



Treatment of lateral canthal rhytides with a medium depth chemical peel with or without pretreatment with onabotulinum toxin type A: a randomized control trial

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ABSTRACT

Background: Combination therapies used to treat the photoaged skin have become more popular as studies demonstrate greater efficacy and improved clinical outcomes compared to single treatment modalities.

Objectives: To evaluate the safety and effectiveness of treating the lateral canthal rhytide complex with a Jessner's and 35% TCA peel with and without pretreatment with BTX-A.

Methods: Twenty-six subjects with Fitzpatrick skin types I–III were randomized to receive treatment of their lateral canthal rhytide complex with a Jessner's and 35% TCA peel with or without pretreatment with BTX-A. A single blinded dermatologist assigned a lateral canthal wrinkle score of subjects' at baseline and week 8–10. **Results:** Comparison between the two treatment groups demonstrated that the group receiving combination treatment had significantly greater improvement in wrinkle reduction as compared to the group only receiving the chemical peel ($P = 0.002$). In addition, there was no significant association between skin type and treatment groups ($P = 0.11$).

Conclusions: These findings suggest that treating the lateral canthal rhytide complex with a combination of BTX-A followed by Jessner's and 35% TCA peel is more effective than chemical peel alone. These results are independent of skin type and demonstrate an additional treatment strategy for lateral canthal rhytides.

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Introduction

Lateral canthal rhytides, commonly referred to as crow's feet, are wrinkles of the lateral periorbital skin that are caused by contraction of the orbicularis oculi muscles (Lowe et al., 2005); they commonly affect women and contribute to an aged appearance. Repetitive movement over time induces atrophy of overlying skin and subcutaneous tissue compounded by pigmentary and textural changes brought on by chronic photodamage. To improve the appearance of this region, a variety of procedures from the cosmetic armamentarium may be employed singly or more frequently in combination: chemical peels, injectable botulinum toxins and dermal fillers, nonablative and ablative laser treatments, and a diverse array of topical agents (Tierney and Hanke, 2010).

Onabotulinum toxin type A (onaBTX-A) is extensively used in clinical practice to treat the hyperdynamic facial muscles that can create rhytides (Lowe et al., 2005). Injection into the muscles causes a reversible immobilization of muscle contraction by inhibiting acetylcholine release

from the cholinergic nerve terminal innervating the muscle (Lowe et al., 2005). OnaBTX-A not only relaxes the overactive muscles that produce dynamic wrinkles, but it can also be used as an adjunctive procedure to supplement resurfacing procedures like chemical peeling (Tung et al., 2011). By reducing activity of specific muscle groups with onaBTX-A before peeling, the overlying skin is less subject to the deleterious effects of repetitive movement (Tung et al., 2011). In this reduced kinetic state, healing can progress relatively undisturbed, and new collagen production will be more uniform (Tung et al., 2011).

Chemical peels are used for a variety of therapeutic indications, including facial rhytides, pigmentary changes, textural irregularities, and precancerous skin lesions (Monheit, 2001; Tung et al., 2011). They produce controlled exfoliation and damage of the epidermis and variably affect the dermis, depending on the peel type (Tung et al., 2011). Medium depth peels such as trichloroacetic acid (TCA) initially cause necrosis of the epidermis as well as all or part of the papillary dermis with attendant inflammation of the reticular dermis (Monheit, 2001; Tung et al., 2011). During the regeneration phase, the treated skin is shed followed by re-epithelialization and stimulation of collagen synthesis in the dermis (Monheit, 2001; Tung et al., 2011). The combination of Jessner's superficial peel with 35% TCA medium strength peel is designed to produce rejuvenation in a well-tolerated and

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Grade 0 = no wrinkles
 Grade 1 = mild wrinkles
 Grade 2 = moderate wrinkles
 Grade 3 = severe wrinkles

Fig. 1. Facial Wrinkle Severity Scale (FWSS). Grade 0 = no wrinkles. Grade 1 = mild wrinkles. Grade 2 = moderate wrinkles. Grade 3 = severe wrinkles.

reproducible manner (Landau, 2006; Tung et al., 2011). After this peel, improvement of skin qualities including sallowness, atrophy, and fine rhytides can be expected (Tung et al., 2011). This combination peel is frequently used to treat mild to moderate photoaging in skin types I–III due to its predictable clinical benefits and minimal risk of complications (Landau, 2006; Tung et al., 2011).

Combination therapies used to rejuvenate photoaged skin have become more popular as there is growing evidence to support greater efficacy and improved clinical outcomes compared with single treatment modalities. Our study compares the safety and efficacy of medium depth chemical resurfacing (Jessner's and 35% TCA peel) with and without adjunctive administration of onabTX-A in the treatment of mild to moderate rhytides in the lateral canthal region.

Methods

Study design

This study was a rater blinded, randomized controlled trial. After attaining approval for this study by the Loyola University Health System Institutional Review Board, patients were recruited via the clinicaltrials.gov website and from the outpatient dermatology clinic in La Grange, Illinois.

Subject selection

Twenty-six subjects were enrolled in this study. Included subjects could be 30 to 75 years old with a skin type from I to III in good general health and with a mild to moderate lateral canthal rhytide complex of at least 1 on the four-point facial wrinkle severity scale (FWSS) (Fig. 1). Exclusion criteria included pregnancy and lactation, prior treatment in the periorbital region with botulinum toxin injections within the previous six months, ablative laser resurfacing (previous six months), nonablative skin tightening procedure (previous six months), medium-to-deep chemical peels or dermabrasion (previous six months), temporary hyaluronic acid soft-tissue augmentation

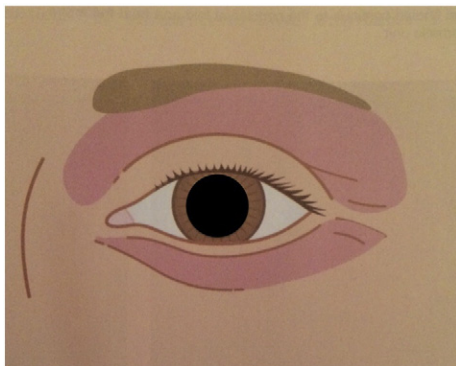


Fig. 2. The designated areas indicate where to start and stop peeling in the periocular region.

material (prior year), semi-permanent (poly-L-lactate or calcium hydroxylapatite) soft tissue augmentation material (prior two years), any permanent soft tissue augmentation material, and any surgical lifting procedure. Also excluded were persons planning to receive any of the above cosmetic procedures within the subsequent six months and individuals with active infections of the face; allergies to albumin, Aquaphor (Beiersdorf, Hamburg, Germany), or petrolatum ointment; a history of neuromuscular disorders; or a bleeding diathesis.

Study procedures

At the screening and initial treatment visit, subjects' medical history and Fitzpatrick skin type were recorded. Baseline photographs were also obtained, and a blinded physician assigned a lateral canthal wrinkle score using the four-point FWSS (Fig. 1). Subjects were then randomized by a computer program to one of two groups: group A received pretreatment with onabTX-A before application of the combined chemical peel of Jessner's solution to the entire face followed by 35% TCA only to the upper and lower eyelids (Fig. 2); group B received treatment with the chemical peels alone. Patients randomly assigned to group A received onabTX-A injections to their lateral canthal wrinkles at the baseline visit. One week after onabTX-A injections, group A patients returned to clinic to receive application of the chemical peels. Those randomly assigned to group B received application of the chemical peels one week after their baseline visit. Wound care instructions were reviewed with subjects both before and after their chemical peels. The same dermatologist performed all procedures to avoid inter-physician variability in technique.

At weeks 1, 4, and 10 after application of chemical peels, subjects were seen in follow-up for photography. Blinded FWSS ratings were made at week 10 based on evaluation of photographs. At each visit, adverse events and any changes to medications were recorded. Over the counter topical steroids preparations (hydrocortisone 1% ointment) were recommended for "spot" treatment in any subjects with excess focal erythema. All data was collected at Loyola University Health System, in the division of Dermatology.

OnabTX-A injection technique

Areas to be treated were cleansed with 70% alcohol; 7.5 units of onabTX-A (reconstituted with bacteriostatic-preserved saline resulting in a concentration of 5 units/0.1 mL) was injected into the lateral canthal rhytides via 3 to 4 injection points, 1 cm lateral from the orbital rim on each side, resulting in 15 total units of onabTX-A. A 0.5 inch 32-gauge needle was used. OnabTX-A was given 7 days before the chemical peel in patients randomly assigned to Group A only.

Chemical peel technique

After thorough cleansing of the entire face with a mild cleanser and water followed by gentle removal of surface oil with alcohol wipes, two coats of the Jessner's peel solution were applied to the entire face and left in place for three minutes until mild erythema with fine white speckling appeared. Afterward, three to four coats of the 35% TCA peel solution were applied to the upper lid from the inferior edge of the brow to the entire lid surface up to the supratarsal crease (Fig. 2). On the lower lid, two coats of the 35% TCA peel were applied from the orbital rim to within 3 mm of the lower lash line (Fig. 2). The 35% TCA peel was left in place until a white frost with background erythema appeared (a Level 2 frost according to the frosting grading system) [Appendix I]. Next, cool water compresses were placed on the face for five minutes. A light application of triamcinolone acetonide 0.1% ointment was then applied to the entire face. On the morning following the peel, subjects were advised to cleanse with a mild,

Table 1
Lateral canthal wrinkle scores determined by the four-point facial wrinkle severity scale.

	Chemical peel only	BTX-A and chemical peel	<i>p</i> value*
Mean age	51.86	47.27	.13
Pretreatment scores	2.71	2.45	.16
Post-treatment scores	1.79	0.55	.002
Difference pretreatment vs. posttreatment	0.93	1.91	.001

BTX-A, botulinum toxin type A.

Mean values presented.

* *p* value using Wilcoxon tests.

fragrance-free cleanser followed by application of either petrolatum or Aquaphor ointment four to five times per day for the first two days and then three times daily until re-epithelialized.

Primary outcome measures

Our primary objective was to evaluate the safety and efficacy of sequential use of onabotulinum toxin type A with Jessner's and TCA peels for the treatment of mild to moderate periorcular rhytides. We also compared the relative effectiveness of using chemical peels alone versus chemical peels with adjunctive onabotulinum toxin type A. Lateral canthal wrinkle scores using the four-point FWSS were assessed at baseline and week 10 (Fig. 1).

Statistical analysis

Data was analyzed with the Wilcoxon signed-rank test for paired comparisons. Blinded rater scores and age were compared between treatments (onabotulinum toxin type A plus peel vs. peel alone). In addition, Fisher's exact test was used to examine the association between skin type and treatments.



Fig. 3. Subject treated with combination (onabotulinum toxin type A + chemical peel) at baseline (left) and at 10 weeks (right).



Fig. 4. Subject treated with combination (onabotulinum toxin type A + chemical peel) at baseline (left) and at 10 weeks (right).

Results

Twenty-six subjects were consented and enrolled, and 25 completed the study. The mean age of the subjects was 48 years old (range: 39–65). Mean blinded ratings are displayed in Table 1.

When assessed at week 10, the mean FWSS scores in subjects receiving combination treatment (i.e., onabotulinum toxin type A + chemical peels – Group A post score = 0.55) were significantly ($p = .002$) lower than FWSS scores in patients treated with peels only (post score = 1.79). Although all subjects in the combination arm demonstrated improvement from baseline, only 12 out of 14 treated with chemical peel alone (i.e., Group B) showed improvement in lateral canthal rhytides. Compared with baseline, FWSS scores were decreased by a significantly ($p = .001$) greater amount on average at week 10 with combination treatment (onabotulinum toxin type A and peels score difference = 1.91) compared with peels alone (peels only score difference = 0.93). There was a significantly greater improvement in lateral canthal rhytides in those receiving combination treatments compared with those who received chemical peel alone ($p = .002$) (Figs. 3 and 4). There was no significant difference in pretreatment wrinkle scores or patient age between groups ($p = .16$, $p = .13$, respectively; Table 1). In addition, there was no significant association in skin type between groups ($p = .11$, Fisher's exact test).

All but one subject completed the study. The subject who withdrew only received the initial onabotulinum toxin type A treatment without complication; she stated that she could not continue to participate in the study due to work schedule limitations. No serious adverse events were reported. Only two subjects experienced mild irritant dermatitis from the chemical peel within five days of the procedure, which fully resolved with application of topical steroids of lower strength (desonide 0.05% ointment applied twice a day for three days). Both of these subjects had skin type I and were from Group A.

Discussion

The results of this study found that treating lateral canthal rhytide complex with a combination of onabotulinum toxin type A injections followed by Jessner's and 35% TCA peel is more effective than treatment with the

chemical peel alone. In addition, this combination procedure regimen is well tolerated. We did not find any correlation between treatment efficacy and skin type. With respect to mild adverse events, both subjects who experienced mild irritant dermatitis had type I skin.

The use of a combined approach in the treatment of photoaged skin has become more popular over the years. In the literature, studies and case reports have highlighted the success of multimodal regimens (involving adjunctive neuromodulator with fillers, intense pulse light, and laser resurfacing) within the aesthetic realm for improvement of rhytides and photodamage (Carruthers and Carruthers, 2003; Carruthers and Carruthers, 2004; Dubina et al., 2013; Goldman and Wollina, 2010; Kadunc et al., 2007; Khoury et al., 2008; Tierney and Hanke, 2010). Botulinum toxin has also proven helpful within the surgical sphere to minimize postoperative scar formation (Flynn, 2009; Gassner et al., 2006).

OnaBTX-A is commonly used in combination treatment regimens due to its beneficial effect on wound healing (Gassner et al., 2006). When facial muscles are weakened by onaBTX-A, the overlying immobilized skin can regenerate more efficiently and collagen remodeling is more uniform (Tung et al., 2011). OnaBTX-A is known to have a rapid onset of activity with peak benefits usually occurring approximately one-week posttreatment (Carruthers and Carruthers, 1998; Lowe et al., 2005). For this reason, many practitioners advocate pretreatment with neuromodulators before other aesthetic procedures to attain maximal synergy (Carruthers and Carruthers, 1998; Carruthers and Carruthers, 2003; Carruthers and Carruthers, 2004; Dubina et al., 2013; Kadunc et al., 2007; Khoury et al., 2008; Landau, 2006; Tung et al., 2011). In a randomized, blinded, split-face study, Khoury et al. (2008) found that a significantly higher proportion of patients showed improvement in small wrinkles and fine lines with intense pulse laser plus BTX-A versus intense pulse laser alone (Khoury et al., 2008). In addition, a small pilot randomized controlled trial examined the effects of BTX-A pretreatment with chemabrasion (35% TCA peel with manual dermabrasion) (Kadunc et al., 2007). Kadunc et al. (2007) found that the use of adjunctive pretreatment of BTX-A improved both short- and long-term results of perioral rhytide chemabrasion.

Beneficial effects of onaBTX-A treatment on wound healing have also been shown to reduce scarring after traumatic forehead laceration repair and Mohs surgery (Flynn, 2009; Gassner et al., 2006). A prospective, blinded, placebo-controlled study demonstrated that BTX-A induced immobilization of forehead wounds enhanced wound healing and improved cosmesis (Gassner et al., 2006). In addition, a retrospective analysis found that administration of intraoperative BTX-A treatment in patients undergoing surgical reconstruction following Mohs procedure and reconstruction improved wound healing by reducing skin tension and facilitating the apposition of wound edges (Flynn, 2009).

This study is limited because no group received BTX-A alone. Our study highlights the tolerability and efficacy of combination treatment using

onaBTX-A and chemical peels for improvement of the lateral canthal rhytide complex in skin types I through III. However, it would be beneficial for future studies to evaluate the role of BTX-A alone versus combination therapies. Overall, although many resurfacing methods exist, a neuromodulator and medium depth chemical peel pairing offers reliable, cost-effective rejuvenation for mild to moderate perioral rhytides.

Appendix I. Frosting Grading System (FGS)

Level of Frost I = speckled white, mild erythema

Level of Frost II = Even white coat, background erythema

Level of Frost III = Solid white, opaque, no background erythema, penetration into reticular dermis.

References

- Carruthers J, Carruthers A. The adjunctive usage of botulinum toxin. *Dermatol Surg* 1998;11:1244–7.
- Carruthers J, Carruthers A. A prospective, randomized, parallel group study analyzing the effect of BTX-A (Botox) and nonanimal sourced hyaluronic acid (NASHA, Restylane) in combination compared with NASHA (Restylane) alone in severe glabellar rhytides in adult female subjects: treatment of severe glabellar rhytides with a hyaluronic acid derivative compared with the derivative and BTX-A. *Dermatol Surg* 2003;8:802–9.
- Carruthers J, Carruthers A. The effect of full-face broadband light treatments alone and in combination with bilateral crow's feet Botulinum toxin type A chemodenervation. *Dermatol Surg* 2004;3:355–66.
- Dubina M, Tung R, Bolotin D, Mahoney AM, Tayebi B, Sato M, et al. Treatment of forehead/glabellar rhytide complex with combination botulinum toxin a and hyaluronic acid versus botulinum toxin a injection alone: a split-face, rater-blinded, randomized control trial. *J Cosmet Dermatol* 2013;4:261–6.
- Flynn TC. Use of intraoperative botulinum toxin in facial reconstruction. *Dermatol Surg* 2009;2:182–8.
- Gassner HG, Brissett AE, Otle CC, Boahene DK, Boggust AJ, Weaver AL, et al. Botulinum toxin to improve facial wound healing: a prospective, blinded, placebo-controlled study. *Mayo Clin Proc* 2006;8:1023–8.
- Goldman A, Wollina U. Facial rejuvenation for middle-aged women: a combined approach with minimally invasive procedures. *Clin Interv Aging* 2010;5:293–9.
- Kadunc BV, Trindade DE, Almeida AR, Vanti AA, Di Chiacchio N. Botulinum toxin A adjunctive use in manual chemabrasion: controlled long-term study for treatment of upper perioral vertical wrinkles. *Dermatol Surg* 2007;9:1066–72.
- Khoury JG, Saluja R, Goldman MP. The effect of botulinum toxin type A on full-face intense pulsed light treatment: a randomized, double-blind, split-face study. *Dermatol Surg* 2008;8:1062–9.
- Landau M. Combination of chemical peelings with botulinum toxin injections and dermal fillers. *J Cosmet Dermatol* 2006;2:121–6.
- Lowe NJ, Ascher B, Heckmann M, Kumar C, Fraczek S, Eadie N, et al. Double-blind, randomized, placebo-controlled, dose-response study of the safety and efficacy of botulinum toxin type A in subjects with crow's feet. *Dermatol Surg* 2005;3:257–62.
- Monheit GD. Medium-depth chemical peels. *Dermatol Clin* 2001;19:413–25.
- Tierney EP, Hanke CW. Recent advances in combination treatments for photoaging: review of the literature. *Dermatol Surg* 2010;6:829–40.
- Tung RC, Rubin MG, Dover JS, Alam M. Combinations of Therapy in: Chemical Peel (Monheit GD). 2nd ed. Philadelphia: Saunders Elsevier; 2011. p. 133–46.