

Use of Onion Extract, Heparin, Allantoin Gel in Prevention of Scarring in Chinese Patients Having Laser Removal of Tattoos: A Prospective Randomized Controlled Trial

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BACKGROUND With rapid advancement in cutaneous laser therapy, Q-switched lasers have become the standard treatment for tattoo removal. The longer wavelength Q-switched Nd:YAG laser is used when removing tattoos in darker skin patients to avoid scarring and permanent pigment changes. Nevertheless, the local experience revealed that nearly 25% of the Chinese patients developed scarring. Meanwhile, multiple clinical studies have shown that Contractubex gel (Merz Pharma, Frankfurt, Germany) was effective in the treatment and prevention of hypertrophic scars and keloids.

OBJECTIVE To evaluate the efficacy of Contractubex gel in the prevention of scarring after laser removal of tattoos in Chinese patients.

METHODS A total of 120 Chinese patients with 144 professional blue-black tattoos were recruited into the study. They were randomly assigned into the Contractubex group or the control group. All patients were treated with a QS 1,064-nm Nd:YAG laser using a 3-mm spot size, a 10-Hz repeat rate, a pulse duration of 6 nanoseconds, and fluences that ranged from 3.6 to 4.8 J/cm² (mean fluence, 4.2 J/cm²). The treated areas were assessed 3 months after the last treatments for clinical clearance and complications.

RESULTS Fifty-two patients with 61 tattoos in the Contractubex group were able to achieve a mean clearing rate of 82.3 ± 11.6%. There were 7 tattoos in 7 patients that developed scarring, 4 patients had permanent hypopigmentation, and 3 patients had transient hyperpigmentation. In contrast, 55 patients with 68 tattoos in the control group had a mean clearing rate of 80.4 ± 11.3%. Among them, 16 tattoos in 14 patients developed scarring, 4 patients had permanent hypopigmentation, and 5 patients had transient hyperpigmentation. Although there was no significant difference in age, sex, fluence, treatment session, and clinical clearance between the two groups, the Contractubex group had a statistically significantly lower rate of scarring than the control group ($p < .05$).

CONCLUSION Contractubex gel is effective in scar prevention in Chinese patients having laser removal of tattoos.

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Decorative tattoos are very popular among Asian teenagers. Unlike their previous generation, these tattoos are regarded as a kind of style and fashion instead of for identification purposes.

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poses like Triad members. Unfortunately, most of these tattoos are placed impulsively or under enormous peer group pressure by unqualified people in back streets with high risk of transmission of hepatitis and HIV. Still, most of the people in Hong Kong associate decorative tattoos with crime and violence. As a result, these youngsters are confronted by tremendous social and family pressure. The trend is that more and more young adults request that recently placed tattoos be removed.

Traditionally, tattoos were removed by tissue destruction like surgical excision, dermabrasion, salabrasion, chemicals, cryosurgery, and infrared coagulation.¹⁻⁸ Stigmatized scarring and dyspigmentation, however, were as undesirable as the original tattoos. With recent advancements in laser technology, tattoos can be removed without significant side effects. It had been shown that the Q-switched laser systems are effective in clearing tattoos, especially the blue-black tattoos, with little complications.⁹⁻¹⁵ These lasers have also been proven to be useful and safe in darkly pigmented skin despite the fact that there is more melanin competing as target chromophore.^{16,17} The local experience was, however, otherwise. The authors found that Chinese patients with Fitzpatrick types III-V required higher fluence to achieve the desirable clinical response, and nearly 25% of them developed scarring (Figure 1). In addition, the



Figure 1. Significant scarring developed after four laser treatments.

initial observation also revealed that Q-switched Nd:YAG 1,064-nm laser had less scarring and dyspigmentation as shown in other studies.^{10,13,16} Meanwhile, some clinical studies demonstrated that Contractubex gel (Merz Pharma, Frankfurt, Germany) (components: 10% aqueous onion extract, 50 U heparin per gram of gel, 1% allantoin) was effective in the treatment and prevention of hypertrophic scars and keloids.¹⁸⁻²⁰ The purpose of this study was to evaluate the efficacy of Contractubex gel in the prevention of scarring after laser removal of blue-black tattoos in Chinese patients.

Methods

The trial was carried out in a single center at the Laser Center of Prince of Wales Hospital, Hong Kong. A total of 120 Chinese patients with 144 professional blue-black tattoos without previous treatment were recruited into the study. They were randomly assigned into the Contractubex group or the control group, with 60 patients in each group. Informed consent was obtained

from all subjects. The study protocol conformed to the guidelines of the 1975 Declaration of Helsinki and was approved by our institutional review board.

Patients in the Contractubex group applied Contractubex gel to the treatment areas twice daily in between laser treatment sessions and patients in the control group did not apply anything. All patients were treated with a QS 1,064-nm Nd:YAG laser using a 3-mm spot size, a 10-Hz repeat rate, a pulse duration of 6 nanoseconds, and fluences that ranged from 3.6 to 4.8 J/cm² (mean fluence, 4.2 J/cm²) at 8- to 10-week intervals. The fluence used was dependent on the density of ink presented and observed clinical response. Fluence would be gradually increased until the treatment end point of whitening of treated areas or bleeding occurred. All patients had EMLA cream (Astra, Sodertälje, Sweden) applied 1 hour before treatment, and Tegaderm (3M Health Care, Neuss, Germany) was used to occlude the area. The cream was removed immediately before treatment by using dry gauze. After treatment, Bactroban (Glaxo-SmithKline, Middlesex, England) antibiotic cream was applied to the treated area, and patients were advised to reapply the cream twice daily until the wounds had healed up. After that, patients in the Contractubex group applied Contractubex gel to the treatment areas twice daily until the next laser treatment session. Patients in both groups were advised to apply

sun block (SPF 15) between treatment sessions.

The treated areas were assessed 3 months after the last treatments for clinical clearance and complications by a plastic surgeon not involved with the study. Statistical analyses were conducted by using the paired Student's *t* test. Figures are expressed as means \pm SDs. The statistical level was regarded as significant if $p < .05$.

Results

A total of 52 patients with 61 tattoos had completed the study in the Contractubex group. There were 32 men and 20 women. Their ages ranged from 19 to 57 years with a mean age of 37.7 ± 6.8 years. The mean duration of the presence of the tattoos was 16.1 ± 5.5 years with a range of 5 to 32 years (Table 1). They had received a mean of 5.3 ± 1.2 treatment sessions (range, 4–8) with a mean fluence of 4.3 ± 0.3 J/cm² (range, 3.8–4.8 J/cm²) and were able to achieve a mean of $82.3 \pm 11.6\%$ clearing rate (range, 60%–100%). They had been followed up from 13 to 20 months with a mean of

TABLE 2. Treatment Results

Variable	Group		p Value
	Contractubex	Control	
Treatment session	5.3 \pm 1.2	5.4 \pm 1.3	.28
Fluence (J/cm ²)	4.3 \pm 0.3	4.1 \pm 0.7	.03
Percentage of patients with clearing	82.3 \pm 11.6	80.4 \pm 11.3	.19
Number of patients with			
Scarring	7	16	<0.5*
Hypopigmentation	4	4	.93
Hypopigmentation	3	5	.51

*Statistically significant.

15.5 ± 2.6 months. Seven tattoos (11.5%) in 7 patients developed scarring, 4 patients (7.7%) had permanent hypopigmentation, and 3 (5.8%) patients had transient hyperpigmentation. Among the 8 patients who had dropped out from the study, 5 patients defaulted follow-up and 3 patients stopped applying Contractubex gel because of itchiness. There was no other complication associated with the application of Contractubex gel. Figure 2A shows a representative example of a left deltoid professional tattoo before treatment, with 95% clearing after 5 laser treatments (Figure 2B).

In the control group, 55 patients with 68 tattoos completed the

study. Five patients dropped out from the study because 4 of them had defaulted follow-up and 1 patient was pregnant and stopped treatment. Among those 55 patients who had completed the study, there were 31 men and 24 women. Their ages ranged from 29 to 54 years with a mean age of 37.6 ± 6.2 years. The mean duration of the presence of the tattoos was 15.5 ± 5.9 years with a range of 6 to 28 years. They had received a mean of 5.4 ± 1.3 treatment sessions (range, 4–8) with a mean fluence of 4.1 ± 0.7 J/cm² (range, 3.6–4.8 J/cm²) and were able to achieve a mean of $80.4 \pm 11.3\%$ clearing rate (range, 60%–100%). Sixteen tattoos (23.5%) in 14 patients developed scarring, 4 patients (7.2%) had permanent hypopigmentation, and 5 patients (9%) had transient hyperpigmentation.

By applying the paired Student's *t* test, the Contractubex group had a statistically significant lower rate of scarring than the control group ($p < .05$). There was no significant difference in age, sex,

TABLE 1. Demographic Data

Variable	Group	
	Contractubex	Control
Number of patients	52	55
Number of tattoos	61	68
Sex (M/F)	32/20	31/24
Mean age (years)	37.7 \pm 6.8	37.6 \pm 6.2
Duration of tattoos (years)	16.1 \pm 5.5	15.5 \pm 5.9



Figure 2. (A) Left deltoid professional tattoo. (B) 95% clearing after five laser treatments.

fluence, treatment session, or clinical clearance between the two groups (Table 2).

Discussion

Lasers have revolutionized the treatment of tattoos in the past two decades. The history of treating tattoos with lasers can be dated back to the 1960s when Goldman and colleagues²¹ first reported the application of radiation from a Q-switched ruby laser on a tattoo of man. Unfortunately, the use of ruby laser on tattoos was curtailed by technical difficulties at that time. In the following 20 years, carbon dioxide and argon lasers were used to remove the implanted pigments of tattoos by vaporization of cutaneous layer and thermal denaturation of collagen.²²⁻²⁵ This gross tissue destruction method inevitably ended up with significant scarring. With the development of the concept of selective photothermolysis and the advancement of technology in Q-switched laser systems, tattoo ink can be removed effectively and safely nowadays.¹⁰⁻¹⁵ Since Reid and coworkers²⁶ published the first

successful selective removal of black tattoo ink by Q-switched ruby laser at 694 nm in 1983, other groups confirmed the role of Q-switched ruby laser in tattoo removal.²⁶⁻²⁸ Its strong affinity for melanin, however, frequently results in hypopigmentation that limits its treatment in Asian persons with dark skin. The Q-switched Nd:YAG 1,064-nm laser was shown to have less melanin absorption and deeper penetration and hence less scarring and dyspigmentation.^{10,13,16} There were two studies demonstrated that this laser system was effective with few complications in darkly pigmented skin.^{16,17} Nevertheless, local experience found that Chinese patients with Fitzpatrick types III-V required higher fluence to achieve the desirable clinical response, and nearly 25% of them developed scarring. The study conducted by Jones and associates¹⁷ involved eight darkly pigmented patients with amateur tattoos only. Grevelink and coworkers¹⁶ had an even smaller series of four patients with tribal tattoos. Both of these studies had too small patient numbers and too relatively easy amateur tattoos to

yield any meaningful conclusion. In this study, the scarring rate was 23.5% in the control group, which was significantly higher than these two studies. To reduce the scarring rate, one should use the smallest fluence that could achieve the clinical end point. The fluence used was dependent on the density of ink presented and observed clinical response. In general, the higher the density of ink presented, the less the fluence required. Therefore, lesser fluence was required during the first treatment session, and professional tattoos required less fluence compared to amateur tattoos as a result of higher ink density. Nevertheless, more scarring in professional tattoos than amateur tattoos was encountered. The reason might be that higher ink density could result in more energy delivered to an area and hence more scarring.

With the high percentage of scarring in Chinese patients, the need to reduce this complication is imminent. At the Burns Unit of Prince of Wales Hospital, Hong Kong, Contractubex gel is used in treating approximately 180 burn patients each year to prevent hypertrophic scar formation. Contractubex gel treatments are started immediately after burn wounds or donor sites have been healed up. The treatment continues for 3 to 4 months and ceases when there is no sign of hypertrophic scar formation. The authors found that the chance of hypertrophic scar formation re-

duced from 20% in general to 13%. Moreover, the duration of active scar and symptoms like itchiness and pain was also diminished. Approximately 6.8% patients developed light itchiness after the application of Contractubex gel, which was probably related to the pharmacologic action of active ingredients rather than allergy. These findings were demonstrated in other studies as well.¹⁸⁻²⁰ Willital and Heine²⁰ studied the effect of Contractubex gel on fresh scars after thoracic surgery in children and adolescents. They randomly assigned 45 young patients with fresh scars after thoracic surgery and found that there was a reduction of the increase of scar width in the Contractubex gel-treated group compared to the untreated group after 1 year of the treatment. Moreover, there were fewer hypertrophic or keloidal scars in the treated group, and there was no complication associated with the use of Contractubex gel.²⁰ That was the reason why Contractubex gel was selected in this trial. The exact mechanism of action of Contractubex gel is still unknown. In vitro studies have shown fibroblast-inhibiting properties of onion extract contained in Contractubex gel.^{29,30} In these studies, onion extract reduced the proliferative activity and the production of substances in the extracellular matrix. Consequently, this extract counteracts the fibroproliferative response in scars. It is believed that the flavonoids (quercetin and kaempferol) in

onion extract account for its fibroblast inhibition and other antiproliferative effects. Heparin, another active ingredient in Contractubex gel, may play a part too. In vitro experiments revealed that heparin was able to interact strongly with collagen molecules. It induced the formation of thicker fibrils, typical for a mature tissue, and also promoted intermolecular bonding in collagen.^{30,31} Therefore, heparin and onion extract affected scar development by their inhibitory effects on inflammatory processes, fibroblast proliferation, and the synthesizing capacity of fibroblasts.²⁹⁻³¹

This study confirmed that Contractubex gel was effective, safe, and simple to apply in the prevention of scarring in Chinese patients having laser removal of tattoos. It reduced the risk of scarring significantly from 23.5% to 11.5%. Contractubex gel is recommended to be used in dark skin patients receiving laser treatments of tattoos.

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