Clinical Assessment of the Safety and Effectiveness of Nonablative Fractional Laser Combined with Transdermal Delivery of Botulinum Toxin A in Treating Periocular Wrinkles

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Summary: The upper and lower eyelids are traditionally contraindicated for subcutaneous botulinum toxin A (BTX) injection because of possible complications. We assessed the clinical safety and effectiveness of nonablative fractional laser (NAFL) combined with transdermal delivery of BTX in the treatment of periocular wrinkles. Thirty patients who had periocular wrinkles were treated with 1,565-nm NAFL in combination in the left periocular area and normal saline in the corresponding area of the right eye. VISIA skin detector was used to photograph and compare the changes induced by treatment. We also recorded the comfort level of the patients. All 28 patients could tolerate the pain caused by the laser treatment and showed no apparent discomfort during percutaneous drug delivery. No chromatosis or ptosis of upper eyelids occurred after the treatment. We used VISIA to detect changes at 1 week, 1 month, 3 months, and 6 months, respectively, after the treatment. The periocular wrinkles decreased, and the flabbiness of eyelids was significantly reduced. The upper and lower eyelids are traditionally contraindicated for subcutaneous BTX injection, as it may cause complications. The treatment combining 1,565-nm NAFL and transdermal delivery of BTX can decrease periocular wrinkles and flabbiness while avoiding complications to the greatest extent. None of the 28 patients who had completed the treatment suffered from complications or adverse effects; all were satisfied with the treatment outcome. (Plast Reconstr Surg Glob Open 2016;4:e1004; doi: 10.1097/GOX.0000000000001004; Published online 30 August 2016.)

Aging is often first evinced by periocular wrinkles. Periocular wrinkles are the first wrinkles in the face. The cardinal symptoms include flabbiness of upper eyelids, crow’s feet, and wrinkles and flabbiness of lower eyelids. Traditional treatment for this condition is surgical, which results in pain and long postoperative recovery period, often with unsatisfactory outcome.

Botulinum toxin (BTX) is a potent neurotoxin protein derived from the Clostridium botulinum bacterium. It exerts its effect at the neuromuscular junction by inhibiting the release of acetylcholine, which causes temporary chemical denervation. The emergence of BTX revolutionized facial rejuvenation and periocular wrinkle reduction. It has definitive clinical effect in treating crow’s feet, one of its first indications in cosmetic surgery. However, BTX injection into upper and lower eyelids for wrinkle reduction should proceed with great caution; in fact, it is usually contraindicated. Ablative laser (e.g., carbon dioxide fractional laser) may decrease periocular wrinkles to some extent. However, for patients of the Mongolian race, the treatment by ablative fractional laser may result in such complications as chromatosis and prolonged erythema, if improper postoperative care occurs. On the other hand, the nonablative fractional laser (NAFL) can penetrate the epidermis and reach the corium without significant epidermal injury. In addition, it can control the size of heat coagulation holes to within 50 to 70 μm, so that the skin can regenerate within 24 hours. As a result, adverse reactions, such as chromatosis, are rare, and erythema can resolve completely within 72 hours. Therefore, it seems to be an optimal transdermal method. Recently, we found that combining...
the NAFL with transdermal delivery of BTX is safe and effective for periorcular wrinkles, especially wrinkles and flabbiness of upper and lower eyelids.

Our research prospectively assessed the safety and effectiveness of combining the 1,565-nm (NAFL) with transdermal delivery of BTX for periorcular wrinkles. We used VISIA skin detector to collect the data on posttreatment periorcular wrinkles in 4 return visits and compared the photographs before and after treatment. Patients also gave feedback on their level of satisfaction on the treatment outcome. VISIA is a detector to assess the situation of skin and give precise data, which include wrinkles, pores, spots, skin texture, ultraviolet A/ultraviolet B dark spots, porphyrins etc. The data collected show the skin condition, which is the higher score the better with comparison to people in the same age group.

SUBJECTS

Clinical Data
We selected 30 patients (both men and women) with different degrees of periorcular wrinkles and skin flabbiness.

Inclusion Criteria
Patients were 35 to 60 years old, with Fitzpatrick skin levels III to IV, and had not received BTX injection in the treatment region over the previous 6 months.

Exclusion Criteria
Patients with any of the following conditions were excluded from the study: infection in the target area; periorcular injection of BTX within the past 6 months; deep laser ablation within 1 year; skin level V or VI; poor skin regenerative capacity; cicatrix; HIV; hepatitis; weak immunity; pregnancy; lactation; strong sensitivity to BTX; carrying antibodies against BTX; and allergy to milk proteins.

TREATMENT

BTX A
Hundred units per bottle (Botox, Allergan Company, Calif.).

Fractional Laser
One thousand five hundred sixty-five–nanometer NAFL (Crown of the King, Lumenis Company) to treat the crow’s feet in the area of upper and lower eyelids and outer canthus wrinkles.

Procedure
After routine disinfection, using the 1,565-nm (NAFL) to treat the periorcular area covering the upper eyelid, outer canthus, temporal area, lower eyelid, and inner canthus, with the treatment density of 100 to 200 and energy of 30 to 50 mJ for once, without repeating of illumination spot. The face was covered with sterile gauze. Dilute 100 U BTX with 5mL normal saline. Then, spray 5 to 15 U solution in the periorcular area of the patient’s left eye, and spray normal saline in the corresponding area of the right eye as control.

Postoperative Care
Covered with sterile mask to retain moisture for 15 minutes; compress with an ice pack. Covered the face on the same day of treatment and used regular skin care product on the next day.

Follow-up
Follow-up visits in 1 week and 1 to 6 months after initial treatment. Photographs taken before and after treatment were compared. Pretreatment measurements on VISIA skin detector were used as the baseline. During the follow-ups, bilateral areas (treatment vs control) were compared to determine the effectiveness.

Assessment of Changes
During each follow-up, we compared the number of wrinkles with the pretreatment value (Student t test, \( p < 0.05 \)). In addition, we also assessed muscle tone of the upper eyelid in the treatment area by self-report of the patient.

RESULTS

Safety
All 30 patients could tolerate the pain caused by the fractional laser treatment and showed no apparent discomfort during percutaneous drug delivery. No chromatosis or ptosis of upper eyelid occurred after the treatment.

Treatment Effects
Twenty-eight of the 30 patients completed the study. The VISIA skin detector detected the wrinkles and skin flabbiness in the treatment area before and after the treatment. Based on the assessment of the improvement in overall facial beauty (Global Aesthetic Improvement Scale; Table 1), as well as improvement of the wrinkles, obtained from the VISIA data before and after the treatment, the treatment significantly improved periorcular wrinkles and skin flabbiness. The decreases on the treatment (left) side over different periods are 33% ± 8% (first week), 37% ± 8% (first month), 35% ± 8% (second month), 31% ± 8% (third month), 27% ± 8% (fourth month), 21% ± 8% (fifth month), and 16% ± 8% (sixth month). The decreases on the control (right) side are 17% ± 8% (first week), 19% ± 8% (first month), 18% ± 8% (second month), 16% ± 8% (third month), 13% ± 8% (fourth month), 11% ± 8% (fifth month), and 10% ± 8% (sixth month). After treatment, 3 patients were greatly satisfied (improvement: >40%), 22 patients quite satisfied (improvement: 37–39%), and 3 patients satisfied (improvement: 26%–35%). There were no obvious adverse reactions (like chromatosis or homme rouge) after the treatment. The patients were more satisfied with the left side (treatment) compared with the right side (control) (Figs. 1–2).

DISCUSSION

Our study indicates that the new treatment for periorcular wrinkles by combining 1,565-nm (NAFL) and
transdermal delivery of BTX gained high level of patient satisfaction. Although the mechanism of transdermal delivery of BTX is unclear, clinical reports on wrinkle treatment with intradermal BTX injection have suggested that it could mitigate the risk of neutralizing antibodies while retaining good efficacy and safety.\(^1\) Currently, there is no universally effective treatment for wrinkles and skin flabbiness of upper and lower eyelids. Thus, the treatment plan is developed by doctors based on the condition of individual patients.\(^2\) Most patients cannot suffer and are unwilling to accept traditional surgery and its side effects, such as lacrimal gland prolapse, excessive levator contraction,\(^3\) or the complications because of carbon dioxide fractional laser. Compared with nonablative laser, CO\(_2\) laser treatment is more painful\(^4\) and 92% of the patients will develop postinflammatory hyperpigmentation. It takes more than 5 weeks for the hyperpigmentation to disappear.\(^4\) In this regard, there are no complications such as pigmentation and erythema. Our combination treatment is a safe and effective new alternative.

In Table 1, we use VISIA to detect the effect of treatment at 1 week, 1 month, 2 months, 3 months, and 6 months after the treatment, and the effect reaches the best results in the first 3 months and will decay along the time. Because of different situations of involved patients, such as age, skin texture, different aging process, and genetic factor, the effect and maintenance time will be different. Even so, the patients still have great satisfaction. Periocular wrinkles of patients reduced by 33% on average 1 week after treatment. BTX is effective for crow’s feet in different degrees, comparable with the report in another study.\(^5\) Most of the patients were middle aged or young. They are appropriate candidates for the single course of treatment, as it causes no loss of working time. The pain during treatment is bearable. The average recovery period was 2 days.\(^6\) There was almost no complication, and the cost of the treatment was affordable.

A previous study\(^4\) compared the effect of intramural injection of BTX versus saline and reported no significant change in size of pores or sebum secretion.\(^8\) The authors speculated that microlesion caused by the sy-

### Table 1. Satisfaction Evaluation of Patients in Both Treatment Groups

| Time          | -1 | Void | Slightly Improved | Significantly Improved | Totally Improved | Score |
|---------------|----|------|-------------------|------------------------|------------------|-------|
| First week    | 5  | 0    | 23                | 0                      | 0                | 51    |
| First month   | 5  | 0    | 25                | 0                      | 1                | 55    |
| Second month  | 4  | 0    | 24                | 0                      | 0                | 52    |
| Third month   | 6  | 0    | 22                | 0                      | 0                | 50    |
| Sixth month   | 10 | 0    | 18                | 0                      | 0                | 46    |

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![Fig. 1. Images show the wrinkle degree in periocular area of patient’s left eye and right eye before the treatment. The 2 pictures below show the wrinkle degree after the 1,565-nm NAFL treatment and then spraying Botox in the left eye and spraying normal saline in the corresponding area in the right eye as control.](image-url)
ringe needle, rather than BTX, underlay the observed improvement in skin texture and tightness. Because the treatment of (NAFL) can repair the wound surface and smooth wrinkles, 1,565-nm laser not only improves the skin texture and color of stretch marks but also helps tighten the atrophy parts and smooths the band continuously. Therefore, we conducted a split-face study. Although treatment with saline injection improved wrinkles and flabbiness of the treatment region, the BTX-treated side presented a better efficacy and higher level of patient satisfaction.

Laser-assisted transdermal delivery of BTX has a stringent requirement on the laser penetration depth. Insufficient penetration results in ineffective treatment, whereas excessive penetration may lead to skeletal muscle paralysis. The choice of appropriate penetration depth is particularly important in treating upper and lower eyelids. We will investigate the correlation between BTX penetration into muscles and muscular paralysis.

In summary, combining 1,565-nm (NAFL) with transdermal delivery of BTX can reduce periocular wrinkles to a large extent, which has gained a high level of patient satisfaction. This method could also significantly reduce the risk of complications in the upper and lower eyelids caused by BTX injection, hence expanding the range of indications for BTX injection. In the future, we will further study the optimal dosage and the time window of sustained efficacy.

Fig. 2. Images show the wrinkle degree in periocular area of patient’s left eye and right eye before the treatment. The 2 pictures below show the wrinkle degree after the 1,565-nm NAFL treatment and then spraying Botox in the left eye and spraying normal saline in the corresponding area in the right eye as control.

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PATIENT CONSENT
The patients provided written consent for the use of their image.

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