PICO+4: THE SINGLE-SYSTEM ANSWER TO MULTIPLE APPLICATIONS IN THE REMOVAL OF PIGMENTED LESIONS AND TATTOOS

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Abstract

The nanosecond domain Q-switched Nd:YAG laser, operating under the theory of selective photothermolysis at the wavelengths of 532 nm and 1064 nm, has become the treatment of choice for removal of tattoos and pigmented lesions, offering highly selective pigment removal with minimal thermal damage to the adjacent tissues. However the ns-based approach has some limitations due to the mostly thermal nature of the reaction, and in tattoo removal, the increasing variety of colors used often results in incomplete removal of the tattoo. Moving into the picosecond domain removes the photothermal nature of the reaction, replacing it with a nonlinear photoacoustic effect. With its 750 picosecond beam, Lutronic's PICO+4 also uniquely offers 2 more picosecond wavelengths in addition to the 1064 and 532 nm wavelengths. This paper sets out to explore the rationale behind this novel system and its efficacy in the removal of a large variety of pigmented lesions and tattoos, in addition to skin rejuvenation and a variety of other indications.

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Introduction

Very soon after Maiman developed the first laser in 1960, based on a synthetic ruby crystal as its medium, followed swiftly in the subsequent 4 years by the argon, Nd:YAG and CO2 lasers [1], this new and unique light source found a role in clinical applications starting with ophthalmology in the mid 1060s, followed quickly by dermatology. The ruby laser operated in the pulsed mode, delivering its 694.3 nm beam in the millisecond domain. With a 1 ms pulse, the ruby laser in Ohshiro's hands gave excellent and selective treatment results for large hemangiomas and pigmented nevi [2]. The other three systems started out delivering continuous wave (CW) mode, with the beam optically or electronically shuttered to give selected exposure times, usually from 100 ms upwards. With its blue (488 nm) and green (514.5 nm) wavelengths, the argon laser offered pigment-selective treatment for blood- and melanin-anomaly group lesions, but even with 100 ms pulsewidths, there was collateral thermal damage due to conducted heat travelling from the targeted pigment into the surrounding tissues [2]. The CO2 laser wavelength of 10600 nm was very highly absorbed in water, making it an ideal surgical laser capable of coagulating, vaporizing and incising tissue with good precision, but still leaving a zone of secondary thermal damage adjacent to the incised or vaporized tissue, the extent of this zone of residual thermal damage being dependent mostly on the exposure time. The Nd:YAG laser was much less well absorbed in water, so its first applications in CW were bulk coagulation of tissue with poor precision. The pulsed dye laser appeared in 1969, with wavelengths in the yellow waveband and a pulsewidth of around 500 µs, and became recognized as the optimum system to treat vascular lesions with minimal thermal spread.

In 1983, Anderson and Parrish put forward their theory of selective photothermolysis [3], whereby laser energy, at an appropriate wavelength for the target chromophore and with a pulse width equal to or less than the thermal relaxation time of the chromophore, was capable of selectively destroying the target with minimal damage to surrounding tissues. The technique of Q-switching a laser beam to produce an ultrashort ns-domain pulse of high peak power was proposed by Gould as early as 1958 [4], but did not find clinical applications till the late 1980s and early 1990s [5,6] thereby demonstrating the ideal system to fulfil the theory of selective photothermolysis, particularly for tattoo removal.

In 2012, reports began to appear on the application of a novel picosecond alexandrite laser in the treatment of tattoos, including those with blue and green ink [7,8]. This approach was hailed by the Anderson group as "A good, old idea" [9], *i.e.*, taking Anderson's original concept of selective photothermolysis one stage further. The problem with the alexandrite laser was the comparative high absorption in melanin with the 755 nm wavelength, meaning that in darker skin phenotypes, such as Asian type III and darker, there was potential for post-inflammatory hyperpigmentation (PIH) formation. Picosecond-domain Nd:YAG lasers then made an appearance in 2014 [10], with the 1064 nm wavelength being much more appropriate for darker skin types. A more recent report suggested the ability of the 1064 nm and 532 nm wavelengths of the ps-domain Q-switched Nd:YAG to treat multicolored tattoos with minimal hyper- and hypopigmentation [11].

In 2014 Lutronic advanced the concept of the workhorse SPECTRA Q-switched Nd:YAG system even further through the development of the ns Q-switched SPECTRA XT, which offered two new wavelengths with the world's first New Generation Gold Toning (595 nm) and the RuVY Touch (660 nm) handpieces, a superior quick pulse-to-pulse (Q-PTP) mode for more sensitive or delicate skin and the high-fluence Revital skin rejuvenation technique. Based on that proven technology Lutronic is now proud to present the **PICO+4**, the first ps-domain Nd:YAG system with 4 wavelengths including the standard 1064 nm and 532 nm wavelengths, offering the potential to treat multicolored tattoos even more effectively.

The PICO+4 System

Lutronic's new PICO+4 system delivers a true 750 ps pulse at the wavelengths of 1064 nm and 532 nm, plus 2 wavelengths from solid dye handpieces, namely 595 nm and 660 nm. Figure 1 shows the physical characteristics of the system, and Table 1 provides the technical specifications.

Fig 1: PICO+4 system components

Table 1: PICO$^+$4 System specifications

Item	Specification
Medium	Nd:YAG
Wavelengths	1064 nm, 532 nm, 595 nm, 660 nm
Pulse width	750 ps; 2 ns
Max pulse energy	600 mJ @ 750 ps; 800 mJ @ 2 ns
Max spot size	10 mm
Max pulse rate	10 Hz

The range of spot sizes from the zoom and collimated handpieces will allow targeting lesions precisely, while the large spot size (up to 10 mm at 1064 nm) from the collimated handpiece will ensure a new efficient and safe treatment, our so-called 'Pico Toning' with the 750 ps beam. A new feature with these handpieces is that the aiming beam expands or contracts to fit the spot size selected for added accuracy. The selection of spot sizes from the Gold Toning$^+$ (2 mm and 5 mm) and the RuVY Touch$^+$ (2 and 3 mm) will allow improvement on the already excellent results being achieved in the clinical field with these wavelengths from the ns-domain SPECTRA XT. The new Focused Dots handpiece (only available for the 1064 nm wavelength) delivers 81 focused micro-sized beams over a 7.4 x 7.4 mm spot for efficient "cold" skin rejuvenation, wrinkles, skin textural problems and mild scar revision. Table 2 summarizes the available handpieces.

Table 2: Handpieces available with the PICO$^+$4

Handpiece		Wave-lengths
Zoom		1064 nm
		532 nm
Pico Toning Collimated		1064 nm
		532 nm
Gold Toning$^+$		595 nm
RuVY Touch$^+$		660 nm
Focused Dots		1064 nm

The PICO$^+$4 offers a very wide range of fluences, wider than any other ps-domain lasers, to ensure the ideal parameters to achieve the desired tissue effect. This range is illustrated in Figure 2, left panel, compared with that of a typical competitor ps-domain system. Rather than have the user search for the desired fluence setting with the usual up and down arrows on the touch screen, which could take time because of the large range available, the PICO$^+$4 has a "jog and shuttle" type adjuster to allow speedy but precise fluence selection (Figure 2, right panel).

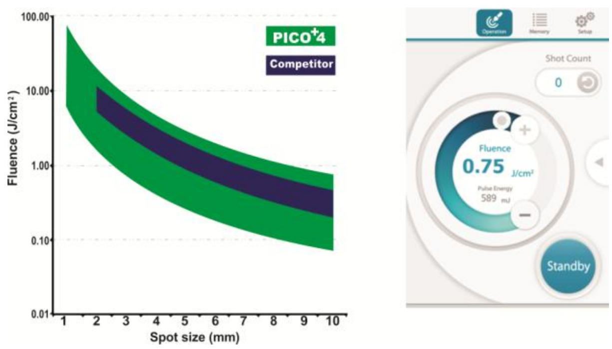

Fig 2: (Left panel): Range of available fluences compared for the PICO$^+$4 and a competitor.
(Right panel): Jog and Shuttle control on the touch screen GUI(Graphical User Interface) for rapid fluence selection

Rationale behind Picosecond Delivery

Although selective photothermolysis gives precise destruction of pigmented targets in pulse widths lower than the thermal relaxation time of the pigment being targeted, the destruction is still achieved mainly through a photothermal reaction although some photoacoustic effect is generated under certain circumstances, so some damage will still occur to the cell or tissue containing the target. Particularly where multiple shots are being fired, or pulse-stacking is employed, this damage can become too extensive and defeat the selective object of the treatment. In darker Fitzpatrick skin phototypes, such as Asian type 3 skin and darker, such thermal damage generated at the dermoepidermal junction can result in an inflammatory response, running the risk of PIH formation and increasing patient downtime.

To help prevent this occurring, particularly in the treatment of melasma, the low fluence multi-pass technique of laser toning was developed using the ns-domain Q-switched 1064 nm wavelength. One study demonstrated the efficacy of this technique in removing the pigmentation from zebrafish *in vivo*, whereby pigment was removed at the appropriate fluence, but the pigment-containing cells were not only left intact, but left alive with no sign of imminent apoptotic death, whereas cellular apoptosis was noted in zebrafish treated over that threshold fluence [12]. The authors called this phenomenon "subcellular selective photothermolysis", as it took the conventional theory of selective photothermolysis one stage further towards higher selectivity and greater sparing of surrounding structures. Subcellular selective photothermolysis is the concept underpinning the low-fluence laser toning approach.

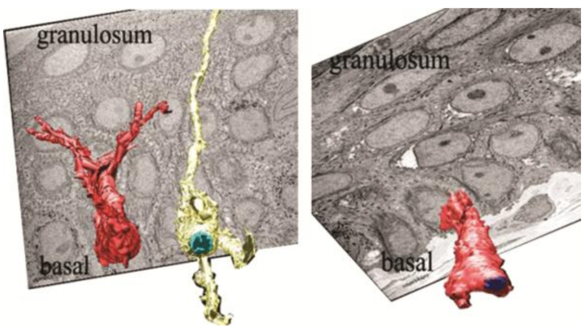

Fig 3: The left panel shows 2 computer-rendered melanosomes in 3-dimensions in skin from a melasma patient before laser toning with dendrites reaching well up into the stratum spinosum. The right panel, taken after treatment, shows the melanosome is alive, but with truncated dendrites. Daughter keratinocytes in the stratum spinosum are also alive, but have few melanin granules, unlike those in the left panel. (Courtesy of Prof IH Kim, Seoul, South Korea)

A subsequent *in vivo* study on low-fluence laser toning in human melasma subjects showed good clearance of the treated side in the split face melasma treatment segment of the trial [13]. Ultrastructural analysis using 3-dimensional scanning topography and transmission electron microscopy in the same study showed removal of melanosomes from laser toning-treated melanocytes and keratinocytes with the cells left alive. In the case of the melanocytes, however, they had apparently undergone a dendrectomy although the main body of the cell was intact (Figure 3). The same study also found lower levels of the pigmentation-inducing enzymes tyrosinase and tyrosinase- associated proteins in the treated tissue.

This was subcellular selective photothermolysis illustrated in human melasma patients, with multiple passes at low fluences delivered in the ns domain by a 1064 nm Q-switched Nd:YAG laser. However, even with the laser toning approach, the endpoint is still gentle heating of the target tissue with mild erythema. It could be possible to inadvertently overdo the local heating with subsequent damage-related inflammation and potential PIH formation, even with the subcellular selective photothermolysis approach. On the other hand, some studies have reported discrete spots of leukoplakia in the remnant melsama lesions following laser toning [14], and concluded that there had been excessive damage to the melanocytes due to secondary heat being conducted from the target melanosomes. It has to be said, however, that these studies used much higher fluences than those recommended by the authors in Reference 13 above but the data on the leukoplakia formation indicate that some even more selective approach is needed to make sure that the laser-induced damage is as completely confined to the target pigment as possible. The advent of the picosecond domain laser was believed to embody that concept of even greater selectivity and damage confinement [9].

If using laser pulses equal to or slightly less than the thermal relaxation time (TRT) of the target pigment produced good results, then it was postulated as early as 1999 by Herd and colleagues that using pulses significantly less than the TRT of melanosomes and melanin granules, *i.e.* in the ps domain, should get even better results, and indeed should induce a nonlinear reaction in the target so that destruction would not be thermal, but photoacoustic in nature [15]. Certainly in the treatment of tattoos, the Q-switched ns-domain laser became the treatment of choice, but true efficacy is somewhat limited to younger tattoos inked in with blue and black pigment. When tattoos are older and more faded, due to the progressive descent of pigment into the dermis, or where there are other colors, efficacy is less. Bencini and colleagues studied tattoo removal in 352 patients with ns-domain Q-switched lasers at 755 nm, 1064 nm and 532 nm [16]. After 10 sessions, only 47% of the patients had what was considered successful removal, and even after 15 sessions, successful removal was not achieved in around 25% of the patients. Some other approach is obviously required, and the ps-domain laser is believed to represent that approach.

In fact, from current ps laser reports, a number of advantages are emerging over existing ns-based systems:

- Results are better, and achieved faster meaning fewer sessions are required.
- The skin reaction is more forgiving, with less pain and scarring.
- Patient downtime is less, and there are fewer side effects.
- Finally, treatment of tattoos resistant to ns-domain treatment has been found possible with the ps-domain approach.

Table 3: Lasers compared by the relationship between beam mode, exposure domain and tissue effect

Beam mode	Exposure domain	Unit	Tissue effect
Continuous wave (CW) [switched / gated]	Seconds (fractions)	s (ms x 10^2 ~)	Conducted heat effect Tissue selective vaporization / coagulation
Pulsed	Milliseconds	≤ 1 s (≤ 1 x 10^{-3} s)	Radiant heat effect (Selective photothermolysis) Semi-cell selective
Short pulsed (PDL) Superpulsed Ultrapulsed	Microseconds	µs (1 x 10^{-6} s)	Radiant heat effect (Selective photothermolysis) Cell selective
Q-switched	Nanoseconds	ns (1 x 10^{-9} s)	Radiant heat effect ~ photomechanical effect Subcellular selective photothermolysis
Pico-laser	Picoseconds	ps (1 x 10^{-12} s)	Nonlinear athermal effect photoacoustic ~ plasma Precisely pigment selective, damage confinement

However, when Ross and colleagues compared pigment removal using a ps-domain laser (0.65 J/cm², 35 ps) with ns-domain systems (0.65 J/cm², 10 ns and 8.0 J/cm², 10 ns), all at 1064 nm, they reported that higher efficacy was achieved with the ps compared with the lower fluence ns system, but the best result was achieved with the high fluence ns system [17]. The conclusion was that ps-domain pulses could be more effective for pigment removal, but would require higher fluences. The PICO+4 delivers the highest fluence among competitor ps-domain systems, with large spot sizes. The importance of the larger spot sizes and higher fluences is better penetration with less energy lost to lateral scattering, enabling the ps laser energy to reach and destroy deeper-sited pigments.

The tissue effect generated by a laser (for the same wavelength and spot size) depends on the power and the beam mode of the laser and its exposure domain. Table 3 explores this relationship for current lasers, showing the evolution from the previous generation of continuous wave systems, through pulsed to ns-domain Q-switched lasers and finally the latest ps-domain systems, such as PICO+4.

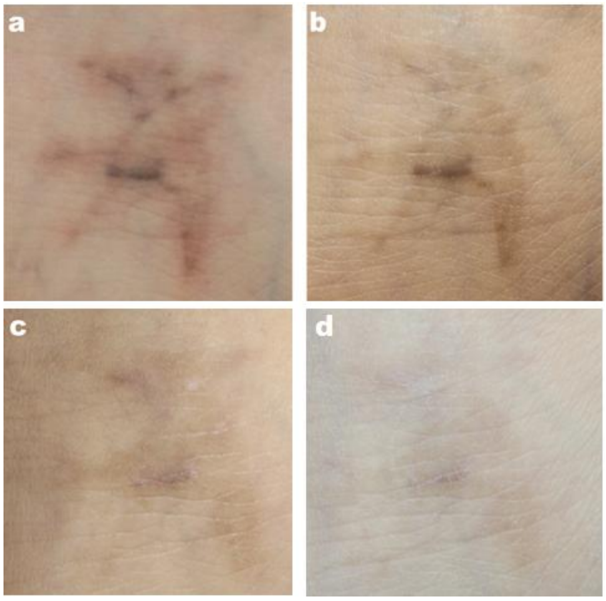

Fig 4: Efficacy of the PICO+4 in tattoo removal. (a): Tattoo at baseline. Note treatment-resistant pigment. (b): Very good clearance of the recalcitrant pigment after 1 PICO+4 session. (c): After 6 weeks, a second session was given with the PICO+4. (d): After a further 6 weeks, a third session was given with the PICO+4 and further clearance of the remnant pigment has been achieved. No textural or adverse pigmentary changes to the skin have occurred. (Photography courtesy of GS Lee MD, Seoul, South Korea)

There comes a stage in the ps domain when, as the exposure domain decreases with very small spot sizes, the peak power density (the function of the incident power and the unit area irradiated) is so high that absorption of the photon energy in the target starts to create nonlinear athermal photoacoustic effects, and even results in the creation of plasma. This is not ideal, since all incident energy is quenched in the plasma spark [17], and thus cannot penetrate deeper into the target tissue, for example to reach deeper-lying tattoo pigment. Hence the spot size of the ps-domain beam should be as large as possible in relation to the target to ensure deeper penetration to reach deeper-lying targets with minimized loss of intrabeam energy through lateral scattering. The large spot sizes of the PICO+4 system ensures deeper penetration to reach deeper-lying tattoo pigment. Figure 4a shows an example of a 3-year-old tattoo previously treated at another clinic with both ns-domain (4 sessions) and ps-domain (2 sessions) lasers by other manufacturers, where there was a considerable amount of residual treatment-resistant pigment. The PICO+4 was applied (1064 nm, spot size 3 mm, 2.4-3.2 J/cm²), and the good result after a single session is seen in Figure 4b. Further sessions were given at 6-week intervals at the same parameters, and very good removal of the previous treatment-resistant pigment has been achieved as seen in Figure 4c and 4d. Note the lack of any textural or adverse pigmentary changes to the skin.

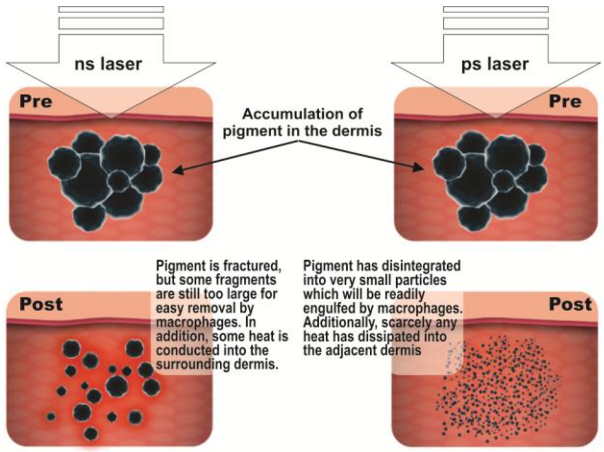

Fig 5: Effect on accumulations of pigment compared between the conventional ns (nanosecond) and new ps (picosecond) lasers

The advantage of the ps-domain beam over the ns-domain beam is therefore in the more efficient photoacoustic destruction of pigment targets with virtually no collateral dissemination of heat, especially in large accumulations of pigment such as are found in some tattoos and illustrated in Figure 5, comparing schematically the effect of a ns and ps beam

An experiment was designed to compare a standard ns-domain Q-switched Nd:YAG laser with the PICO+4 system in the treatment of a simulated tattoo in a skin phantom. The skin phantom was prepared as follows. A polyacrylamide hydrogel was prepared by mixing 5% (w/v) bovine serum albumin (Sigma-Aldrich, St. Louis, MO, USA) in distilled water. After degassing, a 25% (v/v) aqueous solution of 40% (w/v) acrylamide (Sigma-Aldrich) was added to the mixture. Then, polymerization was initiated by adding 10% (v/v) of 1 mol/L of TRIS buffer at pH 8 (Sigma-Aldrich) and 0.84% (v/v) of a 10% (w/v) ammonium persulfate solution (Sigma-Aldrich). After an additional degassing, 0.05% (v/v) of N,N,N',N'-tetramethylethylenediamine (Sigma-Aldrich) was added for polymerization. The final mixture was then immediately poured into a rectangular polycarbonate housing and allowed to set solid in a refrigerator at 4°C. When the skin phantom had set, black tattoo ink was drawn into a syringe and injected into the center of the phantom while the needle was steadily withdrawn from the gel, leaving a linear zone of Indian ink particles in the center of the phantom representing the target "tattoo" for the experiment.

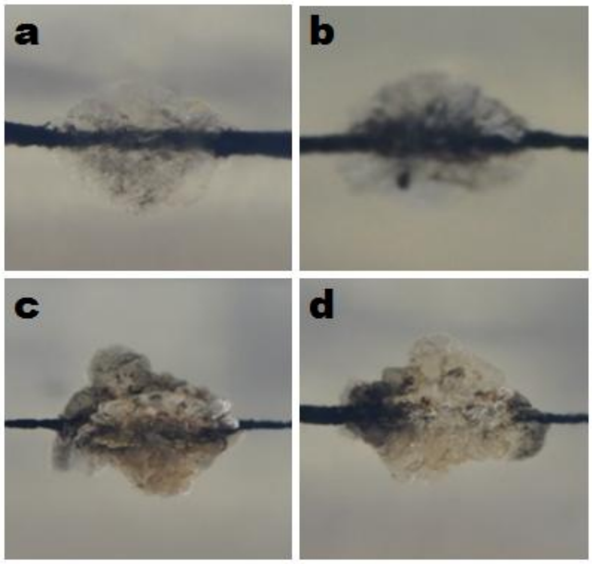

Fig 6: A simulated tattoo in a skin phantom irradiated with the ns- (a, c) and ps- (b, d) domain lasers. (a, b): Single pass, 4 mm spot, 4.8 J/cm², ns and ps lasers, respectively. (c): Ten passes, 5 ns, 1064 nm, 4 mm, 4.8 J/cm². (d): Five passes at 5 ns followed by additional five passes at 750 ps, with other parameters the same. See text for details. (Photography courtesy of SB Cho MD, Seoul, South Korea)

The "tattoo" in the phantom was then irradiated with a standard 1064 nm 5 ns Q-switched Nd:YAG laser and the 1064 nm 750 ps PICO+4, both with a single pass at a spot size of 4 mm and a fluence of 4.8 J/cm², giving the results seen in Figure 6a and 6b. The indian ink particles appear better disrupted with the ps-domain shot, in accordance with the osmotic power of the photoacoustic effect associated with the ps-domain laser. The effect on the "tattoo" at ten passes with the 5 ns system (Figure 6c) were then compared with five passes at 5 ns followed by additional five passes at 750 ps (Figure 6d). With the ten ns-domain passes (6c), the indian ink particles have been dispersed but without significant fragmentation. In Figure 6d, however, the ink particles appear not only dispersed, but also more efficiently destroyed. These findings suggest the more effective destruction of pigment particles with the ps-domain laser at the same parameters as the ns-domain system.

From the preliminary results on the Indian ink in our skin phantom, it would follow that the ps-domain laser could offer advantages over the ns-pulse width in the treatment of melanogenic lesions. Figure 7 shows the good results obtained with the PICO+4 in the treatment of freckles (ephelides) in a 22-year-old female, single session, 532 nm, 750 ps, 1.5 mm spot, 1.1-1.4 J/cm².

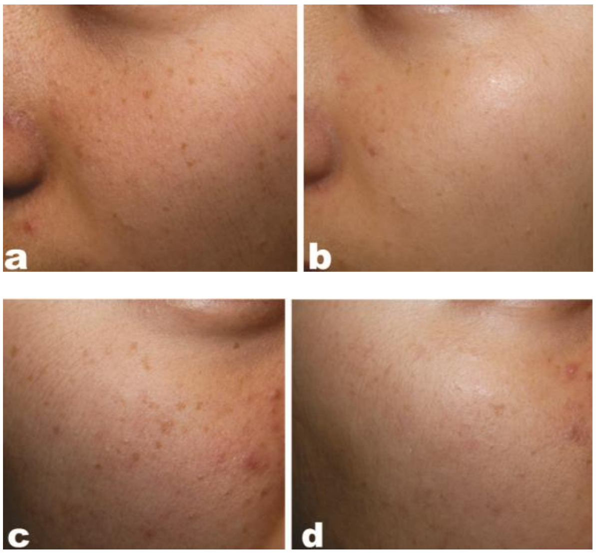

Fig 7: Freckles in a 22-year-old female at baseline (a, c) and after a single treatment with the PICO^{+}4 (b, d). Excellent clearance has been achieved, with minimal damage to the overlying epidermis. (Photography courtesy of GS Lee MD, Seoul, South Korea)

Conclusions

In preliminary application of the PICO^{+}4 in tattoos in phantom skin and human subjects, the PICO^{+}4 has shown safe and effective treatment with good pigment removal, even in deeper-sited pigments which have proved recalcitrant to ns-domain Q-switched laser treatment, and even to competitor ps-wavelength systems. Further basic and clinical studies will show that the PICO^{+}4 system, with its large spot sizes, variety of handpieces and four wavelengths, offers consistent, safe and effective removal of tattoos, even those with multiple colors and others which have proved resistant to treatment with the ns-domain Q-switched laser, in addition to good clearance of epidermal and dermal pigmented lesions, and a range of skin rejuvenation indications.

References

1: Calderhead RG: The Medical Laser. In Calderhead RG, Photobiological Basics of Photosurgery and Phototherapy. 2011, Hanmi Medical Press, Seoul, South Korea. pp 1-6.

2: Ohshiro T: The Naevus. In Ohshiro T (Ed) Laser Treatment for Naevi. 1995, John Wiley and Sons, Ltd, Chichester, UK. pp 1-37.

3: Anderson RR, Parrish JA: Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation. Science, 1983; 220: 524-527.

4: Taylor N. LASER: The inventor, the Nobel laureate, and the thirty-year patent war. 2000, New York: Simon & Schuster. p. 93.

5 Anderson RR, Margolis RJ, Dover J, *et al.*: Selective photothermolysis of cutaneous pigmentation by Q-Switched Nd:YAG laser pulsed at 1064 nm, 532 nm, and 355 nm. J Invest Dermatol, 1989; 93: 28-32.

6: Kilmer SL, Anderson RR: Clinical use of the Q-switched ruby and the Q-switched Nd:YAG (1064 nm and 532 nm) lasers for treatment of tattoos. J Dermatol Surg Oncol, 1993; 19: 330-338.

7: Brauer JA, Reddy KK, Anolik R, Weiss ET *et al.*: Successful and rapid treatment of blue and green tattoo pigment with a novel picosecond laser. Arch Dermatol, 2012;148:820-823.

8: Saedi N, Metelitsa A, Petrell K, Arndt KA, Dover JS: Treatment of tattoos with a picosecond alexandrite laser: a prospective trial. Arch Dermatol, 2012; 148: 1360-1363.

9: Ibrahimi OA, Sakamoto FH, Anderson RR: Picosecond laser pulses for tattoo removal: a good, old idea. JAMA Dermatol, 2013; 149: 241.

10: Freedman JR, Kaufman J, Metelitsa AI, Green JB: Picosecond lasers: the next generation of short-pulsed lasers. Semin Cutan Med Surg, 2014; 33: 164-168.

11: Bernstein EF, Schomacker KT, Basilavecchio LD, Plugis JM, Bhawalkar JD: A novel dual-wavelength, Nd:YAG, picosecond-domain laser safely and effectively removes multicolor tattoos. Lasers Surg Med, 2015; [Epub ahead of print].

12: Kim JH, Kim H, Park HC and Kim IH: Subcellular selective photothermolysis of melanosomes in adult zebrafish skin following 1064 nm Q-switched Nd:YAG laser irradiation. J Invest Derm, 2010; 130: 2333-2335.

13: Mun JY, Jeong SY, Kim JH, Han SS, and Kim IH: A low fluence Q-switched Nd:YAG laser modifies the 3D structure of melanocytes and ultrastructure of melanosomes by subcellular-selective photothermolysis. J Elect Micros, 2011; 60: 11–18.

14: Chan NP, Ho SG, Shek SY, Yeung CK, Chan HH: A case series of facial depigmentation associated with low fluence Q-switched 1,064 nm Nd:YAG laser for skin rejuvenation and melasma. Lasers Surg Med, 2010; 42: 712-719.

15: Herd RM, Alora MB, Smoller B, Arndt KA, Dover JS: A clinical and histologic prospective controlled comparative study of the picosecond titanium:sapphire (795 nm) laser versus the Q-switched alexandrite (752 nm) laser for removing tattoo pigment. J Am Acad Dermatol, 1999; 40: 603-606.

16: 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; 148: 1364-1369.

17: Ross V, Naseef G, Lin G *et al.*: Comparison of responses of tattoos to picosecond and nanosecond Q-switched neodymium: YAG lasers. Arch Dermatol, 1998; 134: 167-171.