

ORIGINAL ARTICLE

The efficacy of enoxolone in reducing erythema and pain after laser treatment: A randomized split-face pilot study

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Abstract

Background: Enoxolone, derived from licorice, possesses potent anti-inflammatory, and antioxidant properties. However, its effectiveness in alleviating post-laser reactions has not been extensively studied.

Aims: This randomized split-face pilot study aimed to evaluate the effects of enoxolone on skin following laser treatment.

Patients/Methods: Ten healthy subjects underwent non-ablative 1550nm Er:Glass fractional laser treatment and then randomly applied a moisturizer without enoxolone on one side of the face and a dermo-cosmetic formular containing 2% enoxolone mixed with the same moisturizer on the other side. The erythema index (EI), clinician's erythema assessment (CEA), and pain scores were recorded at 30min, 60min, and 24h posttreatment.

Results: The group treated with enoxolone showed significantly lower EI and CEA compared to the control group at 24h posttreatment. Additionally, pain scores were notably reduced in the enoxolone-treated group 30min after treatment.

Conclusions: This study suggests that dermo-cosmetic formular containing 2% enoxolone is effective in reducing erythema and pain following laser treatment.

KEYWORDS

enoxolone, erythema, laser therapy

1 | INTRODUCTION

Enoxolone, also known as glycyrrhetic acid (GA), is a compound derived from the licorice plant (*Glycyrrhiza glabra*).¹ Present in licorice roots as the glycoside glycyrrhizin (GL), it can be converted into GA by beta-D-glucosidase in the intestines or liver upon ingestion.² Notably, enoxolone is one of the most effective anti-inflammatory agents found in licorice. Its anti-inflammatory properties were first highlighted in a 1958 study by Finney,³ and subsequent research

has continued to support these findings.³ Enoxolone significantly reduces inflammatory markers such as TNF-alpha and inhibits the activity of NF-kB. It is renowned for its calming effects on the skin, reducing skin sensitivity, and boasts antioxidant properties. These qualities make it suitable for applications in skin whitening and improving uneven skin tones.⁴

Various dermatological techniques, including laser, radiofrequency, and ultrasound, are employed for skin rejuvenation and tightening. Certain laser treatments aim to stimulate skin

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regeneration by delivering energy to the epidermis and dermis, causing microthermal coagulation. These methods have proven effective in cosmetic enhancements like pore size reduction, skin texture improvement, and skin tone unification.⁵ Effective anesthesia is crucial for patient safety and satisfaction during these procedures, and various topical anesthetics are employed to alleviate pain associated with these treatments. Posttreatment effects of laser procedures can include temporary pain, erythema or redness, and swelling.⁶ These reactions are generally mild, and conservative treatments such as emollients and cold compresses can be effective in minimizing the adverse effects of skin rejuvenation laser therapy. This pilot study aims to explore the efficacy of dermo-cosmetic formular containing 2% enoxolone in facilitating skin recovery following non-ablative 1550nm Er:Glass fractional photothermolysis treatment.

2 | MATERIALS AND METHODS

2.1 | Study design

This study was structured as a split-face pilot study. Due to the clear visibility of erythema following laser treatment, neither randomization nor blinding procedures was utilized. Approval for the study was granted by the Chung-Ang University Hospital Institutional Review Board (IRB No. 2302-018-544), and all participants provided written informed consent after being fully informed about the risks and benefits of the procedure.

2.2 | Subject selection

Participants in this pilot study should be aged between 19 and 70 years, in good physical health, and seeking aesthetic enhancement in the facial region. They willingly signed informed consent forms, agreed to photographic documentation, and were chosen for their ability to be monitored and followed throughout the trial.

The exclusion criteria for participants included a history of hypersensitivity reactions to the investigational product or its components, patients with facial dermatitis, skin infections, or open wounds on the face, individuals currently using functional cosmetics for wrinkle improvement or similar products other than basic items like moisturizers during the trial, pregnant or lactating women, and those planning to become pregnant during the trial period.

2.3 | Treatment

In this clinical trial, topical anesthetic EMLA cream (AstraZeneca, Södertälje, Sweden) was applied to the entire face 30 min before the laser treatment. This was followed by the administration of

a 1550nm erbium glass fractional laser (SELLAS-EVO®, Dinona, Daejeon, Korea) to the entire face (spot density 100 PPA, pulse energy level 20mJ, 1 pass) by the same treating investigator dermatologist. Immediately after the laser treatment, participants applied the provided enoxolone-free moisturizer (Atobarrier cream®, Ameropacific, Seoul, Korea) to one side of their face (control group). On the other side, the same moisturizer, along with a dermo-cosmetic formular containing 2% enoxolone (EtatPur, Naos Inc. France) was applied (treatment group). The application of enoxolone was randomized to one side of the face using an online sequence generator (<http://www.graphpad.com/quickcalcs/index.cfm>). Starting immediately after the laser treatment, three additional applications of the products were performed at approximately 3-h intervals.

2.4 | Efficacy assessment

Clinical digital photographs were captured immediately following the laser treatment and at intervals of 30min, 60min, and 24h posttreatment. The erythema index (EI) was measured using a Mexameter® (Courage & Khazaka GmbH, Cologne, Germany). These measurements were conducted consistently in the frontal cheek area, delineated by the intersection of vertical lines drawn from both eye corners and the corner of the mouth, by the same investigating dermatologist. Three repeated measurements were taken, and their average value was recorded. EI measurements occurred immediately following the laser treatment, and at 30min, 60min, and 24h posttreatment.

An independent dermatologist, not involved in the laser treatment, conducted the clinician's erythema assessment scale (CEA). This scale quantifies the degree of facial erythema. A blinded dermatologist evaluated the patient on a scale ranging from 0 to 4 in five stages: Grade 0 indicated clear skin with no erythema, Grade 1 denoted almost clear skin with slight redness, Grade 2 represented mild erythema with definite redness, Grade 3 indicated moderate erythema and marked redness, and Grade 4 signified severe erythema with fiery redness.

The pain numeric rating scale, a visual analogue scale (VAS), was assessed by subjects through questioning at various time points: during the laser treatment, immediately after, and 30min, 60min, and 24h later. The examiner recorded the pain scores, which ranged from 0 (no pain) to 10 (severe pain), based on the subjects' responses.

2.5 | Safety assessment

During laser treatment and at each subsequent visit, vital signs were checked, and physical examinations were performed. Adverse events (AEs) related to the non-ablative 1550nm fractional laser and the topical moisturizer and ampoule containing enoxolone were evaluated throughout the entire study period.

2.6 | Statistical analysis

We compared the metabolic activities of the treatment groups and controls using one-way analysis of variance (ANOVA) and Tukey's multiple-comparison posttest. Differences between groups were considered significant at a p value of <0.005 . Statistical analyses were conducted using GraphPad Prism 8.0 (GraphPad Software, Inc., CA, USA).

3 | RESULTS

A total of 10 healthy subjects were enrolled and completed the study period. Of these subjects, three were male and seven were female, with an average age of 52.55 ± 15.95 years (ranging from 29 to 60 years).

Immediately after the laser treatment (baseline), the EI was 339.7 ± 81.2 in the control group and 322.8 ± 76.8 in the treatment group. The EI decreased over time in both groups, with a more pronounced reduction in the treatment group. At 24 h posttreatment, the EI was significantly lower in the treatment group at 227.2 ± 66.69 compared to 258.8 ± 73.97 in the control group (Figure 1A).

The CEA remained consistent at 3.1 ± 0.54 in both the treated and control groups, indicating a moderate level of erythema immediately after the laser treatment (baseline). Similar to the EI, the CEA also decreased over time in both groups, with a more pronounced reduction in the treatment group. At 60 min and 24 h posttreatment, the CEA was significantly lower in the treatment group compared to the control group. At 24 h, the control group exhibited slight redness with a score of 1.1 ± 0.7 , whereas the treatment group showed a score of 0.4 ± 0.66 , indicating almost no erythema (Figure 1B).

For the VAS, both sides were rated at 5.5 ± 1.86 immediately after the laser treatment. A significant difference was observed from 30 min posttreatment (3.1 ± 1.51 vs. 1.6 ± 1.36 ; control group vs. treatment group) (Figure 1C).

We compared the overall average values of the indicators assessed immediately after the laser treatment, at 30 min, 60 min, and 24 h, across a total of four evaluations. The average values of both EI, measured by a Mexameter, and CEA, assessed by a dermatologist, were significantly lower in the treatment group. This indicates a significant reduction in erythema following laser treatment with the application of an enoxolone-containing ampoule. In terms of post-procedural pain, the overall average of VAS scores was also significantly lower in the treatment group, indicating a significant decrease in pain following laser treatment with the application of an enoxolone-containing ampoule. (Figure 2). Representative photographs of subject are provided in Figure 3.

Throughout the entire trial period, there were no AEs related to the laser procedures or the application of moisturizer and enoxolone ampoule, with the exception of post-procedural erythema and pain.

4 | DISCUSSION

Licorice (*Glycyrrhiza glabra*), a widely utilized ingredient in confectionery such as cookies and candies, is celebrated for its sweet and mellow flavor. This flavor is derived from a concentrated extract obtained from the plant's roots. Predominantly cultivated in Southern Europe and Asia, licorice has a long-standing history as a medicinal remedy.⁷ A key constituent of the licorice root is glycyrrhizin (GL), a triterpenoid saponin glycoside, which is a major water-soluble component. GA or enoxolone, the primary metabolite of GL, emerges when GL undergoes hydrolysis, resulting in two pentacyclic triterpenoids: 18- α and 18- β GA.² Research has revealed that GA exhibits a vast array of biological and pharmacological activities. Notably, it is recognized for its anti-inflammatory, antioxidant, antiviral, antimicrobial, antitumor, antidiabetic, hepatoprotective, cardiovascular-protective, and neuroprotective effects.⁴

In the field of dermatology, enoxolone has garnered significant attention. Numerous studies have underscored its efficacy in treating various skin disorders, an outcome attributed to its

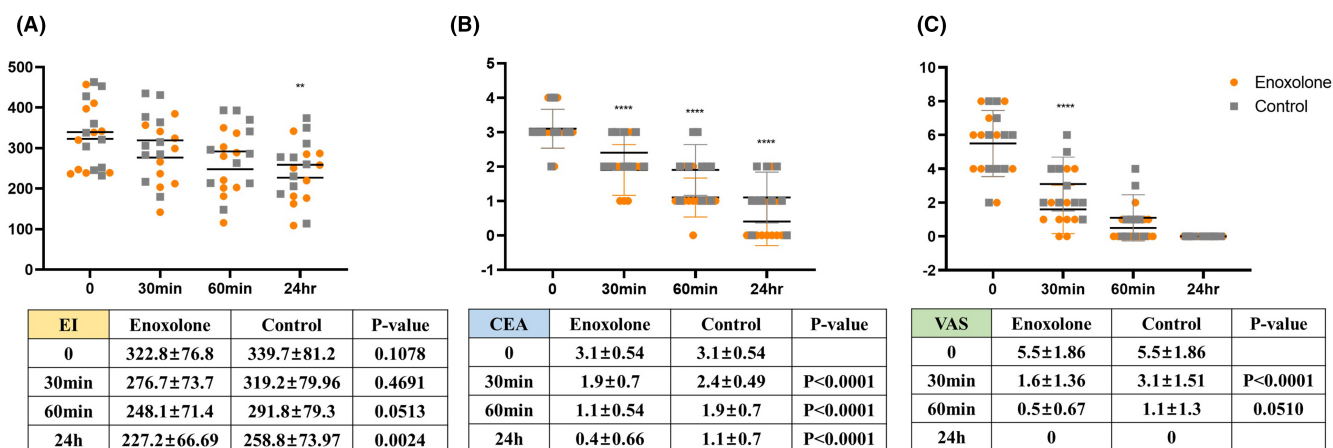


FIGURE 1 Evaluations of (A) Erythema index, (B) Clinician Erythema Assessment Scale, and (C) the Pain Visual Analog Scale at follow-up. **, $p < 0.01$; ****, $p < 0.0001$.

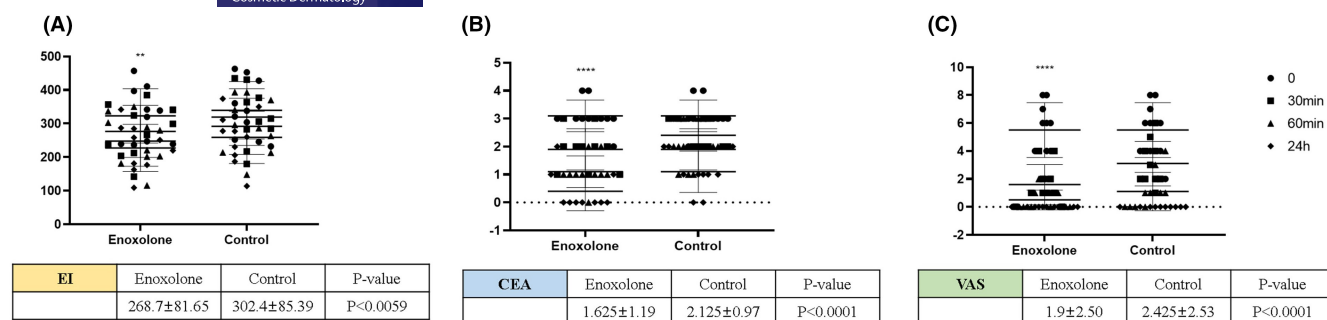


FIGURE 2 Average comparison of (A) Erythema index (B) Clinician Erythema Assessment Scale, and (C) the Pain Visual Analog Scale between the enoxolone treatment group and the control group. **, $p < 0.01$; ***, $p < 0.0001$.



FIGURE 3 Clinical photographs of a representative subject. After laser treatment, the treatment side received a dermo-cosmetic formular containing 2% enoxolone with moisturizer, and the control side received only moisturizer.

anti-inflammatory, antioxidant, and antimicrobial properties.⁸ The anti-inflammatory mechanism of enoxolone is primarily linked to its capacity to inhibit pro-inflammatory mediators. Studies have demonstrated that enoxolone can reduce the production of nitric oxide (NO), prostaglandin E2 (PGE2), leukotriene B4 (LTB4), interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-10 (IL-10). Furthermore, it impedes the translocation of nuclear factor (NF- κ B) regulated gene products and obstructs TNF- α -induced inflammatory responses.⁹⁻¹³ In the clinical dermatologic fields, enoxolone exhibits an effectiveness in reducing erythema in rosacea patients.¹⁴

Based on the established efficacy of enoxolone, we undertook this study anticipating that it would enhance outcomes in photothermolysis laser treatments for skin rejuvenation. The study employed a split-face design, revealing that enoxolone application significantly reduced the EI and scores. Additionally, patients experienced a notable decrease in pain immediately after the procedure. Fractional laser treatment via photothermolysis is renowned for its

effectiveness in treating photoaging, enlarged pores, and uneven skin tone.¹⁵ Nonetheless, fractional laser treatments often result in post-procedure erythema and pain, causing discomfort and making patients reluctant to opt for such treatments. Therefore, physicians are encouraged to consider a variety of posttreatment strategies, such as topical agents and light-emitting diodes, to alleviate discomfort and enhance the overall effectiveness of laser therapy.¹⁶⁻¹⁸ There have been reports indicating the effectiveness of conventional topical treatments such as petrolatum, water spray, epidermal growth factor ointment, panthenol, madecassoside, copper-zinc-manganese, and fusidic acid in controlling reactions like mild erythema following fractional laser treatment.¹⁹⁻²² The findings of this study suggest that dermo-cosmetic formular containing 2% enoxolone application can effectively reduce recovery time after fractional laser treatments.

The anti-inflammatory properties of GA are comparable to the effects of cortisol. GA's structure is akin to that of corticoid

hormones produced in the adrenal cortex. The cortisol-like effect of GA is predominantly due to its inhibition of phospholipase A2.^{23,24} Prior research indicates that GA suppresses the activity of enzymes like 5-lipoxygenase and cyclooxygenase, as well as cyclic adenosine monophosphate phosphodiesterase. It also inhibits the 12-O-tetradecanoylphorbol-13-acetate-induced glucose transport. These actions impede the expression of pro-inflammatory genes, thereby curtailing inflammatory processes such as edema and erythema. As a result, GA exerts its anti-inflammatory effects by reducing the production of inflammatory cytokines and preventing the transformation of arachidonic acid into pro-inflammatory leukotrienes.²⁵⁻²⁷

This study validated the efficacy of dermo-cosmetic formular containing 2% enoxolone in mitigating laser-induced erythema and pain. However, the study was limited by its small participant pool and the absence of double-blind methodology. Therefore, future research should focus on conducting large-scale, randomized, blinded studies to more definitively establish enoxolone's effects on laser responses. Furthermore, it is crucial to elucidate the anti-inflammatory mechanisms of enoxolone in reducing post-laser reactions. It is deemed necessary to conduct in vitro confirmation studies to determine whether the mechanism of erythema alleviation after laser treatment aligns with the known anti-inflammatory mechanism of enoxolone.

AUTHOR CONTRIBUTION

Sun Young Choi: the drafting of the paper. **Young Gue Koh:** revising it critically for intellectual content, conception and design. **Yoon Jin Roh:** analysis and interpretation of the data. **Kui Young Park:** conception and design, final approval of the version to be published.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, PKY, upon reasonable request.

ETHICS STATEMENT

This study's protocol was approved by the Institutional Review Board of Chung-Ang University Hospital (IRB Approval No. 2302-018-544). All participants signed a photo release consent form authorizing the reproduction and distribution of any images collected during the study.

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