Topical Perfluorodecalin Resolves Immediate Whitening Reactions and Allows Rapid Effective Multiple Pass Treatment of Tattoos

Kavitha K. Reddy, MD,* Jeremy A. Brauer, MD, Robert Anolik, MD, Leonard Bernstein, MD, Lori Brightman, MD, Elizabeth Hale, MD, Julie Karen, MD, Elliot Weiss, MD, and Roy G. Geronemus, MD
Laser & Skin Surgery Center of New York, New York, New York

Background and Objective: Laser tattoo removal using multiple passes per session, with each pass delivered after spontaneous resolution of whitening, improves tattoo fading in a 60-minute treatment time. Our objective was to evaluate the safety and efficacy of topical perfluorodecalin (PFD) in facilitating rapid effective multiple-pass tattoo removal.
Study Design: In a randomized, controlled study using Q-switched ruby or Nd:YAG laser, 22 previously treated tattoos were treated with 3 passes using PFD to resolve whitening after each pass ("R0 method"). In previously untreated symmetric tattoos, seven were treated over half of the tattoo with the R20 method, and the opposite half with 4 passes using PFD (R0 method); two were treated over half with a single pass and the opposite half with 4 passes using PFD (R0 method); and six treated over half with a single pass followed by PFD and the opposite half with a single pass alone. Blinded dermatologists rated tattoo fading at 1–3 months. Optical coherence tomography (OCT) imaging of whitening was performed in two tattoos.
Results: Topical PFD clinically resolved immediate whitening reactions within a mean 5 seconds (range 3–10 seconds). Tattoos treated with the R0 method demonstrated excellent fading in an average total treatment time of 5 minutes. Tattoo areas treated with the R0 method demonstrated equal fading compared to the R20 method, and improved fading compared to a single pass method. OCT imaging of whitening demonstrated epidermal and dermal hyper-reflective "bubbles" that dissipated until absent at 9–10 minutes after PFD application, and at 20 minutes without intervention.
Conclusions: Multiple-pass tattoo removal using PFD to deliver rapid sequential passes (R0 method) appears equally effective as the R20 method, in a total treatment time averaging 5 minutes, and more effective than single pass treatment. OCT-visualized whitening-associated "bubbles," upon treatment with PFD, resolve twice as rapidly as spontaneous resolution. Lasers Surg. Med. 45:76–80, 2013. © 2012 Wiley Periodicals, Inc.

Key words: perfluorodecalin; perfluorocarbon; immediate whitening; laser; tattoo; R20; multiple pass

INTRODUCTION

Q-switched laser treatments accomplish safe and effective tattoo removal through repeated targeting of exogenous dermal pigment. The traditional technique consists of a single laser pass delivered every month, resulting in slow tattoo fading over many months to years until clearance [1]. Multiple passes per session have demonstrated improved tattoo fading compared to a single pass method [1]. In order for the multiple-pass method to be effective, laser-induced cutaneous immediate whitening reactions that block light entry must subside before delivery of each pass. Spontaneous resolution of whitening reactions requires an average of 20 minutes after each pass [1]. While the multiple-pass technique appears more effective, without intervention the total treatment time of 60–80 minutes presents difficulties for both patient and physician.

Laser-induced immediate whitening reactions are hypothesized to result from thermally induced cavitation bubble formation [1]. Perfluorodecalin (PFD), a liquid fluorocarbon, has high gas solubility and enhances optical clarity [2,3]. It has been studied in medical applications including as a blood substitute due to oxygen- and carbon dioxide-gas carrying capacities, and FDA-approved use as an ophthalmologic vitreous body replacement [2,4,5]. The safety and efficacy of topical PFD in reduction of Q-switched laser-induced immediate whitening reactions and for rapid and effective multiple-pass tattoo removal was investigated.

METHODS

A randomized, controlled, evaluator-blinded study was designed by the investigators and approved by the

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and have disclosed the following: Perfluorodecalin was provided by ON Light Sciences.

*Corresponding to: Kavitha K. Reddy, MD, 317 East 34th Street, 11th Floor, New York, NY 10016.
E-mail: kavithareddymd@gmail.com

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institutional review board. Adult subjects reporting an unwanted tattoo were recruited. Two groups were included, subjects with tattoos previously treated one month or more before study entry, and subjects with previously untreated, symmetric tattoos. Tattoos containing white ink, or those having received treatment within less than 4 weeks of study entry were excluded. Written informed consent was obtained from subjects. Tattoo characteristics, including color(s), age of tattoo and previous treatment history were recorded. Each tattoo was photographed.

Twenty-two tattoos with a history of prior treatment one month or more before study entry were assigned to treatment with the R0 method over the entire tattoo. These were treated with 3 passes of Q-switched laser, with each pass followed by topical PFD application and subsidence of whitening prior to delivery of the next pass ("R0 method"). In previously untreated symmetric tattoos, halves were demarcated along the axis of symmetry by the treating investigator using a marker, and the halves randomized by coin toss. A blinded research assistant determined the randomization outcome that would represent the PFD-treatment half. Six of these tattoos were assigned to treatment with a single laser pass followed by PFD application compared with a single laser pass alone. Seven were assigned to treatment with the R0 method compared with the R20 method, and two were assigned to treatment with the R0 method compared with the single pass method.

For each tattoo, the treating investigator selected either the Q-switched ruby or the Q-switched Nd:YAG laser based on skin phototype. For Q-switched ruby laser treatment, a fluence of 3.5 J/cm^2 and spot size of 6 mm were applied. For Q-switched Nd:YAG (1064 nm) laser treatment, fluences of 3–5 J/cm^2 and spot size of 4 mm were applied. In each case the entire individual tattoo was treated with the same laser and fluence, regardless of assignment of a portion to PFD treatment. Sterile medical-grade PFD was applied topically over the PFD-assigned treatment area immediately following each laser pass. After PFD application, time until subsidence of the whitening reaction was recorded. Total treatment times were also recorded.

Two to 4 weeks after treatment, subjects were assessed for any adverse events. One to three months after treatment, tattoos were photographed and assessed for degree of fading according to the following scale: 0%, 1–25%, 26–50%, 51–75%, or 76–100%. Blinded dermatologists rated the degree of tattoo fading in tattoo areas treated with PFD and in areas treated without PFD. Optical coherence tomography (OCT) imaging was performed in two tattoos, before laser treatment and every 60 seconds after immediate whitening in an area treated with PFD and another not treated with PFD. Time required for each site to return to its pre-laser OCT appearance was recorded.

RESULTS

Treatments using topical PFD were well tolerated without adverse events. After application of topical PFD, cutaneous immediate whitening reactions were clinically reduced by 75–100% within seconds of application (mean 5 seconds, range 3–10 seconds) (Fig. 1). Spontaneous resolution of whitening reactions occurred within 20 minutes (mean 20 minutes, range 17–22 minutes). Total treatment times using the R0 method averaged 5 minutes (range 3–7 minutes) (Table 1).

Previously untreated symmetric tattoo halves treated with the R0 method demonstrated equal fading in the

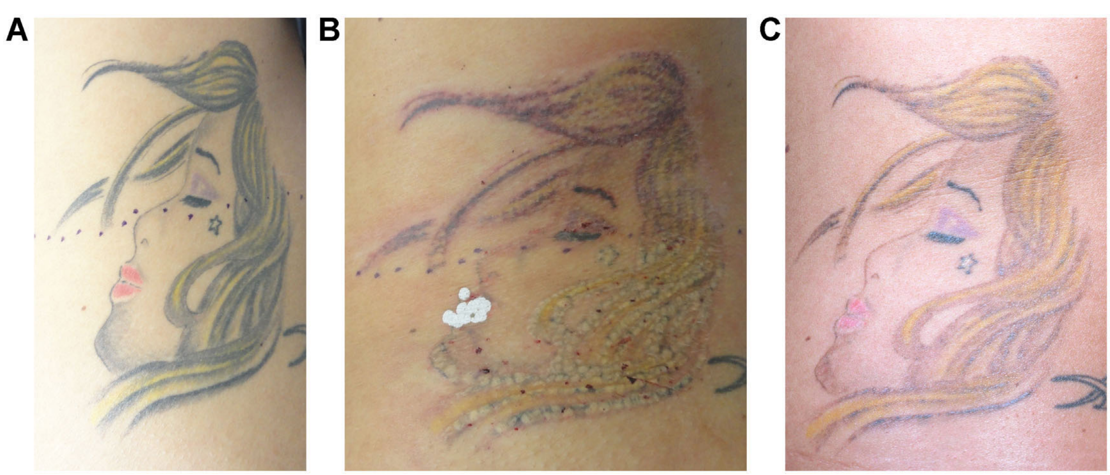

Fig. 1. Tattoo treated with R0 method compared with R20 method. **A**: Previously untreated yellow, purple, red, and black tattoo at the flank. **B**: Tattoo immediately after Q-switched Nd:YAG treatment with the R0 method at superior half and the R20 method at inferior half. Red lips in the tattoo design were treated with a single pass of 532 nm Q-switched Nd:YAG treatment. Immediate whitening reaction is resolved at the superior half after PFD application. **C**: Equal fading of halves observed 1 month after treatment of superior half with R0 method and inferior half with R20 method.

TABLE 1. Tattoo Removal by R0 and R20 Methods

Tattoo removal method	Study arm	n	Time to clinical reduction of immediate whitening (75–100% decrease), mean (range)	Total treatment time, mean (range)	Degree of tattoo fading at follow-up (1–3 months), mean (range)
R20, 4 passes	Previously untreated symmetric tattoos, half of tattoo	7	20 minutes (17–22)	68 minutes (64–72)	51–75% (26–50% to 76–100%)
R0, 4 passes	Previously untreated symmetric tattoos, half of tattoo	7	5 seconds (3–10)	5 minutes (3–7)	51–75% (26–50% to 76–100%)
R0, 3 passes	Previously treated tattoos	22	5 seconds (3–10)	5 minutes (3–6)	51–75% (51–75% to 76–100%)

same number of passes compared to the R20 method, averaging 51–75% (Figs. 1 and 2). In addition, previously untreated symmetric tattoo halves treated with the R0 method demonstrated improved fading compared to the single pass method (Fig. 3). Previously treated tattoos treated over the entire surface with the R0 method demonstrated excellent (≥51%) fading at 1–3 months follow-up. Previously untreated symmetric tattoo halves treated with a single pass method followed by PFD application displayed no significant difference in fading compared to the opposite half treated with a single pass without PFD.

OCT imaging of immediate whitening reactions in two tattoos demonstrated multiple epidermal and dermal hyper-reflective “bubbles,” consistent with the appearance of gas bubbles (Fig. 4). OCT-visualized hyper-reflective “bubbles” disappeared gradually and completely in the first tattoo at 9 minutes after PFD application, in the second tattoo at 10 minutes after PFD application, and at 20 minutes without intervention in each of the tattoos (Fig. 4).

DISCUSSION

Perfluorocarbons are colorless, inert, non-toxic liquids having properties of low surface tension, optical clarity in scattering media, and insolubility in aqueous solutions and in blood [6]. PFD has been investigated for medical use as an oxygen carrier or blood substitute with promising results [4]. The most common application has been in ophthalmology, where the compound has been FDA-approved as an artificial vitreous body substitute [2]. Gas-carrying capacities of PFD allow it to transfer oxygen and likely other gases to and from dermal tissue [7]. Gas transfer through tissue appears to be the most likely mechanism by which PFD reduces or clears laser-induced immediate whitening reactions that result from bubble expansion and collapse during cavitation [2].

Previous *in vitro* experiments by Wesendahl and co-investigators found infrared laser radiation in an aqueous environment promoted formation of fast expanding and collapsing water vapor bubbles, inducing pressure gradients. In the presence of PFD, smaller and slower or no bubbles, with lower pressure gradients generated, were observed to emerge from the treated surface and rise through PFD without accumulating or impairing visibility through the liquid [8]. Bubbles formed after laser radiation in a PFD tissue environment may be the result of tissue debris, as opposed to water vapor [8]. Differences in bubble size and composition in the presence of PFD may

Fig. 2. Tattoo treated with R0 method compared with R20 method. **A**: Previously untreated black tattoo at the upper back. **B**: Immediately after Q-switched Nd:YAG treatment with the R20 method at the superior half and the R0 method at the inferior half. Immediate whitening reaction is resolved at the inferior half after PFD application. **C**: Equal fading of halves observed one month after treatment of inferior half with R0 method and superior half with R20 method.

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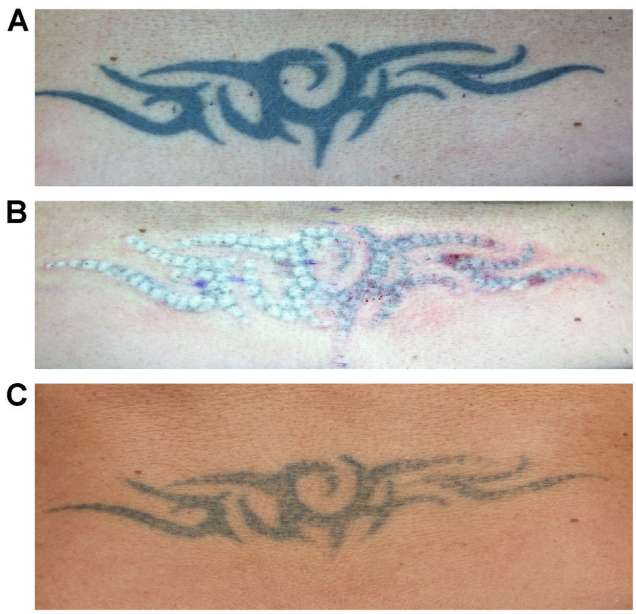

Fig. 3. Tattoo treated with R0 and single pass methods and imaged with optical coherence tomography (OCT). **A**: Previously untreated black tattoo on the lower back before treatment. **B**: After one pass of Q-switched ruby laser over the entire tattoo area and 5 seconds after application of topical PFD to the right half, immediate whitening reaction persists at the left half and is reduced at the right half. Treatment was continued to complete the R0 method at the right half, compared with the single pass method delivered at the left half. Optical coherence tomography (OCT) imaging was performed before and after immediate whitening at both halves (Fig. 4). **C**: Two months after treatment, the R0-treated half (right) demonstrates greater fading than the single pass-treated half (left).

explain the observation that PFD was able to rapidly resolve clinical whitening and presumably permit transmission of light within seconds of application, resulting in effective multiple-pass tattoo fading even when OCT-imaged bubbles persisted until 10 minutes after PFD application.

In addition to clearance of micro-bubbles that limit light penetration, perfluorocarbon properties of optical clarity may also independently increase optical penetration of light in PFD-treated skin. PFD saturates air spaces well when applied to a surface and may increase the depth of penetration of laser treatment [9]. PFD has also been suggested to have potential additional benefits including reduced collateral thermal tissue injury [10]. PFD's high specific gravity is known to cause tissue compression [10]. Protection from thermal damage is a hypothesized benefit based on the ability to compress tissue, and potentially decrease cutaneous blood flow, vascular permeability and edema [11].

Experience with PFD utilization during laser treatments has been described in limited reports in ophthalmology literature [8,10]. Azzolini et al. [10] have compared laser delivery through PFD as compared to balanced salt solution, and found laser power and histologic damage to be similar in both solutions. Wesendahl et al. [8] has reported successful Er:YAG treatment through PFD. In medical applications, sterile medical-grade PFD is recommended. The material safety data sheet classifies the compound as a non-hazardous material, without toxicity or irritation by inhalation, ingestion, skin, or eye contact [12]. Toxic hydrogen fluoride fumes can be produced upon contact with open flames. The liquid must be disposed of appropriately and should not be drained into sinks [12].

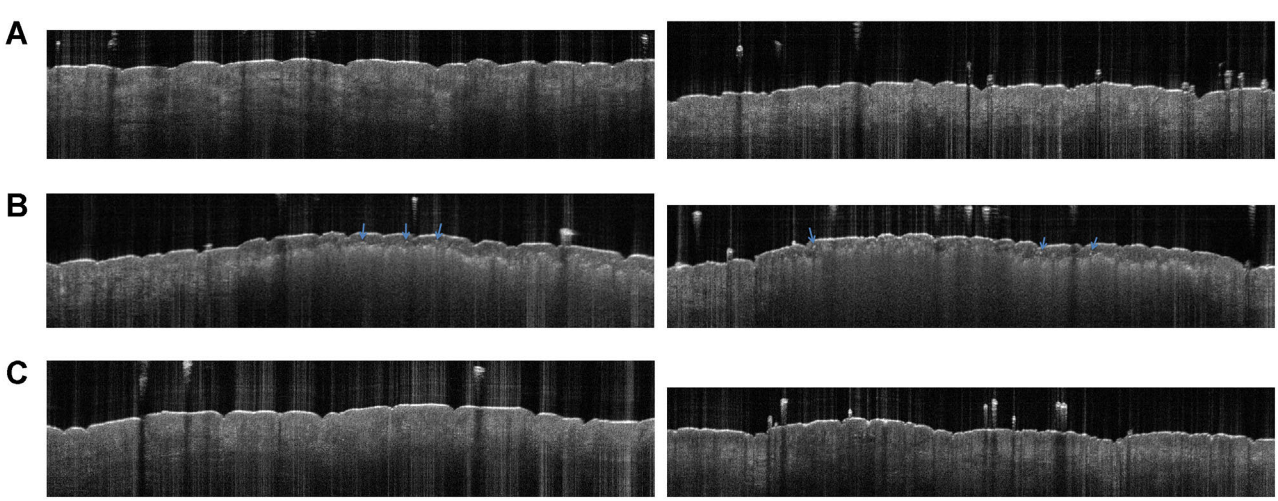

Fig. 4. Optical coherence tomography imaging of immediate whitening reactions before, during, and after spontaneous resolution (left column) and PFD-induced resolution (right column). **A**: OCT images of tattoo areas prior to laser treatment. **B**: OCT images of immediate whitening reactions immediately after laser pulse. Multiple scattered hyper-reflective "bubbles" are visible in the dermis and epidermis (arrows at representative areas). **C**: After PFD application at the immediate whitening reaction on the right side of the tattoo, hyper-reflective "bubbles" gradually disappear and normal pre-laser appearance is restored at 10 minutes after application of topical perfluorodecalin (right column) and at 20 minutes without perfluorodecalin application (left column).

We have observed that immediate whitening reactions produced during Q-switched laser tattoo removal can be clinically reduced within a mean 5 seconds of topical PFD application, and that rapid multiple-pass treatment of tattoos may be accomplished in less than 5 minutes when using PFD. The studied "R0" method appears equally effective as the R20 method in a significantly reduced treatment time. In addition, the R0 method proved more effective than the traditional single laser pass method. These findings may aid in improving efficiency and efficacy of treatment for both patients and physicians by allowing more effective multiple-pass tattoo removal techniques to be rapidly and seamlessly utilized. Q-switched laser tattoo removal with rapid delivery of multiple laser passes per session in less than 5 minutes using PFD to facilitate resolution of the immediate whitening reaction appears to provide a safe and effective innovation in tattoo removal.

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