Journal of Lasers in Medical Sciences

J Lasers Med Sci 2022;13:e16

Original Article

http://journals.sbmu.ac.ir/jlms

doi 10.34172/jlms.2022.16

Evaluation of Efficacy and Safety of Low-Fluence Q-Switched 1064-nm Laser in Infra-orbital Hyperpigmentation Based on Biometric Parameters

Shiva Alavi[1], Azadeh Goodarzi[2], Mohammad Ali Nilforoushzadeh[1], Parvin Mansouri[1*], Mohammad Amin Jafari[2], Somayeh Hejazi[1], Zahra Azizian[1]

[1]Skin and Stem Cell Research Center, Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Dermatology, Rasool Akram Medical Complex, Iran University of Medical Sciences (IUMS), Tehran, Iran

***Correspondence to**
Parvin Mansouri, Skin and Stem Cell Research Center, Tehran University of Medical Sciences, Email: mansouripr@yahoo.com

Received: May 19, 2021
Accepted: September 11, 2021
Published online April 12, 2022

Abstract

Introduction: Dark circles and wrinkles under the eyes are common cosmetic problems, caused by various conditions, especially aging and overproduction of melanin in the epidermis or dermis of the skin. Iin addition to the application of topical lightening agents, different types of lasers, especially the Q-Switched ND:YAG laser, have been used for the treatment of cutaneous hyperpigmentation. Because of a high prevalence of idiopathic eye dark circles (EDCs) or periorbital melanosis and a poor response to available therapies, we decided to evaluate the efficacy and safety of the Fractional QS 1064 nm ND:YAG Laser through a before-after trial.

Methods: 18-65-year-old patients with skin Fitzpatrick phototype of I-V and without any usage of a topical or systemic therapeutic regimen (2-4 weeks before the trial) were enrolled in the study. Each patient was treated with 6 sessions of the Fractional QS 1064 nm ND:YAG Laser at 2-week intervals and assessed for response and possible side effects or recurrences through 4 outcome measures, including Visoface-based color and erythema, melanin index and lightness (Before the fourth and sixth sessions of the therapy; also 1 week and 3 months after finishing the trial).

Results: The changes of Visoface-based color and erythema, the melanin pigment amount by the Mexameter (melanin index) and the degree of lightness by the Colorimeter of patients after 6 months of intervention were statistically significant ($P<0.001$).

Conclusion: The fractional QS 1,064 nm ND:YAG Laser is an effective and safe therapy in EDCs since objective outcomes like the reduction of the melanin index and improving lightness and subjective ones like the reduction of darkness and erythema were confirmed.

Keywords: Eyelids dark circle; Periorbital hypermelanosis; Q-switched 1064-nm laser; Hyperpigmentation; Hypermelanosis.

Introduction

Dark circles and wrinkles under the eyes are common and annoying cosmetic problems caused by various conditions, especially aging and overproduction of melanin in the epidermis or dermis of the skin.[1] Pigment and vascular structures may play important roles in developing eye dark circles (EDCs), but usually there is not an accurate classification of etiological and structural changes in EDCs. This classification could help dermatologists with better management of EDCs.[2] In dermatology, Pigmentation-related disorders are the third cause of disease with significant social and psychosocial problems which usually have a natural resistance to therapy. Skin lightening agents are used to target hyperactive and hyperplastic melanocytes or inhibit various stages of melanin synthesis.[3,4]

Checking the history of inflammatory disorders and skin phototype is the most important role for treating post-inflammatory hyperpigmentation in patients.[5-8] In addition to using topical lightening agents, different types of lasers, especially the Q-Switched ND: YAG laser, have been used for treating cutaneous hyperpigmentation. The Q-Switched ND: YAG laser is known as a selective photothermolysis system with a therapeutic effect on epidermal and dermal pigmentation and also vascular structures that can facilitate the migration of melanophages.[6,9-18] Therapeutic methods for post-inflammatory hyperpigmentation, melasma and nevic lesions through the Q-Switched ND: YAG laser have been shown to have a proper efficacy with minimum tissue-damage and side effects.[18-22] Because of a high prevalence of idiopathic EDCs or periorbital melanosis and its cosmetic importance and poor response to available therapies,[19-22] in this study, we decided to evaluate the efficacy, safety and satisfaction of Fractional QS 1,064 nm Nd:YAG laser treatment through a before-after trial.

Please cite this article as follows: Alavi S, Goodarzi A, Nilforoushzadeh MA, Mansouri P, Jafari MA, Hejazi S, et al. Evaluation of efficacy and safety of low-fluence q-switched 1064-nm laser in infra-orbital hyperpigmentation based on biometric parameters. *J Lasers Med Sci.* 2022;13:e16. doi:10.34172/jlms.2022.16.

Materials and Methods

The assessor, analyst and data processor were blinded in this trial, while the two other assessors, the physician and the patients knew the type of treatment. This before-after study included patients with EDCs, that were referred to dermatology clinic of Skin and Stem Cells Research Center in Tehran University of Medical Sciences (SSRC).

According to previous studies, the assessors estimated the efficacy of topical modalities in hyperpigmentation at about 10% and for the laser at about 40%. Considering 30% improvement in hyperpigmentation, power = 90% and $\alpha = 0.05$, the number of patients needed to treat was calculated about 27. Finally, given the probable failure of the patients to follow up, thirty-seven patients were enrolled in the study.

Eligibility Criteria

This clinical trial included patients with EDC, who were confirmed in terms of mental health by an expert psychologist, and they also met the inclusion criteria, including ages between 18 to 65 years, skin Fitzpatrick phototype of I-V and no usage of topical or systemic therapeutic regimen (from 2 and 4 weeks before the trial). These patients were enrolled in the study by using a simple convincing method.

The exclusion criteria in this study were patients who do not attend regular intervention and follow-up sessions, patients with any ulcer or infection in the intervention area and photosensitive dermatoses like lupus erythematosus, patients who have excessive caffeine intake (> 6 glass per 1 day), and patients with the recent low sleep period (less than which was routine in their lifestyle) and anemia.

Patient recruitment

All of the patients involved in this study were justified about the design and aim of the study and also probable side effects. The patients could leave the study for any reason whenever they desired. Informed consent was obtained from the patients.

Intervention and Follow-up

Each patient received 6 sessions of the Fractional QS 1064 nm Nd:YAG laser at 2-week intervals, and they were assessed for response and possible side effects or recurrences through 4 outcome measures including Visoface-based color and erythema, melanin index and lightness (Before fourth and sixth sessions of the therapy, also 1 week and 3 months after the last treatment session). All patients were photographed and objectively examined by Mexameter MX 18 and Colorimeter CL 400 systems at baseline and at the special times during the trial. For the reduction of pain before each therapeutic session, xylocaine-P cream was applied peri-orbitally. The HELIOS Fractional QS 1064 nm Nd:YAG laser was used with the frequency of 5 Hz, energy of 1000 J/cm^2, and Pass of 2-3. Given the fact that most Iranian people have skin type 3 and 4, the least invasive protocol was utilized for all patients, using the minimum effective setting of the laser device. Based on patient compliance and not having any complications, energy increased by 50 J/cm^2 in each consequent session up to maximum of 1200 J/cm^2. An eyeshield was utilized for all patients, as Mid-IR laser radiation can cause ocular injuries.[23] If moderate to severe erythema, ulcer, post-inflammatory hyper-pigmentation (PIH) or worsening of EDC occurred during the use of the laser, the primary investigator stopped the procedure and proper treatment like hydroquinone (HQ) based agents were applied.[24] Moreover, after each therapeutic session, it was proposed to use an ice pack for 10 minutes and then apply betamethasone ointment twice daily (for the reduction of inflammation) and zinc oxide ointment 3-4 times daily (for repairing) that continued for 2-3 days until the relief of erythema. Close adherence to the use of anti-solar creams was extremely recommended. In each session, patient satisfaction and probable side effects like erythema, bulla, ulcer, pain, burn, darkness and PIH were recorded as no, mild, moderate and severe.

In this clinical trial study, efficacy evaluation of the laser in pigmentary changes of EDC was performed using many methods. Lightness was assessed by Colorimeter CL 400 of the Multi Probe Adaptor System (MPA) and the Melanin index was assessed by Mexameter MX 18 of the MPA as objective outcome measures. Darkness degree and erythema, based on the photographs of Visoface, were assessed as subjective outcome measures and scored via the VAS (visual analogue scale) from 0 to 100.

Statistics and Data Analysis

Statistical analysis was performed by SPSS software (version 20.0). The one-way analysis of variance and Tukey HSD test were used to compare the data between the groups. P value less than 0.05 was considered statistically significant for all tests.

Results

The total number of the patients participating in this study was 37, out of whom 28 (4 male and 24 female) patients finished the trial, and their response, therapeutic side effects, and satisfaction with this treatment method were assessed. The average age of the patients in the intervention group was 38.40 ± 11.94 years (min: 19; max: 59). All patients had skin types 3 and 4, except 4 patients (10.8%) who exhibited skin type 2. Changes of Visioface-based color and erythema, the melanin pigment amount by the Mexameter (melanin index) and the degree of lightness by the Colorimeter of patients after 6 months of the trial were statistically significant ($P < 0.001$) (Table 1). Changes of Visioface-based color and erythema, the melanin pigment amount by the Mexameter (melanin index) and the degree of lightness by the Colorimeter of

Table 1. Efficacy of Fractional QS 1,064 nm Nd:YAG Laser for Treating Eye Dark Circles in a 6-Month Period (a 2.5-Month Period of Therapy and a 3-Month Period of Follow-up After the Last Treatment Session)

Variables	N	Mean ± SD		Mean Percent Change (%) ± SD	*P* Value
		Before the Intervention Initiation	After 3 Months of the Last Intervention Session		
Visioface color	28	-6.052 ± 2.62	-3.79 ± 1.94	-38.03 ± 24.01	< 0.001
Visioface erythema	28	405.57 ± 72.24	361.54 ± 66.18	-10.01 ± 11.53	< 0.001
Melanin index	28	260.85 ± 76.85	202.53 ± 66.46	-22.15 ± 10.60	< 0.001
Colorimeter (lightness)	28	-11.22 ± 11.01	3.07 ± 10.95	160.13 ± 303.13	< 0.001

A *P* value less than < 0.001 was considered statistically significant in the intervention group of patients.

female patients after 3 months of the last intervention session were statistically significant ($P < 0.001$), but in men, only the melanin pigment amount and the degree of erythema showed statistically significant difference before and after 3 months of the last intervention session of the trial ($P < 0.03$) (Figures 1, 2; Table 2). None of the patients reported any severe side effects during the treatment and follow-up period; only mild erythema or irritation was reported in few patients, which did not last more than few days. Also, most of the patients (86%) were highly satisfied with the treatment results.

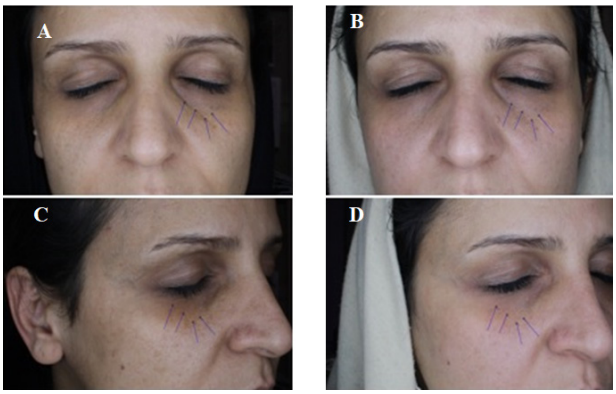

Figure 1. Infra-orbital Hyperpigmentation Treatment Process on the Right and Left Sides Based on Visioface Results (A,C) Before the Treatment Initiation on Day (0) and (B,D) 3 Months After the last Treatment Session.

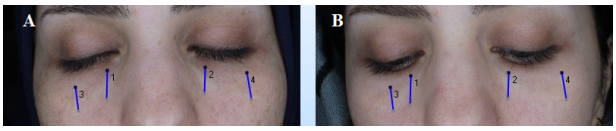

Figure 2. Closed-up Focusing in the Infra-orbital Hyperpigmentation (A) Before the Treatment Initiation and (B) 3 Months After the Last Treatment Session.

Discussion

Periorbital hyperpigmentation has different causes such as genetics, post-inflammatory hyperpigmentation due to atopic dermatitis, periorbital edema, excessive vascularity and aging.[25] Also, it has been mentioned that dermal melanization or post-inflammatory hemodynamic congestion with a prominent role of melanin and hemoglobin is very important in this context.[26] However, histologic evaluations have exhibited that there is a poor relation between melanosis reduction in the skin and improvement of EDCs.[27,28] Thus, it can be claimed that the mechanism of improvement in periorbital hyperpigmentation is not quite well known and more histologic studies integrated with clinical trials are needed.

There are different topical treatment agents for this problem, such as hydroquinone, kojic acid, azelaic acid and retinoic acid, and chemical peeling and laser therapy are the most common treatment modalities.[29-31] Various lasers are used such as Q-switched ruby laser (694 nm) for Fitzpatrick skin type 1-3, Q-switched Alexandrite (skin types 4 and 5), Nd:YAG laser (1064) for skin types 5 and 6 and ablative laser resurfacing.[3,16] Other lasers including Pulsed Dye laser, Diode laser, 1320 Nd-YAG and intense pulsed light fractional lasers such as CO_2 and Erb:YAG lasers act by controlled tissue injury. In a study by Momosawa et al, 3 sessions of the ruby laser with tretinoin and hydroquinone were used for 6 weeks, and 15 out of 18 patients got satisfying results.[24] In another study in Japanese people, the efficacy of the ruby laser was approved.[27]

The Lutronic dual pulsed Q-switched Nd: YAG laser was the first and only FDA-approved Q-switched laser for the treatment of melasma.[20-22] However, this approach requires multiple sessions in each week during the treatment period, and also it shows a higher recurrence rate in comparison to other treatment modalities (64-81%).[32] Combining this approach with the long-pulsed Nd: YAG laser or Intense pulsed light might be beneficial for decreasing the recurrence rate.[33,34] Also, Ustuner et al combined the Q-switched Nd: YAG laser with microneedling for the treatment of recalcitrant melasma and observed promising results.[35] However, in the present study, the Fractional QS 1064 nm Nd:YAG Laser was applied alone, along with supportive ointments to decrease erythema after laser therapy.

In a study by Xu et al, 30 women were treated with a low-fluence Q-switched 1064-nm laser at 4.2 J/cm^2 with 3.5 mm spot size and pulse duration of 8 ns at 3-4-day intervals. The melanin deposition was assessed by reflectance confocal microscopy in vivo, a narrow-band reflectance spectrophotometer, and a skin hydration measurement instrument. A significant decrease of the melanin index was observed in the upper dermis.[36] In a review by Agrawal

Table 2. Efficacy of Fractional QS 1064 nm Nd:YAG Laser Response in the Treatment of Eye Dark Circles in a 6-Month Period of Trial Based on Gender (a 2.5-Month Period of Therapy and a 3-Month Period of Follow-up After the Last Treatment Session)

Variables		N	Mean ± SD		Mean Percent Change (%) ± SD	*P* Value
			Before the Intervention Initiation	3 Months After the Last Intervention Session		
Visioface color	Male	4	-6.71 ± 4.67	-5.01 ± 2.80	-17.19 ± 32.90	0.263
	Female	24	-5.94 ± 2.27	-3.57 ± 1.75	-41.50 ± 21.14	<0.001
Visioface erythema	Male	4	466.25 ± 63.19	426 ± 62.93	-8.69 ± 4.70	0.031
	Female	24	395.46 ± 73.34	350.80 ± 61.50	-10.23 ± 12.36	<0.001
Melanin index	Male	4	225 ± 86.90	175.5 ± 61.35	-20.80 ± 5.28	0.032
	Female	24	266.84 ± 75.41	207.04 ± 67.42	-22.37 ± 11.30	<0.001
Colorimeter (lightness)	Male	4	-9.55 ± 11.15	1.5 ± 13.07	201.03 ± 181.25	0.089
	Female	24	-11.5 ± 11.302	3.34 ± 10.86	153.31 ± 321.31	<0.001

et al, it was shown that Q–switched Nd:YAG could be a good modality to treat periorbital hyperpigmentation.[37] However, in a recent systematic review by Michelle et al, it was concluded that laser treatments are only mildly to moderately efficient in vascular and pigmented types of periorbital hyperpigmentation.[25] Also, a recent clinical trial compared this treatment modality with carboxy therapy and showed that less invasive, less expensive and more effective results can be achieved by carboxy therapy in comparison to the Q–switched Nd: YAG laser.[38] On the other hand, Mhatre et al claimed that the Q–switched Nd: YAG laser shows variable and inconsistent results in the treatment of facial pigmentary lesions in such a way that some patients may show aggregation of pigmentation, so the patient should be warned about it before starting the treatment and it should be mentioned in informed consent.[39] However, in the present study, none of the patients observed significant side effects such as PIH, and only few patients had mild erythema or irritation.

The current pilot study presented promising positive clinical outcomes regarding the effectiveness of Q-switched Nd: YAG by the assessments of biometric parameters. These days one of the most popular lasers for pigmentation is QS 1064 nm Nd:YAG. We used the fractional laser method for patients with EDCSs in 6 months' duration (2.5 months' duration of intervention and around 3 months' duration of follow-up), which resulted in a statistically significant improvement of pigmentary changes with a good safety profile and patients' satisfaction. Although the contribution of the female-male ratio was not proportionate, females, unlike males, exhibited significant changes in all indices. Furthermore, given the fact that nearly 90% of patients exhibited skin types 3 and 4, which are the most prevalent skin type among Iranian people, the outcomes of this study were not analyzed separately for each skin type. The outcome of this clinical trial study showed the beneficial effect of Q-switched Nd:YAG by evaluating its effect by biometric parameters.

In the present study, this treatment approach was utilized for only adult patients, so it is recommended to evaluate it in different age groups. Also, it is beneficial to record the duration and etiology of periorbital hyperpigmentation and their relation with treatment success, which should be evaluated in future clinical trials. On the other hand, it is beneficial to assess the effects of the moderation of low-density lipoproteins in serum, which characterize the severity of atherosclerosis and can cause the deposition of bilirubin under the eyes. Furthermore, for more accurate results and recommendations, it is better to conduct studies with larger sample size, equivalent gender and age distribution, and parallel-group designs.

The authors of this study have worked on various aspects of melasma and other pigmentary disorders for better management and therapy,[40-45] and now it seems that this hot topic could answer some questions and concerns about one of the most encountered pigmentary disorders in the field of dermatology, namely periorbital hyperpigmentation or dark circles under the eyes.[44]

Conclusion

On the basis of our study, the Fractional QS 1064 nm Nd:YAG laser is an effective and safe therapy in EDCs since objective outcomes like the reduction of the melanin index and improvement in lightness and subjective ones such as the reduction of darkness and erythema were confirmed and observed after the trial. Although there was a significant response regarding the reduction of the melanin index and erythema of DEC in men, the final color and darkness did not show a significant difference after the trial. A safety profile and satisfaction with treatment were appropriate.

Acknowledgement

The funding of this study was prepared by the Skin and Stem Cells Research Center (SSRC) at Tehran University of Medical Sciences (TUMS), Tehran, Iran. Also, the authors would like to thank Rasoul-e-Akram Medical Complex Clinical Research Development Center (RCRDC) for its technical and editorial assistance.

Conflict of Interests

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics Considerations

The current study was registered at the IRCT (Iranian Registry of Clinical Trials) and the study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (IRCT registration number: IRCT20080901001159N31; Ethics committee reference number: IR.TUMS.REC 1394.854).

Financial Support

Skin and Stem Cells Research Center (SSRC) at Tehran University of Medical Sciences (TUMS), Tehran, Iran.

Informed consent

Informed consent was obtained from the patients for participating in the study, and the right of the subjects was protected.

References

1. Mitsuishi T, Shimoda T, Mitsui Y, Kuriyama Y, Kawana S. The effects of topical application of phytonadione, retinol and vitamins C and E on infraorbital dark circles and wrinkles of the lower eyelids. *J Cosmet Dermatol*. 2004;3(2):73-75. doi:10.1111/j.1473-2130.2004.00070.x.
2. Huang YL, Chang SL, Ma L, Lee MC, Hu S. Clinical analysis and classification of dark eye circle. *Int J Dermatol*. 2014;53(2):164-170. doi:10.1111/j.1365-4632.2012.05701.x
3. Sarkar R, Arora P, Garg KV. Cosmeceuticals for hyperpigmentation: what is available? *J Cutan Aesthet Surg*. 2013;6(1):4-11. doi:10.4103/0974-2077.110089
4. Bandyopadhyay D. Topical treatment of melasma. *Indian J Dermatol*. 2009;54(4):303-309. doi:10.4103/0019-5154.57602
5. Davis EC, Callender VD. Postinflammatory hyperpigmentation: a review of the epidemiology, clinical features, and treatment options in skin of color. *J Clin Aesthet Dermatol*. 2010;3(7):20-31.
6. Desai SR. Hyperpigmentation therapy: a review. *J Clin Aesthet Dermatol*. 2014;7(8):13-17.
7. Saedi N, Ganesan AK. Treating hyperpigmentation in darker-skinned patients. *J Drugs Dermatol*. 2013;12(5):563-567.
8. Grimes PE. Management of hyperpigmentation in darker racial ethnic groups. *Semin Cutan Med Surg*. 2009;28(2):77-85. doi:10.1016/j.sder.2009.04.001
9. Na SY, Cho S, Lee JH. Intense pulsed light and low-fluence Q-switched Nd: YAG laser treatment in melasma patients. *Ann Dermatol*. 2012;24(3):267-273. doi:10.5021/ad.2012.24.3.267
10. Ho S, Yeung C, Chan N, Shek S, Kono T, Chan H. A retrospective analysis of the management of acne post-inflammatory hyperpigmentation using topical treatment, laser treatment, or combination topical and laser treatments in oriental patients. *Lasers Surg Med*. 2011;43(1):1-7. doi:10.1002/lsm.21010
11. Kim S, Cho Kh. Treatment of procedure-related postinflammatory hyperpigmentation using 1064-nm Q-switched Nd: YAG laser with low fluence in Asian patients: report of five cases. *J Cosmet Dermatol*. 2010;9(4):302-306. doi:10.1111/j.1473-2165.2010.00527.x
12. Arora P, Sarkar R, Garg VK, Arya L. Lasers for treatment of melasma and post-inflammatory hyperpigmentation. *J Cutan Aesthet Surg*. 2012;5(2):93-103. doi:10.4103/0974-2077.99436
13. Oram Y, Akkaya AD. Refractory postinflammatory hyperpigmentation treated fractional CO2 laser. *J Clin Aesthet Dermatol*. 2014;7(3):42-44.
14. Zawar VP, Agarwal M, Vasudevan B. Treatment of Postinflammatory Pigmentation Due to Acne with Q-Switched Neodymium-Doped Yttrium Aluminum Garnet In 78 Indian Cases. *J Cutan Aesthet Surg*. 2015;8(4):222-226. doi:10.4103/0974-2077.172196
15. Rivas S, Pandya AG. Treatment of melasma with topical agents, peels and lasers: an evidence-based review. *Am J Clin Dermatol*. 2013;14(5):359-376. doi:10.1007/s40257-013-0038-4
16. Sofen B, Prado G, Emer J. Melasma and post inflammatory hyperpigmentation: management update and expert opinion. *Skin Therapy Lett*. 2016;21(1):1-7.
17. Morais OOd, Lemos ÉFL, Sousa MCdS, Gomes CM, Costa IMC, Paula CDRd. The use of ablative lasers in the treatment of facial melasma. *An Bras Dermatol*. 2013;88(2):238-242. doi:10.1590/S0365-05962013000200009
18. Kim YJ, Whang KU, Choi WB, Kim HJ, Hwang JY, Lee JH, et al. Efficacy and safety of 1,064 nm Q-switched Nd: YAG laser treatment for removing melanocytic nevi. *Ann Dermatol*. 2012;24(2):162-167. doi:10.5021/ad.2012.24.2.162
19. Sahni K, Kassir M. Dermafrac™: An innovative new treatment for periorbital melanosis in a dark-skinned male patient. *J Cutan Aesthet Surg*. 2013;6(3):158-160. doi:10.4103/0974-2077.118420
20. Nilforoushzadeh MA, Alavi S, Heidari-Kharaji M, Hanifnia AR, Mahmoudbeyk M, Karimi Z, et al. Biometric changes of skin parameters in using of microneedling fractional radiofrequency for skin tightening and rejuvenation facial. *Skin Res Technol*. 2020;26(6):859-66. doi.org/10.1111/srt.12887
21. Nilforoushzadeh MA, Zolghadr S, Heidari-Kharaji M, Alavi S, Mahmoudbeyk M. A comparative study of the efficacy of fractional neodymium-doped yttrium aluminum garnet (Nd: YAG) laser therapy alone and in combination with erbium: YAG laser therapy: tracing and objective measurement of melanin index in macular amyloidosis. *Lasers Med Sci*. 2020;35(5):1171-1177. doi:10.1007/s10103-020-02954-y
22. Alavi S, Abolhasani E, Asadi S, Nilforoushzadeh M. Combination of Q-switched Nd: YAG and fractional Erbium: YAG lasers in treatment of melasma: a randomized controlled clinical trial. *J Lasers Med Sci*. 2017;8(1):1-6. doi:10.15171/jlms.2017.01
23. Parver DL, Dreher RJ, Kohanim S, Zimmerman P, Garrett G, Devisetty L, et al. Ocular injury after laser hair reduction treatment to the eyebrow. *Arch Ophthalmol*. 2012;130(10):1330-1334. doi:10.1001/archophthalmol.2012.1988
24. Momosawa A, Kurita M, Ozaki M, Miyamoto S, Kobayashi Y, Ban I, et al. Combined Therapy Using Q-Switched Ruby Laser and Bleaching Treatment with Tretinoin and Hydroquinone for Periorbital Skin Hyperpigmentation in Asians. *Plast Reconstr Surg*. 2008;121(1):282-288. doi:10.1097/01.prs.0000293869.00522.ec
25. Michelle L, Foulad DP, Ekelem C, Saedi N, Mesinkovska NA. Treatments of periorbital hyperpigmentation: A systematic review. *Dermatol Surg*. 2021;47(1):70-74. doi:10.1097/DSS.0000000000002484
26. Eberlin S, Del Carmen Velazquez Pereda M, de Campos Dieamant G, Nogueira C, Werka RM, de Souza Queiroz ML. Effects of a Brazilian herbal compound as a cosmetic eyecare for periorbital hyperchromia ("dark circles"). *J Cosmet Dermatol*. 2009;8(2):127-35.
27. Watanabe S, Nakai K, Ohnishi T. Condition Known as "Dark Rings Under the Eyes" in the Japanese Population is a Kind of Dermal Melanocytosis Which can be Successfully Treatedby Q-Switched Ruby Laser. *Dermatol Surg*. 2006;32(6):785-9. doi:10.1111/j.1524-4725.2006.32161.x

28. WEST TB, ALSTER TS. Improvement of Infraorbital Hyperpigmentation following Carbon Dioxide Laser Resurfacing. *Dermatol Surg*.1998;24(6):615-6. doi:10.1111/j.1524-4725.1998.tb04216.x
29. Roh MR, Chung KY. Infraorbital dark circles: definition, causes, and treatment options. *Dermatol Surg*. 2009;35(8):1163-71. doi:10.1111/j.1524-4725.2009.01213.x
30. Freitag FM, Cestari TF. What causes dark circles under the eyes? *J Cosmet Dermatol*. 2007;6(3):211-5. doi:10.1111/j.1473-2165.2007.00324.x
31. Pissaridou MK, Ghanem A, Lowe N. Periorbital Discolouration Diagnosis and Treatment: Evidence-Based Review. *J Cosmet Laser Ther*. 2020;22(6-8):217-225. doi:10.1080/14764172.2021.1899238
32. Saad A. News in the treatment of periorbital hyperpigmentation. *J Dermatol & Ther.* 2017;1(106):20-3.
33. Omi T, Yamashita R, Kawana S, Sato S, Naito Z. Low Fluence Q-Switched Nd: YAG Laser Toning and Q-Switched Ruby Laser in the Treatment of Melasma:A Comparative Split-Face Ultrastructural Study. *Laser Ther*. 2012;21(1):15-21. doi:10.5978/islsm.12-OR-03
34. Cymbalista N, Torezan L, Osorio N, Mattos R, Valente N, editors. Treatment Of Eyelid Hyperpigmentation With Qs Ruby Laser And Intense Pulsed Light Device. *Lasers Surg Med*. 2002;30:66.
35. Ustuner P, Balevi A, Ozdemir M. A split-face, investigator-blinded comparative study on the efficacy and safety of Q-switched Nd:YAG laser plus microneedling with vitamin C versus Q-switched Nd:YAG laser for the treatment of recalcitrant melasma. *J Cosmet Laser Ther*. 2017;19(7):383-390. doi:10.1080/14764172.2017.1342036
36. XU TH, YANG ZH, LI YH, Chen JZ, Guo S, Wu Y, et al. Treatment of infraorbital dark circles using a low-fluence Q-switched 1,064-nm laser. *Dermatol Surg*. 2011;37(6):797-803. doi:10.1111/j.1524-4725.2011.01956..x
37. Agrawal S. Periorbital hyperpigmentation: Overcoming the challenges in the management. *Nepal J Dermatol, Venereol Leprol*. 2018;16(1):2-11.
38. Nilforoushzadeh MA, Heidari-Kharaji M, Alavi S, Zolghadr S, Mahmoudbeyk M, Nikkhah N. Comparison of carboxy therapy and fractional Q-switched ND: YAG laser on periorbital dark circles treatment: a clinical trial. *Lasers Med Sci*. 2021;36(9):1927-1934. doi:10.1007/s10103-021-03274-5
39. Mhatre M, Malkud S, Mysore V. Efficacy and safety of Q-switched Nd: YAG laser in the treatment of facial pigmentary lesions: A retrospective observational study. *Iran J Dermatol*. 2021;24(1):24-31.
40. Lajevardi V, Ghayoumi A, Abedini R, Hosseini H, Goodarzi A, Akbari Z, et al. Comparison of the therapeutic efficacy and safety of combined oral tranexamic acid and topical hydroquinone 4% treatment vs. topical hydroquinone 4% alone in melasma: a parallel-group, assessor-and analyst-blinded, randomized controlled trial with a short-term follow-up. *J Cosmet Dermatol*. 2017;16(2):235-242. doi:10.1111/jocd.12291
41. Behrangi E, Baniasadi F, Esmaeeli S, Hedayat K, Goodarzi A, Azizian Z. Serum iron level, ferritin and total iron binding capacity level among nonpregnant women with and without melasma. *J Res Med Sci*. 2015;20(3):281-283.
42. Goodarzi A, Behrangi E, Sadeghzadeh-Bazargan A, Roohaninasab M, Hosseini-Baharanchi FS, Shemshadi M, et al. The association between melasma and iron profile: a case-control study. *Russ Open Med J*. 2020;9(2):1-5.doi:10.15275/rusomj.2020.0202
43. Ehsani A, Noormohammadpour P, Goodarzi A, Shahshahani MM, Hejazi SP, Hosseini E, et al. Comparison of long-pulsed alexandrite laser and topical tretinoin-ammonium lactate in axillary acanthosis nigricans: A case series of patients in a before-after trial. *Caspian J Intern Med*. 2016;7(4):290-293.
44. Roohaninasab M, Sadeghzadeh-Bazargan A, Goodarzi A. Effects of laser therapy on periorbital hyperpigmentation: a systematic review on current studies. *Lasers Med Sci*. 2021;36(9):1781-1789. doi:10.1007/s10103-020-03241-6
45. Ghassemi M, Hosseinchi S, Seirafianpour F, Dodangeh M, Goodarzi A. Non-alcoholic fatty liver and lipid profile status in patients with melasma: A case-control study. *J Cosmet Dermatol*. 2021;20(11):3656-3660. doi:10.1111/jocd.14014