly lower with the PSL, and after two sessions of properly administered treatment there was no difference between the two lasers in the profile of other adverse effects.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Fig S1. CONSORT flow diagram.