The efficacy and the adverse reactions of laser-assisted tattoo removal – a prospective split study using nanosecond and picosecond lasers

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Abstract

Background Laser pulses with nanosecond duration (NSL) have been the golden standard to destroy the pigment particles in skin. It is still controversially discussed whether picosecond pulses (PSL) are superior for tattoo removal.

Objectives To compare the efficacy and the adverse reactions of nanosecond and picosecond laser pulses in a comparative study.

Methods The prospective study included 23 subjects with 30 black or coloured tattoos, which were split into two halves treated with either a new PSL (532, 1064 nm) or standard NSL (694 nm). The lasers were applied at regular time intervals of 4 weeks for up to eight treatments. Tattoo clearance (primary endpoint), pain and adverse reactions (secondary endpoints) were appraised by physicians, blinded observers, and by subjects. The extent and duration of adverse reactions were additionally assessed by using a questionnaire and photo-documentation after each treatment session.

Results The tattoo clearance appeared to be more effective for PSL compared to NSL but without statistical significance (P > 0.05). Pretreated tattoos responded better to laser treatments than previously untreated tattoos. Subjects felt significantly less pain with PSL than with NSL (P < 0.001). Transient adverse reactions were statistically less pronounced lasting shorter for PSL as for NSL, especially blistering, pruritus, and burning sensation. Hypopigmentation appeared after NSL treatments only, whereas hyperpigmentation was caused by both lasers. No scarring was detected with either laser.

Conclusions Both laser systems enable acceptable clearance of most tattoos in the present study. PSL cause less collateral skin damage as compared to NSL.

Conflict of interest
The authors declare no conflict of interest.

Funding sources
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Introduction
Tattooing is an ancient procedure to stain the skin of humans and its history goes back thousands of years.1 Nowadays, the western world considers tattoos as decorative body art and everybody, usually tattooists in tattoo parlours, perform tattooing. In the past decades, tattooing has become increasingly popular and surveys revealed that in the USA 29% of population has one tattoo at least (2016),2 in France 17% (2019),3 Germany 20% (2019),4 Brazil 22% (2019),5 and China 12% (2019).5

About 5% of tattooed individuals at least desire tattoo removal6 that requires an effective and safe procedure. Surgical excision may remove a tattoo completely, but it leaves scars, therefore limited to small tattoos.7 The first laser treatments of tattoos were published by Goldman and co-authors in the Journal of Investigative Dermatology in 1965.8

The principle of selective photothermolysis should work for the destruction of tattoo pigment particles in the dermis that leads to fading of a tattoo colour.9–11 Due to the small size of pigment particles, the principle would require short pulse duration of nanoseconds at least. In addition to short pulse duration, the fragmentation of pigment particles requires a very high laser intensity of laser pulses.
Since the work of Goldman 1965, various clinical studies provided evidence that nanosecond pulses of Q-switched lasers may be effectively and safely applied for tattoo removal but tattoo clearance is frequently incomplete despite a high number of consecutive treatments. Therefore, the use of shorter pulse durations in the picosecond range at higher intensities was aimed to overcome such incomplete tattoo clearance. The application of picosecond laser pulses was also mentioned to provide better results not only in black tattoos but also in coloured tattoos.

At present, only a few studies exist that compare the nanosecond pulses and picosecond pulses in a prospective clinical study of tattoo removal, unfortunately with some contradictory findings. One clinical study showed that picosecond pulses are not superior to nanosecond pulses after two consecutive laser treatments. Another study with one to four laser treatments yielded statistically significant superiority of the picosecond lasers compared to the nanosecond laser for tattoo clearance, but not for polychromic tattoos. A study protocol with four consecutive treatments revealed also a superiority of picoseconds as compared to nanoseconds, but now also for polychromic tattoos.

The present clinical study compared a standard nanosecond Q-switched laser (ruby laser), used for tattoo removal for decades, and a picosecond laser (Nd:YAG laser) using a split-tattoo protocol. One half of each tattoo was treated with nanosecond laser, the other half with picosecond laser. This study investigated tattoo clearance for both lasers with up to 8 consecutive sessions, which may represent a typical number in tattoo removal regardless of the laser device used.

The goals of the present study were the comparison of efficacy in removing tattoos for nanosecond and picosecond lasers as well as an in-depth analysis of adverse reactions in the course of the study. The evaluations were based on the study physicians, three blinded observers (dermatologists), and the treated subjects who received a questionnaire after each single treatment session.

Material and methods

Study population and baseline characteristics

The study included 23 subjects with overall 30 tattoos consisting of three amateur tattoos and 27 professional tattoos. The majority of subjects were female (N = 20) and the mean age of all subjects was of 33.2 ± 9.3 years (range 22–59). The skin type of the subjects was II (32%), III (60%), or IV (8%) according to Fitzpatrick classification.

When the subjects showed up for the first treatment, the age of tattoos ranged from 3 to 39 years with a mean value of 13.4 ± 7.1 years, of which 6 tattoos were pretreated and 24 were not pretreated. The colour of the tattoos was black (N = 24) or multi-coloured (N = 6) with colours red, green, blue, and pink. The tattoos were located on the arms, legs, head/neck, or trunk with sizes that ranged from small (<25 cm²) to large (>100 cm²).

Laser devices and treatment

A picosecond Nd:YAG laser (PicoClear, Almalaser, Germany) with two wavelengths at 532 or 1064 nm (PSL-532, PSL-1064) delivering pulse durations of 300 or 350 ps, respectively. A nanosecond Ruby laser (Sinon, Almalaser, Germany) with a wavelength of 694 nm and a pulse duration of 20 ns (NSL). Before treating the complete tattooed skin area, a small test treatment was performed to find the appropriate radiant exposure (J/cm²) by appraising immediate skin reaction (whitening).

Study design and evaluation

This was a prospective, self-controlled clinical study that compared the efficacy of tattoo removal using two different laser devices. Prior to treatment, each tattoo was randomly split into two equally sized parts, one part was treated with PSL and the other with NSL. On the PSL side of each tattoo, the black part of tattoos was treated with PSL-1064 and any coloured part with PSL-532 only. On the NSL side of each tattoo, this part was treated with NSL regardless of the colour. The primary endpoints of the study were defined as assessment of the clearance of black tattoos with NSL compared to PSL-1064 and the clearance of coloured tattoos with NSL compared to PSL-532.

Secondary endpoints were pain, and the rate and extent of adverse reactions in relation to the respective laser device. The treatments for all subjects were performed at a time interval of 4 weeks. Since the NSL is frequently assumed to require more treatment sessions than for PSL, the tattoo treatments involved up to maximal eight sessions to receive a preferably complete picture of tattoo clearance for both lasers. The treatment was stopped in case no further improvement was observable. The number of treatments was the same for NSL and PSL for each tattoo.

Exclusion criteria were increased sensitivity to light, scars or florid inflammation of the tattooed skin or area immediately surrounding it, pregnant and lactating females. 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 after receiving approval from the ethics committee of the University Medical Centre Regensburg, Germany (approval number: 19-1468-101).

Three dermatologists, not involved in laser treatments, acted as independent blinded observers. They compared baseline image (taken prior to treatment) with post-treatment tattoo image (2–3 months after last treatment) grading the clearance of a tattoo in percent using the following scale: 5 = poor clearance (<25%), 4 = fair clearance (25%–49%), 3 = good clearance (50%–74%), 2 = excellent clearance (75%–94%), and 1 = almost complete clearance (>94%). All tattoos were photographed.
before and after each treatment session using a digital camera (Canon EOS D80, Tokyo, Japan).

Subjects were asked to assess the pain of each laser treatment using scores of a visual analogue scale (VAS) ranging from 0 to 10 immediately post treatment. All subjects received a questionnaire after each treatment session, in which they were asked to appraise the success of each treatment session in regard to each laser modality. They used grades to value the treatment response of their tattoos at follow-up visits ranging from 1 (excellent), 2 (good), 3 (moderate), 4 (fair), 5 (poor), and 6 (no effect). They also documented the occurrence and duration of adverse reactions with the help of a checklist. Subjects also took photographic images at home to document skin reactions related to laser treatments.

Skin cooling and anaesthetics
In two consecutive treatments during the study, subjects received two different procedures prior or during laser treatment. First procedure was the application of an anaesthetic cream 60 min prior to laser treatment (EMLA, Aspen Germany GmbH, Munich, Germany). Second procedure was skin cooling using a cold air device during the entire laser treatment (Zimmer Cryo6, Neu-Ulm, Germany). The first full treatment was performed with none of these procedures to enable a comparison of pain perception.

Statistical analysis
Mean values and standard deviation (SD) were calculated and presented for quantitative characteristics. In particular, the values of tattoo clearance, duration of adverse reactions, and pain scores, presented as mean ± SD, were compared for the two laser devices (NSL, PSL) using the non-parametric Mann–Whitney U-test or Kruskal–Wallis test. P-values were two-sided and considered statistically significant when <0.05. Assuming a power of 80% and a significance level of 5%, 30 tattoo samples should be sufficient to show a significant difference of tattoo clearance for NSL and PSL. This allows the test of the null hypothesis that PSL is superior to NSL. All analyses were performed using SPSS statistics software version 26.0.0 (IBM SPSS Software, Armonk, NY, USA).

Results
Primary endpoint – clearance of tattoos
The mean radiant exposure was 3.4 ± 1.3 J/cm² (NSL), 2.1 ± 0.8 J/cm² (PSL-1064), or 0.8 ± 0.4 J/cm² (PSL-532). The mean number of laser treatments in the study was 5.5 ± 1.9. In case of blinded observers, the use of PSL-1064 for black tattoos appears to be more effective as compared to NSL (Fig. 1). However, the differences of mean values showed no statistical significance with all P-values >0.05 (Table 1) consisting of all groups. Only the direct comparison of tattoos with and without pretreatment yielded a statistically significant difference for each laser (P < 0.05). Also, the clearance of coloured tattoos showed no difference for NSL and PSL treatments (P > 0.05, Table 1).

Secondary endpoint – pain assessment
When including all procedures (none, cold air, anaesthetic cream), the NSL treatment revealed a mean pain score of 5.8 ± 1.9 (NSL), 4.9 ± 1.7 (PSL-1064), and 4.0 ± 1.8 (PSL-532). The mean scores of NSL and PSL-1064 were statistically different (P < 0.001). The pain scores of no procedure were additionally compared to scores when using cold air or anaesthetic cream (Table 2). The differences were statistically not
Table 1 Tattoo clearance assessed by blinded observers and patients

| Laser                          | Blinded observers | Patients' satisfaction |
|-------------------------------|-------------------|-----------------------|
| **All black tattoos**         |                   |                       |
| NSL                           | 2.5 ± 1.3         | 2.9 ± 1.8             |
| PSL-1064                      | 2.3 ± 1.4         | 3.1 ± 1.9             |
| **Black tattoos non-pretreated** |                   |                       |
| NSL                           | 2.9 ± 1.3         | 3.0 ± 1.0             |
| PSL-1064                      | 2.6 ± 1.4         | 3.3 ± 1.1             |
| **Black tattoos pretreated**  |                   |                       |
| NSL                           | 1.5 ± 0.5         | 2.5 ± 0.8             |
| PSL-1064                      | 1.4 ± 0.7         | 2.6 ± 0.4             |
| **Coloured tattoos non-pretreated** |             |                       |
| NSL                           | 4.1 ± 1.5         | 3.2 ± 1.1             |
| PSL-532                       | 4.0 ± 1.8         | 4.0 ± 1.6             |

Secondary endpoint – adverse skin reactions

Due to the time span of 4 weeks between two consecutive treatments, the study physicians could document long-lasting adverse reactions only. Mild textural alterations of skin were seen in 4/30 (NSL), 8/30 (PSL-1064), or 2/30 (PSL-532) of tattoos but no scars. Hyperpigmentation showed 2/30 (NSL) or 4/30 (PSL-1064) of tattoos, but none for PSL-532. Hypopigmentation was found for NSL-treated tattoos only (3/30). Examples are shown in Fig. 5, where NSL treatment caused typical hypopigmentation, whereas PSL treatment left hyperpigmentation behind.

Additional information was gained by asking subjects in the follow-up visits and by evaluating all the questionnaires, which were filled by the subjects after every treatment session. The simple evaluation of the frequency of adverse reactions per tattoo revealed that the most common skin reactions after laser treatment of tattoos were erythema and swelling followed by blistering, burning, crusting, bleeding, and pruritus. Adverse reactions appeared for some tattoos in one treatment session only, for some tattoos more frequently or even in every treatment session. Consequently, a more in-depth evaluation was performed by summing up the frequencies of adverse reactions for all treatment sessions, which involved the treatment of black tattoos using NSL and PSL-1064. The results showed statistically significant differences between NSL and PSL-1064 for blistering (P < 0.001) and bleeding (P = 0.004), but not for erythema (P = 0.880), swelling (P = 0.871), pruritus (P = 0.499), crusting (P = 0.297), and burning (P = 0.224). Figures 7 and 8 exemplarily show the extent of blistering 2–5 days after a treatment session, which was limited to the NSL-treated skin area.

The mean duration of self-reported adverse reactions such as erythema, swelling, blistering, burning, crusting, and pruritus ranged for both laser devices from about 7 to 15 days (Table 3). The values showed no statistical difference for the laser devices, except for pruritus (P = 0.029), which was shorter for PSL-1064 as compared to NSL.

Discussion

The present study showed that a mean number of about five treatments produced an acceptable clearance of most of the involved tattoos, in particular black tattoos. The laser treatment of black tattoos (non-pretreated and pretreated) showed an excellent clearance (>74%) in 64% (PSL) or 55% (NSL) of tattoos. The PSL-1064 laser seems to be superior to NSL, especially for the group of tattoos with clearance of >94% (Fig. 1). However, the overall differences of the mean results showed no statistical significance when comparing PSL and NSL (P > 0.05, see Table 1), which refutes the null hypothesis of the primary endpoints. Noteworthy, the light absorption of black pigments varies less than 20% in the spectral range from 400 to 1100 nm, which covers all laser wavelengths used for tattoo removal. Thus, the wavelength of lasers used in the studies for black tattoos should play a minor role if at all. The tattoo clearance after PSL treatments in the present study is comparable to results of other, non-comparative studies using only PSL for tattoo removal.
Blinded observers rated the clearance of coloured tattoos as less effective compared to black tattoos, regardless of the respective colour and the laser applied (Table 1). Coloured pigments show various absorption spectra. A few published clinical studies on the clearance of coloured tattoos using different PSL devices exist and the reported results appear somewhat ambiguous. The results of our study match the findings of other comparative studies, which also show comparable clearance of coloured tattoos when treated with PSL or NSL, sometimes with sporadic exceptions for a few colours (Table 4).

Pretreated black tattoos responded better to both laser devices with \( P = 0.007 \) (NSL) and \( P = 0.025 \) (PSL-1064; Table 1) that is

Table 2 Pain scores without and with procedures like cold air or anaesthetic cream

| Laser                | NSL  | PSL-1064 | PSL-532 |
|----------------------|------|----------|---------|
| Mean values, overall| 5.8 ± 1.9 | 4.9 ± 1.7 | 4.0 ± 1.8 |
| No procedure         | 6.0 ± 1.7 | 5.0 ± 1.6 | 4.6 ± 1.6 |
| With cold air        | 5.8 ± 2.0 | 5.1 ± 1.9 | 3.9 ± 1.8 |
| With anaesthetic cream | 5.4 ± 1.9 | 4.2 ± 1.8 | 3.4 ± 1.2 |

Adverse reactions were documented in the questionnaire that was filled by the subjects after each treatment session. The results are shown as the frequency of treated tattoos for all lasers (top diagram). The sum over all events during the study is shown for nanosecond duration (NSL) and picosecond pulses (PSL-1064) (bottom diagram).
important when comparing the results of the different studies (Table 4). When removing the results of pretreated tattoos from total evaluation (all black tattoos), the percentages of black tattoos with almost complete clearance (>94%) dropped only slightly from 39% to 37% for PSL, but from 29% to 23% for NSL (Fig. 1) indicating an advantage for PSL in treating black tattoos without pretreatment. The percentage of pretreated tattoos in the present study can be considered small (26%) as compared to the other comparative studies with 70%, 71%, or even 100% pretreated tattoos.20,23,24 One study also observed a different clearance for untreated and pretreated tattoos (Table 4).20 The percentage of pretreated tattoos is unfortunately missing in another comparative study.22 In light of the impact of pretreatments on the evaluation of tattoo clearance, pretreatments should be considered an important detail of each study, also when comparing results of different non-comparative clinical studies among each other.17,26,28,29

The diverse and sometimes unexpected reactions of tattoo pigments to laser treatments in the different clinical studies remain difficult to explain,15,18,20,22,23 because tattoo removal with NSL or PSL pulses is based on partially unexplored mechanisms.10 The use of high intensities of NSL and PSL pulses allows non-linear processes such as two-photon absorption, shock wave generation, and optical breakdown including plasma formation.10,30,31 All these effects may occur at the same time and their respective extent critically depends on the duration and intensity of laser pulse applied. However, these laser parameters were rather different in clinical studies so far (Table 4).10 The present study used NSL and PSL devices, whose pulse duration showed a ratio of about 57 to 67. When comparing to the other studies, this value is in the middle of the smallest value of 7 and the highest value of 286 (Table 4). Despite the small number of comparative studies, the available data might indicate that the advantage of PSL over NSL increases with increasing ratio of pulse durations (Table 4). Thus, any superiority of PSL over NSL could be a matter of pulse duration or pulse duration ratio.

In addition, tattoo removal is not only governed by appropriate laser parameters.10,24,32,33 Fading of tattoo colour requires

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**Figure 7** Black tattoo (non-pretreated) before (left) and after five treatment sessions (right). Nanosecond duration (NSL) below dashed line and picosecond pulses (PSL-1064) above dashed line. An additional photographic image was taken 2 days after second treatment session (middle).

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**Figure 8** Multi-coloured tattoo (non-pretreated) before (a) and after five treatment sessions (d). Nanosecond duration (NSL) above dashed line and picosecond pulses (PSL) below dashed line. In the area treated with PSL, the black or coloured parts were treated with 1064 or 532 nm, respectively. Additional photographic images were taken 2 days (b) and 5 days (c) after second treatment session.

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**Table 3** Duration of adverse reactions (mean days ± standard deviation)

| Laser | NSL     | PSL-1064 | PSL-532 | P-value |
|-------|---------|----------|---------|---------|
| Erythema | 9.7 ± 6.8 | 9.2 ± 6.7 | 11.8 ± 6.2 | 0.229   |
| Swelling | 10.4 ± 6.9 | 10.0 ± 7.0 | 8.0 ± 3.4 | 0.648   |
| Blistering | 10.0 ± 7.2 | 11.5 ± 8.0 | 12.9 ± 6.8 | 0.232   |
| Burning | 9.8 ± 6.5 | 8.8 ± 7.0 | 10.9 ± 6.3 | 0.209   |
| Crusting | 11.6 ± 7.6 | 12.3 ± 7.6 | 15.1 ± 6.6 | 0.084   |
| Pruritus | 9.9 ± 5.1 | 7.3 ± 6.6 | 7.5 ± 0.8 | 0.029   |
transportation of fragmented pigment particles away from skin, e.g., via lymphatic system. Pigment capture–release–recapture may ensure macroscopic stability of tattoos and its partial and unpredictable resistance to laser treatments, which might be diverse for tattooed individuals. As for other clinical studies, the laser treatment of tattoos left a number of tattoos behind, whose clearance remains incomplete regardless of the laser type and number of treatments (Figs 2, 3, and 8).

The partially different extent of adverse reactions after treatment with NSL or PSL might be explained when considering studies in ophthalmological microsurgery, which also investigated the use of NSL and PSL devices. The authors found that about 42% (PSL) or 72% (NSL) of laser pulse energy is converted to mechanical energy (shock waves, bubble formation). The authors concluded that the side effects of laser tissue interaction can be considerably reduced by the use of PSL pulses. Histological investigation of tattooed skin samples likewise showed shock waves leaving small vacuoles behind in the dermis, which is clinically perceived as intermediate whitening of the skin.

Firstly, these findings may explain to some extent the smaller pain scores for PSL compared to NSL. It might be assumed that PSL pulses provoke less collateral damage in skin and thereby less pain (Table 2). Secondly, blistering and bleeding should be considered typical signs of laser-induced shock waves in skin, which were significantly less pronounced for PSL ($P = 0.004$ and $P < 0.001$) as compared to NSL (Fig. 6). The other adverse skin reactions were not significantly different for PSL and NSL, in particular the most frequent reactions erythema and swelling (Table 3). Treatment of the tattooed skin with either laser has the potential to cause pigmentary alteration because the laser pulses may also interact with the endogenous pigment particles. Surprisingly, none of the tattooed skin showed hypopigmentation after treatment with both PSL wavelengths. Contrary to PSL, NSL treatment caused hypopigmentation after treatment, which is rather common for laser light at 694 nm. However, light absorption of melanin at 532 nm (PSL-532) is higher than for 694 nm (NSL), but the treatment of tattoos with PSL-532 caused also no hypopigmentation. Maybe the low radiant exposure of PSL-532 prevented hypopigmentation but also hyperpigmentation. Other studies report different and inconsistent rates of hypopigmentation for a PSL-532.

Contrarily, PSL treatment left a type of darkish hyperpigmentation behind that might be due to excessive melanin and/or ultrafine fragmented black tattoo particles, which are spread in the treated area (Figs 2 and 5). None of the laser treatments in the study entailed scars in the tattooed skin area. After the final treatment, some tattoos showed mild textural alterations. It is often premature to charge the laser treatment with these alterations. The tattooing process itself causes massive skin injuries and the tattoo needles might have caused textural changes, which are hidden by the tattoo colour. Then, the laser treatment removes the colour but simultaneously uncover such textural alterations if caused by the tattooist. The comparison of PSL and NSL regarding the secondary endpoints reveals that the PSL caused less pain and adverse reactions and can be considered smoother and safer for tattoo removal as compared to NSL.

**Table 4** Overview of parameters and results of comparative studies

| Study Year | Pulse duration | Ratio Pulse duration | Number of treatments | Pretreated tattoos | Results black tattoos | Results coloured tattoos |
|------------|----------------|----------------------|----------------------|--------------------|-----------------------|-------------------------|
| present Study | 20 ns | 300 ps | 350 ps | 57 | 5.5 ± 1.9 (up to 8) | 22% | PSL ≈ NSL | PSL ≈ NSL |
| Pinto24 2017 | 5 ns | 450 ps | 450 ps | 11 | 7 – 13 | 2 | 70% | PSL ≈ NSL |
| Lorgeou20 2018 | 5 ns | 375 ps | 450 ps | 11 | 2.0 ± 0.8 (up to 4) | 71.4% | PSL > NSL | PSL > NSL |
| Kono22 2020 | 50 ns | 375 ps | 450 ps | 11 | 4 | not specified | PSL > NSL | PSL > NSL |
| Ross23 1998 | 10 ns | - | 35 ps | 286 | 4 | 100% | PSL > NSL | PSL ≈ NSL |

*Use of two different PSL. Black tattoos only. Except for blue colours. Statistically not significant for 1064 nm lasers.

**Conclusions**

Picosecond pulses application for tattoo removal should be slightly more effective as compared to NSL application in black tattoos but not in coloured tattoos. When comprising all clinical studies on tattoo removal including the present study, the efficacy for black tattoos and in particular coloured tattoos appears somewhat contradictory that demands further explanation. The PSL is significantly less painful as compared to NSL and the pain scores could be significantly reduced by using an anaesthetic cream. PSL shows a smaller rate of other transient adverse reactions like blistering, bleeding, and pruritus. Due to the individual nature of each tattoo, a split-tattoo study should be mandatory to study the effect of laser parameters like pulse duration on tattoo removal. As all clinical studies show limitations, it would be worthwhile to include a PSL in a comparative
