A Prospective Randomized Controlled Study of Oral Tranexamic Acid for Preventing Postinflammatory Hyperpigmentation After Q-Switched Ruby Laser

Harunosuke Kato, MD, Jun Araki, MD, Hitomi Eto, MD, Kentaro Doi, MD, Rintaro Hirai, MD, Shinichiro Kuno, MD, Takuya Higashino, MD, and Kotaro Yoshimura, MD*

BACKGROUND Postinflammatory hyperpigmentation (PIH) is the most common skin complication in Asians after invasive cosmetic treatments.

OBJECTIVE To determine whether oral tranexamic acid (TA) reduces the incidence of PIH after Q-switched ruby laser (QSRL) treatment.

METHODS AND MATERIALS Thirty-two Japanese women underwent QSRL treatment for senile lentigines on the face. They were randomly divided into two groups that did ($n = 15$) and did not ($n = 17$) receive oral TA treatment (750 mg/d) for the first 4 weeks after QSRL treatment. Nineteen participants had melasma-like maculae at baseline. Clinical and colorimetric assessments were performed at baseline and 2 and 4 weeks later.

RESULTS Pigmentation was effectively treated using QSRL at 2 weeks, but PIH was frequently seen at 4 weeks. There was no significant difference in the incidence of PIH between participants who received oral TA and those who did not. The presence of melasma did not influence the effectiveness of the treatment.

CONCLUSION Although oral TA has been reported to have depigmentation effects, it may not be effective for preventing PIH after QSRL. Considering the dosage and duration of treatment, an optimal protocol may be needed to induce the efficacy of this treatment to achieve the PIH-preventing effect of oral TA.

The authors have indicated no significant interest with commercial supporters.

Postinflammatory hyperpigmentation (PIH) is the most frequently observed complication associated with the use of Q-switched lasers for treating hyperpigmented lesions in Asians.[1] Fitzpatrick skin type affects the degree and frequency of PIH. In particular, patients with melasma and darker skin should be monitored for PIH.[1] Although a variety of treatments for PIH have been reported, a reliable method of prevention of PIH has not been established.

A plasmin inhibitor and lysine analog, trans-4-aminomethylcyclohexanecarboxylic acid (TA), prevents binding of plasminogen to the lysine binding site by interfering with the kringle structure of plasminogen molecules.[2] TA is often used to prevent blood loss during surgery, such as cardiac and oral surgery, joint replacement, and liver transplantation.[3] In addition, topical TA has been reported to prevent ultraviolet light (UV)-induced pigmentation in guinea pigs,[4] and TA injection showed an effect in treating melasma.[2] Topical TA inhibits UV-induced plasmin activity by preventing the binding of plasminogen to the lysine binding sites on keratinocytes.[2] This ultimately leads to a decrease in free arachidonic acid and its metabolites, such as prostaglandins,[5,6] decreasing melanocyte tyrosinase activity. Thus, TA can prevent UV-induced melanogenesis. Long-term use of oral TA has also been reported to be effective for melasma when administered for 3 months.[7]

*All authors are affiliated with Department of Plastic Surgery, University of Tokyo School of Medicine, Tokyo, Japan

ISSN: 1076-0512 • Dermatol Surg 2011;37:605–610 • DOI: 10.1111/j.1524-4725.2011.01957.x

We hypothesized that oral TA would be effective for the prophylaxis of laser-induced PIH. The purpose of this study was to assess the prophylactic effect of TA against PIH caused by Q-switched ruby laser (QSRL). We evaluated the incidence and degree of PIH that is frequently seen after QSRL treatment in Asian people with or without oral TA.

Materials and Methods

Study Design

This was a single-center, randomized, parallel-group study. Each participant received TA treatment or not in a randomized manner according to date of birth. The first participant was enrolled on June 30, 2007, and the last participant completed the study on March 12, 2009. Participants were observed until 28 days after QSRL treatment.

Participants

A total of 32 participants with senile lentigines (SLs) (≥ 5 mm in diameter in size) with or without melasma were included in this study. When the participant has multiple SLs, the largest one was chosen for treatment. Participants provided informed consent, and an appropriate institutional review board approved the protocol. All participants were Japanese women aged 23 to 77 (53 ± 14). Participants were randomly divided into two groups. One group received 750 mg/d of TA (Dai-ichi Pharmaceutical, Tokyo, Japan) for 4 weeks after QSRL treatment, and the other group did not receive TA after QSRL. Consequently, participants were classified into four categories (Table 1): group 1 ($n = 6$), participants with no melasma who did not receive TA treatment (ML−/TA−); group 2 ($n = 7$), participants with no melasma who received TA treatment (ML−/TA +); group 3 ($n = 11$), participants with melasma who did not receive TA treatment (ML + /TA−); group 4 ($n = 8$), participants with melasma who received TA treatment (ML + /TA +). People who were pregnant, had keloids, or had undergone concomitant treatments, immunosuppression, isotretinoin treatment, or skin resurfacing procedures within the preceding 3 months were excluded. During the 4 weeks after QSRL treatment, no treatments other than topical UV cream (zinc oxide, SPF = 15) were permitted.

QSRL Treatment

The pigmented area and surrounding normal skin were completely cleansed, and topical lidocaine cream was applied under an occlusive seal for 1 hour before the procedure for local anesthesia. For 694.5-nm QSRL (Model IB101, Niic Co. LTD, Tokyo, Japan) treatment, a spot size of 5 mm, a 1-Hz repeat rate, a pulse duration of 20 ns, and fluences from 4.0 to 5.0 J/m^2 were used. After laser treatment, topical gentamicin sulfate ointment was applied twice a day until the scale or thin crust disappeared (usually 5–7 days). Photographs were taken using a high-resolution digital camera (Canon EOS-D30, Canon, Tokyo, Japan), and spectrophotometry was performed as below for every participant at baseline and 2 and 4 weeks after treatment.

Spectrophotometric Analysis

As an objective measurement of the color of the designated lesion and its surrounding normal skin, a narrow-band reflectance spectrophotometer (Mexameter MX 16, Courage + Khazaka Electronic

TABLE 1. Summary of Patients

Group	*Participants,* n	*Age (Average ± Standard Deviation)*	*Melasma*	*Oral Tranexamic Acid*
1	6	48 ± 16	−	−
2	7	43 ± 11	−	+
3	11	55 ± 12	+	−
4	8	60 ± 11	+	+

GmbH, Köln, Germany) was used.[8] A measuring probe with a diameter of 5 mm emitted light at three predefined wavelengths (568 nm, green; 660 nm, red; and 880 nm, infrared) and measured the light reflected by the skin. Melanin values were measured using two wavelengths (660 and 880 nm) to achieve different absorption rates by the melanin granules. The melanin values were calculated as follows: melanin value = 500/log 5 × ([log infrared−reflection/red−reflection] + log 5). The original area of SLs was recorded by photographing, and the probe of the Mexameter was applied to the spot corresponding to the center of the original area. The average of three measured values was calculated after confirming a minimal variation within the three measurements and considered to be the absolute melanin value.

Evaluation of Changes in Pigmentation

The difference between the absolute melanin values of the SLs and the surrounding normal skin was referred to as the relative melanin value (RMV) of the SLs. RMV indicates the intensity of pigmentation relative to the normal skin around the SL. A negative RMV indicated that the measured spot was lighter than the control. Final improvement, effect of QSRL, and PIH after treatment were calculated as follows:

$$\Delta TI\,(\textit{total improvement}) = \textit{RMV at baseline} - \textit{RMV at 4 weeks}$$
$$\Delta EQL\,(\textit{effect of QSRL}) = \textit{RMV at baseline} - \textit{RMV at 2 weeks}$$
$$\Delta PIH\,(\textit{degree of PIH}) = \textit{RMV at 4 weeks} - \textit{RMV at 2 weeks}$$

Degree of PIH was calculated as above because it usually did not appear at 2 weeks but rather became apparent at 4 weeks.

Statistical Analysis

Measured values were expressed as means ± standard deviations. A t-test was used to compare the population means between groups after confirming that population variances were assumed to be equal. Differences were considered significant for $p < .05$.

Results

Clinical Course

In general, a thin, dark-colored crust formed after laser treatment that came off at approximately day 7. At 2 weeks, slight erythema was usually seen, and pigmentation of the SL had improved. At 4 weeks, PIH was frequently observed, although erythema was reduced. Representative cases are shown in Figure 1. RMV was significantly lower at 2 weeks in all groups, indicating that QSRL was effective against SLs. Thereafter, RMV tended to increase at 4 weeks, suggesting the occurrence of PIH (Figure 2). RMV at 4 weeks was less than that at baseline in most cases, indicating overall reduction in SL pigmentation.

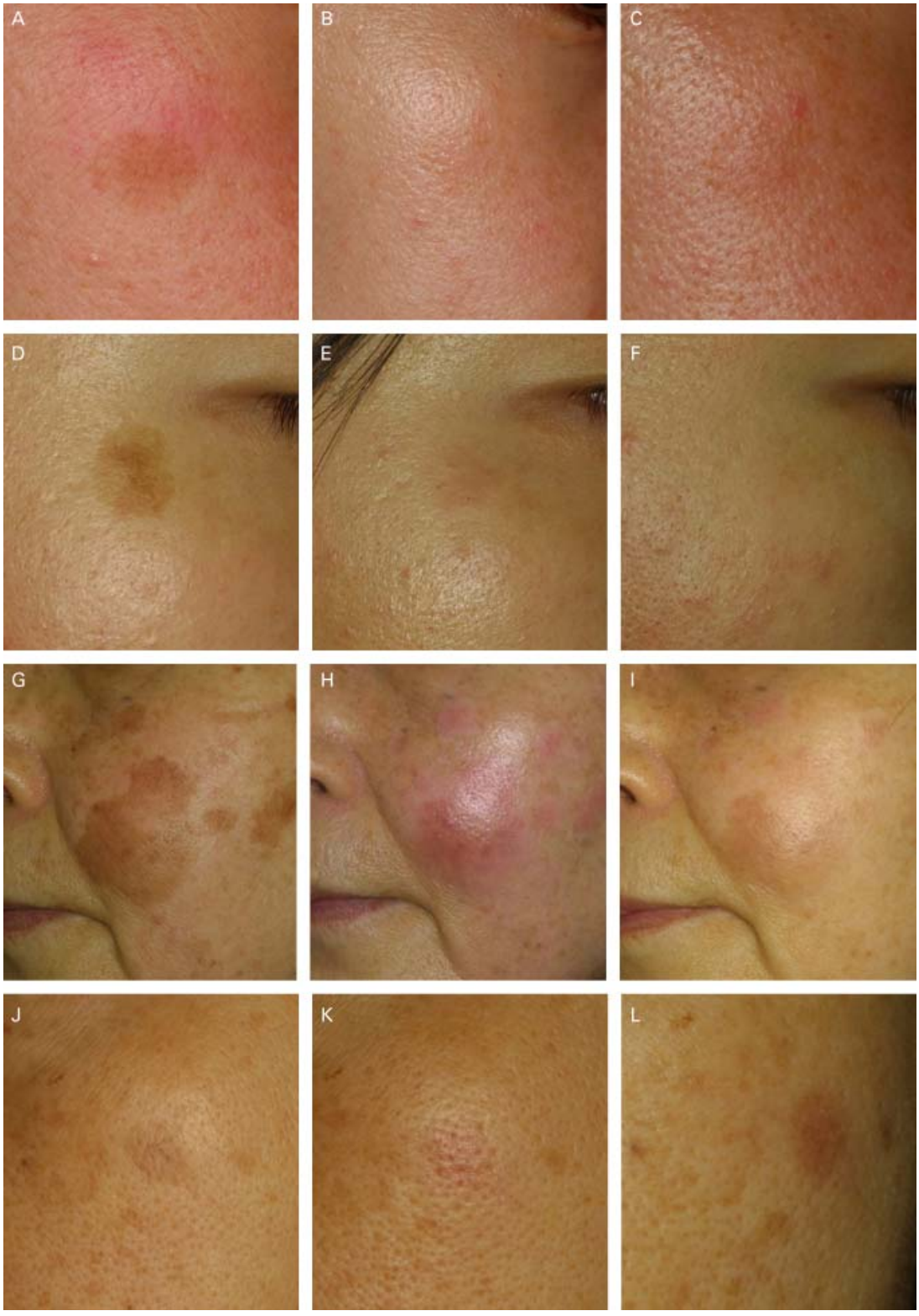
Morphometric Data and Analyses of Pigmentation

The ΔTI values of the groups (ML−/TA−, ML−/TA+, ML+/TA−, and ML+/TA+) were 4.2 ± 2.7, 5.6 ± 5.4, 5.2 ± 4.4, and 4.0 ± 5.5, respectively. The ΔEQL values of the groups (ML−/TA−, ML−/TA+, ML+/TA−, and ML+/TA+) were 3.8 ± 2.9, 3.6 ± 2.5, 3.5 ± 2.7, and 3.3 ± 2.8, respectively. The ΔPIH values of the groups (ML−/TA−, ML−/TA+, ML+/TA−, and ML+/TA+) were 3.8 ± 2.9, 3.6 ± 2.5, 3.5 ± 2.7, and 3.3 ± 2.8, respectively. There were no significance differences in ΔTI, ΔEQL, or ΔPIH between the groups.

Analyses of TA+ and TA− participants indicated that treatment with TA did not influence ΔTI, ΔEQL, or ΔPIH (Figure 3). The use of TA did not prevent induction of PIH in participant populations with or without melasma (Figure 3).

Discussion

PIH, which inflammation-upregulated melanin synthesis in epidermal melanocytes induces, is more commonly seen in populations with darker colored skin such as Asians than in Caucasians. Several paracrine factors derived from fibroblasts or


A
B
C
D
E
F
G
H
I
J
K
L

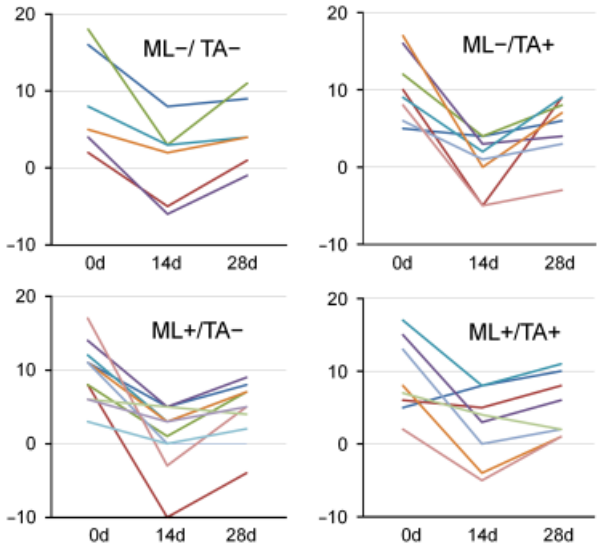


Figure 2. Sequential spectrophotometric data of the four groups. Relative melanin values were measured at baseline and 2 and 4 weeks after treatment. Each line indicates data of individual participants.

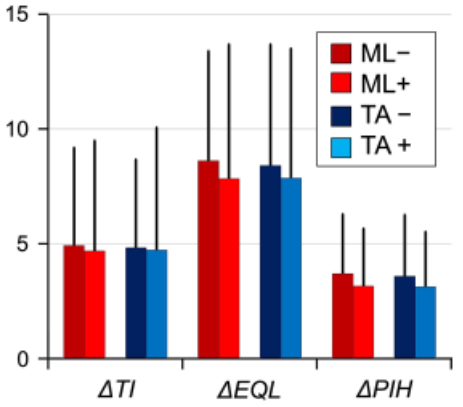


Figure 3. Comparative data of participants with (ML +) and without (ML−) melasma and of participants who took oral tranexamic acid (TA +) and those who did not (TA−). Δ*TI*: total improvement, Δ*EQL*: effects of Q-switch ruby laser, Δ*PIH*: degree of postinflammatory hyperpigmentation (PIH).

keratinocytes, many of which are associated with UV irradiation or inflammatory reactions, such as basic fibroblast growth factor, hepatocyte growth factor, stem cell factor, and interleukin-6, have been reported to stimulate melanogenesis.[9,10]

Q-switched laser treatment, especially QSRL, is known to frequently induce PIH, which is the most common adverse effect of cosmetic treatment in Asian populations. PIH occurred in approximately 40% of participants with Fitzpatrick skin types I to III treated with carbon dioxide (CO_2) resurfacing and in nearly all participants with Fitzpatrick skin types IV to VI.[11] Various treatments for PIH, such as Kojic acid, hydroquinone, Vitamin C, Vitamin E, topical steroids, thioctic acid (α-lipoic acid), glycolic acid, and azelaic acid, have been reported.[12] PIH has also been treated with combination therapies of retinoic acid and hydroquinone,[13–15] but there have been few reports regarding the prevention of PIH. A previous study used glycolic acid or hydroquinone as a pretreatment to prevent PIH before CO_2 laser resurfacing, but preventive effects were not detected.[16]

In this study, there were no statistical differences between the TA + and TA− groups in participants with or without melasma with regard to the degree of PIH after QSRL treatment, although there have been some reports indicating the depigmentation effects of TA. Hyperpigmentation of melasma significantly improves 12 weeks after oral treatment with 1,500 mg/d of TA and 3,000 mg/d of ascorbic acid,[7] and several non-English-language articles have reported positive effects of oral TA (750–1,500 mg/d for 8–16 weeks). Injection of TA (mean injection dose of 1.2 mg for 12 weeks) into skin with melasma was also reported to be effective.[2] We used an oral TA dose of 750 mg/d for 4 weeks for prophylactic purposes. Our dose and duration may not have been sufficient for preventing PIH. PIH occurs within 4 weeks after QSRL irradiation, and 4 weeks of oral TA treatment may not be long enough to induce and

Figure 1. Representative clinical course of the four groups. Participants were divided into four groups. Q-switch ruby laser (QSRL) irradiation was performed in participants without (group 1, A–C, 37-year-old woman; Group 2, D–F, 34-year-old woman) or with (group 3, G–I, 71-year-old woman; Group 4, J–L, 47-year-old woman) melasma (ML). Groups 2 and 4 received oral tranexamic acid (TA) from baseline for 4 weeks. Left (A, D, G, and J), middle (B, E, H, and K), and right (C, F, I, and L) columns were taken at baseline and 2 and 4 weeks after treatment, respectively. Postinflammatory hyperpigmentation after QSRL treatment on the face usually occurred after 2 to 4 weeks.

observe the melanogenesis-suppressing effect of oral TA. It is also possible that the small sample size resulted in the lack of statistically significant differences. It is known that Mexameter measurements can vary considerably according to placement in the lesion, so we recorded the original area, and the center of the area was measured at least three times until minimal variation within the last three measurements was confirmed.

QSRL is effective for treating a variety of hyperpigmented lesions, even in participants with dark skin,[1] although PIH is a frequent adverse effect. Our results showing negative effects of oral TA against post-QSRL PIH suggest that PIH should be prevented using other bleaching agents such as hydroquinone as a representative suppressor of melanin production and tretinoin as a representative accelerator of melanin discharge.

References

1. Sadighha A, Saatee S, Muhaghegh ZG. Efficacy and adverse effects of Q-switched ruby laser on solar lentigines: a prospective study of 91 patients with Fitzpatrick skin Type II, III, and IV. Dermatol Surg 2008;34:1465–8.
2. Lee JH, Park JG, Lim SH, Kim JY, et al. Localized intradermal microinjection of tranexamic acid for treatment of melasma in Asian patients: a preliminary clinical trial. Dermatol Surg 2006;32:626–31.
3. Mannucci PM, Levi M. Prevention and treatment of major blood loss. N Engl J Med 2007;356:2301–11.
4. Maeda K, Naganuma M. Topical *trans*-4-aminomethylcyclohexacarboxylic acid prevents ultraviolet radiation-induced pigmentation. J Photochem Photobiol Biol 1998;47:136–41.
5. Black AK, Greaves MW, Hensby CN, Plummer NA, et al. Increased prostaglandins E2 and F2alpha in human skin at 6 and 24 h after ultraviolet B irradiation (290- 320 nm). Br J Clin Pharmacol 1978;5:431–6.
6. Nordlund JJ, Collins CE, Rheins LA. Prostaglandin E2 and D2 but not MSH stimulate the proliferation of pigment cells in the primal epidermis of the DBA/2 mouse. J Invest Dermatol 1986;86:433–7.
7. Konishi N, Kawada A, Morimoto Y, Watake A, et al. New approach to the evaluation of skin color of pigmentary lesions using Skin Tone Color Scale. J Dermatol 2007;34:441–6.
8. Yoshimura K, Harii K, Masuda Y, et al. Usefulness of a narrow-band reflectance spectrophotometer in evaluating effects of depigmenting treatment. Aesthet Plast Surg 2001;25:129–33.
9. Burd A, Zhu N, Poon VK. A study of Q-switched Nd:YAG laser irradiation and paracrine function in human skin cells. Photodermatol Photoimmunol Photomed 2005;21:131–7.
10. Imokawa G. Autocrine and paracrine regulation of melanocytes in human skin and in pigmentary disorders. Pigment Cell Res 2004;17:96–110.
11. Goldberg DJ. Nonablative laser surgery for pigmented skin. Dermatol Surg 2005;31:1263–7.
12. Rigopoulos D, Gregoriou S, Katsambas A. Hyperpigmentation and melasma. J Cosmet Dermatol 2007;6:195–202.
13. Yoshimura K, Harii K, Aoyama T, Iga T. Experience with a strong bleaching treatment for skin hyperpigmentation in Orientals. Plast Reconstr Surg 2000;105:1097–108.
14. Yoshimura K, Momosawa A, Watanabe A, Sato K, et al. Cosmetic color improvement of the nipple-areola complex by optimal use of tretinoin and hydroquinone. Dermatol Surg 2002;28:1153–7.
15. Kurita M, Kato H, Yoshimura K. A therapeutic strategy based on histological assessment of hyperpigmented skin lesions in Asians. J Plast Reconstr Aesthet Surg 2009;62:955–63.
16. West TB, Alster TS. Effect of pretreatment on the incidence of hyperpigmentation following cutaneous CO2 laser resurfacing. Dermatol Surg 1999;25:15–7.

Address correspondence and reprint requests to: Kotaro Yoshimura, MD, Department of Plastic Surgery, University of Tokyo School of Medicine, 7-3-1, Hongo, Bunkyo-Ku, Tokyo 113-8655, Japan, or e-mail: yoshimura-pla@h.u-tokyo.ac.jp