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Combined Effect of Botulinum Toxin with a Biorevitalizing Solution on Crow's Feet Wrinkles and Neck Rejuvenation: A Case Series Study

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Abstract

Background: Facial and neck aging are multifactorial processes involving both muscular hyperactivity and deterioration of dermal quality. Botulinum toxin type A (BoNTA) improves dynamic wrinkles related to muscle contraction but does not directly address hydration, texture, or overall skin quality. Multimodal approaches combining neuromodulation with dermal revitalization may enhance aesthetic outcomes. **Objective:** This paper aims to evaluate the clinical effects of combining BoNTA with a poly-revitalizing hyaluronic acid-based solution (NCTF®135HA) compared with BoNTA alone for the treatment of crow's feet wrinkles and neck aging. **Methods:** This split-face and split-neck exploratory case series included five female patients (mean age 50.8 years). All patients received BoNTA injections on both sides of the face and neck. One side additionally received three sessions of NCTF®135HA at D0, D30, and D45. Clinical wrinkle scoring, skin quality assessment (radiance and hydration), VISIA® imaging analysis, and Global Aesthetic Improvement Scale (GAIS) evaluations were performed over 60 days. **Results:** At D60, the combination treatment demonstrated a greater reduction in crow's feet and neck wrinkle scores compared with BoNTA alone. For crow's feet, 80% of patients achieved a BCFWS score of 0 - 1 on the combination side versus 20% on the BoNTA-only side ($p < 0.05$). Radiance and hydration significantly improved only on the combination-treated side. VISIA® analysis showed significant improvement in spot and texture parameters with combined treatment, whereas no significant changes were observed with BoNTA alone. Patient-reported GAIS scores favored the combined approach. **Conclusion:** In this exploratory case series, combining BoNTA with NCTF®135HA was associated with greater

short-term improvement in wrinkle severity and skin quality parameters compared with BoNTA alone. These findings support the rationale for a multimodal approach targeting both muscular activity and dermal quality in facial and neck rejuvenation. Larger controlled studies are needed to confirm these results and evaluate long-term outcomes.

Keywords

NCTF®135HA, Botulinum Toxin Type A, Skin Rejuvenation, Facial Aging, Neck Aging, Crow's Feet

1. Introduction

Aging is a complex, multifactorial process affecting the skin but also the architecture (the skeleton) and the subcutaneous tissues (fat, muscles, tendons) [1] [2]. The neck is one of the areas most affected by aging. It is considered as a region where the skin will age most rapidly. This area, which is highly exposed to the sunlight, is particularly fragile [3] [4].

Various factors can explain this rapid and inexorable aging process, including genetics, lifestyle, diet, sun exposure, weight gain and weight loss (inducing a succession of skin dragging and lack of retractation events), hormonal variations, age, and muscular contractions. These factors, combined with a loss of collagen and elastin and accumulation of fat, contribute to the fact that the neck and décolleté areas are particularly prone to signs of aging. Common features associated with neck aging are: age spots, freckles, sun-induced discoloration, excess neck fat (double chin), sagging skin, crepey skin, platysma bands, lines, folds, and wrinkles [5] [6].

Patients will often present with horizontal wrinkles, a lack of firmness, and, in older individuals, a vertical hollow that gives an impression of "strings", defined as platysma bands.

Aging of the neck can be linked to slackening of the skin, but also to the contraction of the muscle of the neck called the platysma. The platysma muscle is a large flat muscle that covers the major part of the neck (anterolateral surfaces), extending from the clavicle to above the mandible into the SMAS layer [7]-[9].

It is very thin and located immediately under the skin, and it plays a key role in the lowering of the angles of the mouth and the lowering of the jowls. Because it is a region frequently subjected to contractions, it leads to the appearance of platysma bands and the rupture of the harmonious oval of the face [10].

Neck sagging and platysma bands can be a major issue in some patients, for whom it becomes complex. Furthermore, in an era where facial rejuvenation is becoming more widely available, a sagging neck may often contrast with a rejuvenated face.

For individuals seeking to avoid surgery and its associated risks, a variety of non-surgical procedures have been developed to address the specific needs of the

neck area.

For this specific area, treatment strategies aim to tighten skin and muscle. A study published in 2017 showed that platysma bands might not only be related to relaxation of the platysma and skin laxity, but are triggered by activity of the platysma muscle itself, affecting skin appearance [11]. Thus, among the various facial and neck treatments, botulinum toxin may be one of the strategies to achieve cervical rejuvenation simply and quickly by reducing muscle cords and improving the oval of the face.

While botulinum toxin will limit the muscular contraction of the platysma muscle responsible for the "cords" located under the chin (turkey neck, baleen), this technique won't achieve improvement of other features affecting overall skin quality, including hydration, elasticity, and firmness.

To fully appreciate the three-dimensional aspects of aging, new solutions are considered and designed to achieve multiple improvements at once, supporting the concomitant use of several techniques [12] [13].

For this reason, we propose combining two procedures: botulinum toxin injections to reduce platysma bands and neck wrinkles with an anti-aging biorevitalizing treatment to firm the skin, smooth the neck, enhance plumpness, decrease skin laxity, promote re-densification, and improve hydration.

In this study, we chose to investigate the synergistic efficacy of NCTF®135HA, a poly-revitalizing complex composed of vitamins, amino acids, minerals, coenzymes, nucleic acids, and antioxidants, combined with non-crosslinked hyaluronic acid for its moisturizing and plumping properties. This widely used treatment will help to recreate the ideal environment for cells and to stimulate the ability of fibroblasts to synthesize collagen and elastin for skin restructuration [14]-[16].

While a few studies have investigated the benefits of botulinum toxin or hyaluronic acid in neck rejuvenation [17]-[24], studies examining the benefits of a multimodal therapeutic approach on human skin remain limited, and the efficacy and safety of such a strategy are poorly documented. Thus, this study aims to demonstrate the rationale of a multimodal treatment strategy, proposing that two techniques act better, faster, and longer than a single treatment to recover neck aging and to improve skin texture and quality.

2. Material and Methods

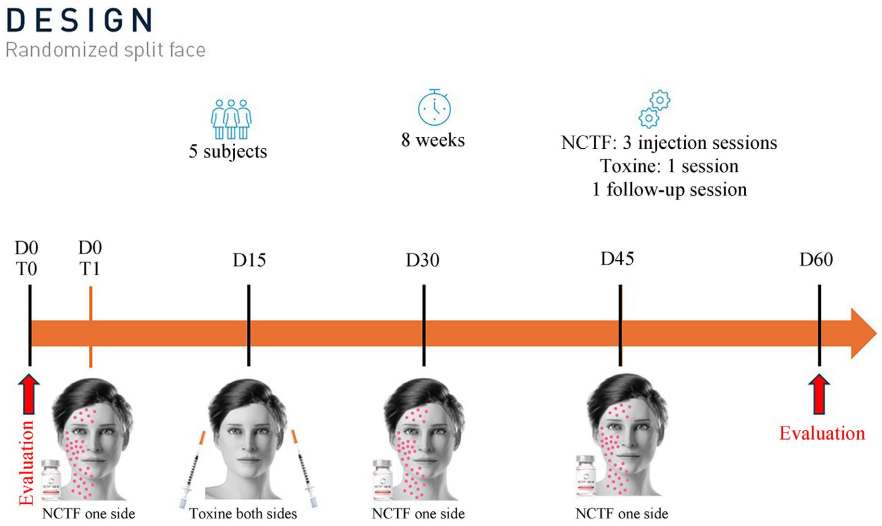
2.1. Patients and Procedures

Five female patients aged 37 to 67 years old (mean age 50.8 years) agreed and provided informed consent to participate in this treatment and analysis.

All patients were non-smokers with Fitzpatrick phototypes I or II, had no history of prior aesthetic procedures in the treated areas, and had not been exposed to excessive sun exposure in the four weeks preceding the study.

The analysis was conducted over a period of 8 weeks. To compare the efficacy of the neuromodulator (BoNTA) alone or in combination with a biorevitalizing solution (NCTF®135HA, FILLMED, France) on the same patient, both sides of the face

and neck were treated with BoNTA (Dysport®, Ipsen, France) while only one side was additionally injected with NCTF®135HA. Baseline evaluation was performed at D0, followed by the first injection of NCTF®135HA on one side of the face and neck. BoNTA injections were performed on both sides at D15, two weeks after the initiation of NCTF®135HA. This staggered schedule was based on the clinical rationale that early dermal revitalization may improve skin hydration, fibroblast activity, and overall dermal density before the onset of neuromodulator-induced muscle relaxation. As BoNTA typically reaches its peak effect approximately 14 days post-injection, this sequencing was intended to ensure that muscle relaxation occurred in a potentially improved dermal environment. The authors acknowledge that this sequential design limits the ability to fully isolate the individual contribution of each treatment to the observed outcomes. Additional NCTF®135HA sessions were administered on the same side at D30 and D45 to maintain a continuous regenerative stimulus throughout the observation period. Final evaluation was conducted at D60 (**Figure 1**). The average procedure duration was 10 - 15 minutes, and no cosmetic care was performed during the study period.



Schematic representation of the split-face and split-neck study design conducted over 8 weeks in five subjects. One side of the face and neck received three sessions of NCTF®135HA injections at D0, D30, and D45, while botulinum toxin (BoNTA) was injected on both sides at D15. Clinical and instrumental evaluations were performed at baseline and at D60.

Figure 1. Study design and treatment protocol.

BoNTA (Dysport®, Ipsen, France) was reconstituted with 2.5 mL of normal saline (0.9% NaCl) per vial. For crow's feet, injections were administered superficially at three points per side: Point 1, 1 cm lateral to the orbital rim directly below the tail of the brow; Point 2, 1 cm lateral to the orbital rim in line with the lateral canthus; and Point 3, 1 cm lateral to the orbital rim and 1 cm below Point 2. Each point received 10 IU, for a total of 30 IU per side. For platysma injections, bands were marked during dynamic contraction. Two rows of three injection points were placed 1 cm apart along each band, with 5 IU administered per point, for a

total of 30 IU per side.

NCTF®135HA (FILLMED, France) was administered from a 3 mL vial using a 3 mL syringe and a two-step technique. After antiseptic cleaning of the face and neck, the first step used a 30G × 12 mm needle at an angle of less than 10 degrees to deliver very superficial epidermal micro-injections approximately 0.5 cm apart across the treatment area, with only the bevel of the needle inserted and gentle pressure applied to the plunger throughout. The second step used a 32G × 4 mm needle at a 45-degree angle, with rapid intradermal injections to a depth of no more than 2 mm, ensuring intradermal placement of the product. Both steps were applied across the full surface of one side of the face and neck.

2.2. Criteria

Inclusion Criteria

Eligible participants were adults aged 30 to 65 years with visible moderate-to-severe horizontal neck lines and lateral canthal lines at rest or during animation, corresponding to a Grade 2 or 3 on the respective scoring scales. Participants were required to provide written informed consent and to adhere to the treatment and follow-up schedule. Women of childbearing potential were required to have a negative pregnancy test prior to enrollment and to use effective contraception throughout the study.

Exclusion Criteria

Exclusion criteria included prior treatment with botulinum toxin, dermal fillers, or energy-based devices in the target areas within the preceding six months; active skin infection or inflammation at injection sites; history of hypertrophic scarring or keloid formation; known hypersensitivity to any component of the study products; neuromuscular disorders such as myasthenia gravis or Lambert-Eaton syndrome; use of medications interfering with neuromuscular transmission (e.g., aminoglycosides); pregnancy or breastfeeding; unrealistic aesthetic expectations; and any planned surgical intervention during the study period.

2.3. Evaluation of Results

Crow's feet severity was assessed using the Bazin Crow's Feet Wrinkle Scale (BCFWS), a seven-point scale ranging from 0 (no wrinkle) to 6 (very deep wrinkles), with lower scores indicating greater improvement. Neck wrinkle severity was assessed using the Bazin Photographic Visual Score, a seven-point scale ranging from 0 (no wrinkle) to 6 (very deep wrinkles), with lower scores indicating greater improvement. Skin radiance was evaluated using a five-point clinical scoring scale ranging from 0 (very dull skin) to 4 (very radiant skin), with higher scores indicating greater improvement. Skin hydration, firmness, and homogeneity were each assessed using a nine-point clinical scoring scale (0 = none, 1 - 3 = light, 4 - 6 = moderate, 7 - 9 = important), with higher scores indicating greater severity; improvements are therefore reflected by lower scores at follow-up relative to baseline. Treatment efficacy was also assessed using the Global Aesthetic Improve-

ment Scale (GAIS), a seven-point scale ranging from −3 (very much worse) to +3 (very much improved), with 0 indicating no change and higher scores reflecting greater perceived improvement.

Before and after photos were documented and assessed by VISIA® Skin Analysis.

2.4. Statistical Analysis

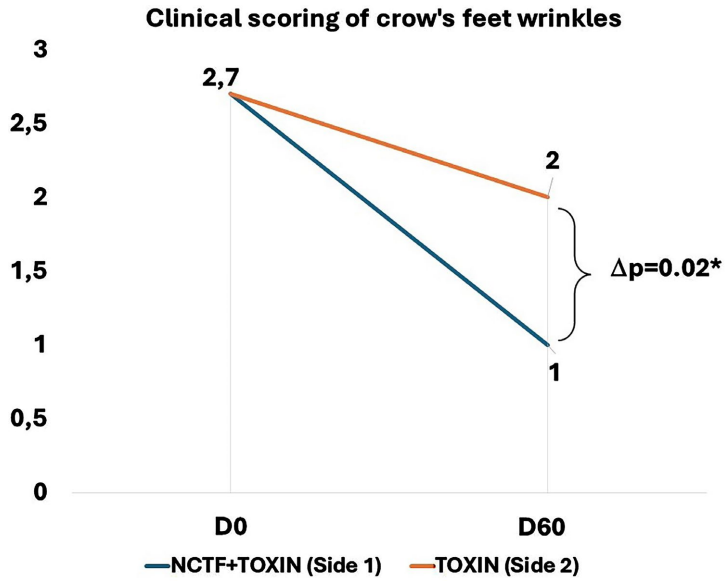
For all quantitative data, the mean and median were determined. The Student t-test was used for comparative analysis.

3. Results

3.1. Clinical Scoring of Crow's Feet and Neck Wrinkles

Both crow's feet and neck wrinkle progression were assessed. The wrinkles-scoring results are presented in Figure 2 and Figure 3.

For crow's feet, mean wrinkle scores decreased from 2.7 at baseline (D0) to 1.0 at D60 on the side treated with the combination of BoNTA + NCTF®135HA, whereas the side treated with BoNTA alone showed a smaller reduction from 2.7 to 2.0 over the same period. The difference in score reduction between the two treatments was statistically significant (Δp = 0.02), indicating greater improvement with the combined approach (Figure 2).

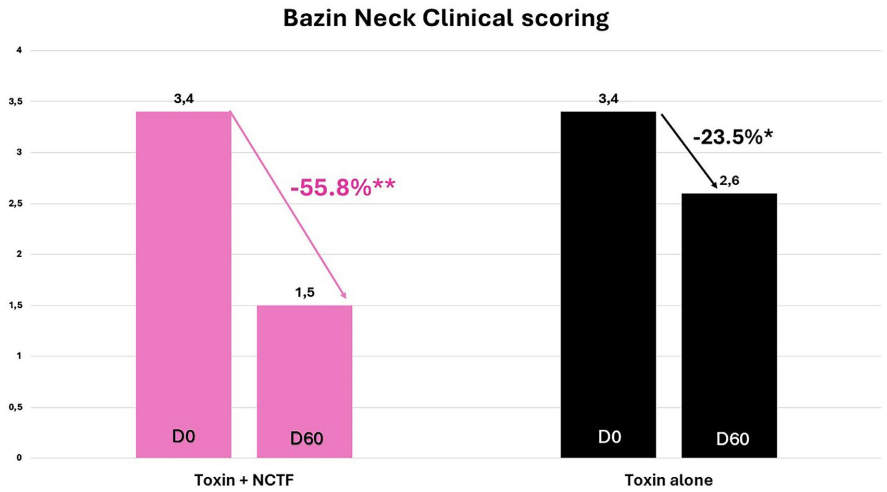


Mean clinical scores for crow's feet wrinkles at baseline (D0) and D60. The side treated with BoNTA + NCTF®135HA showed a greater reduction in wrinkle severity compared with the BoNTA-only side. The difference between treatments was statistically significant (Δp = 0.02).

Figure 2. Clinical scoring of crow's feet wrinkles.

A similar pattern was observed for neck wrinkles. The mean clinical score decreased from 3.4 at D0 to 1.5 at D60 on the BoNTA + NCTF®135HA side, corresponding to a 55.8% reduction. In contrast, the BoNTA-only side showed a more

modest improvement from 3.4 to 2.6, corresponding to a 23.5% reduction. These findings indicate a greater reduction in neck wrinkle severity with the combined treatment compared with BoNTA alone (Figure 3).



Mean clinical scores for neck wrinkles at baseline (D0) and D60. A greater reduction in wrinkle severity was observed on the side treated with BoNTA + NCTF®135HA compared with BoNTA alone, corresponding to reductions of 55.8% and 23.5%, respectively.

Figure 3. Clinical scoring of neck wrinkles.

3.2. Clinical Scoring of Skin Quality

After clinical evaluation, improvements in several skin quality parameters were observed, particularly on the side treated with the combined approach.

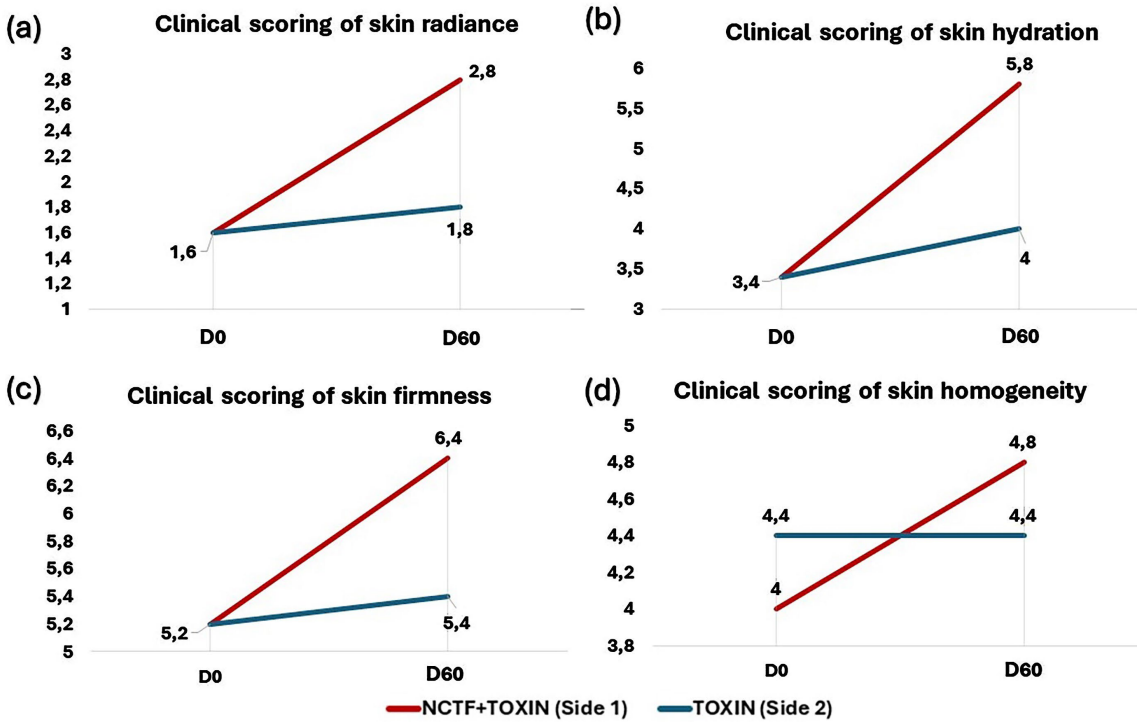
Skin radiance, evaluated using a clinical score ranging from 0 (very dull skin) to 4 (very radiant skin), increased from 1.6 at D0 to 2.8 at D60 on the side treated with BoNTA + NCTF®135HA ($p = 0.005$). A smaller improvement was observed on the BoNTA-only side, where the score increased from 1.6 to 1.8 over the same period (Figure 4(a)).

Similarly, the mean hydration score increased markedly on the side treated with BoNTA + NCTF®135HA, rising from 3.4 at D0 to 5.8 at D60 (mean delta +2.4). In comparison, the BoNTA-only side showed a more modest increase from 3.4 to 4.0 (mean delta +0.6). The difference between the two treatments was statistically significant ($p = 0.02$) (Figure 4(b)).

Skin firmness (Figure 4(c)) showed a slight increase on both treated sides, with a more pronounced improvement on the side treated with BoNTA + NCTF®135HA. Skin homogeneity (Figure 4(d)) remained stable on the BoNTA-only side, while a modest improvement was observed on the combined-treatment side.

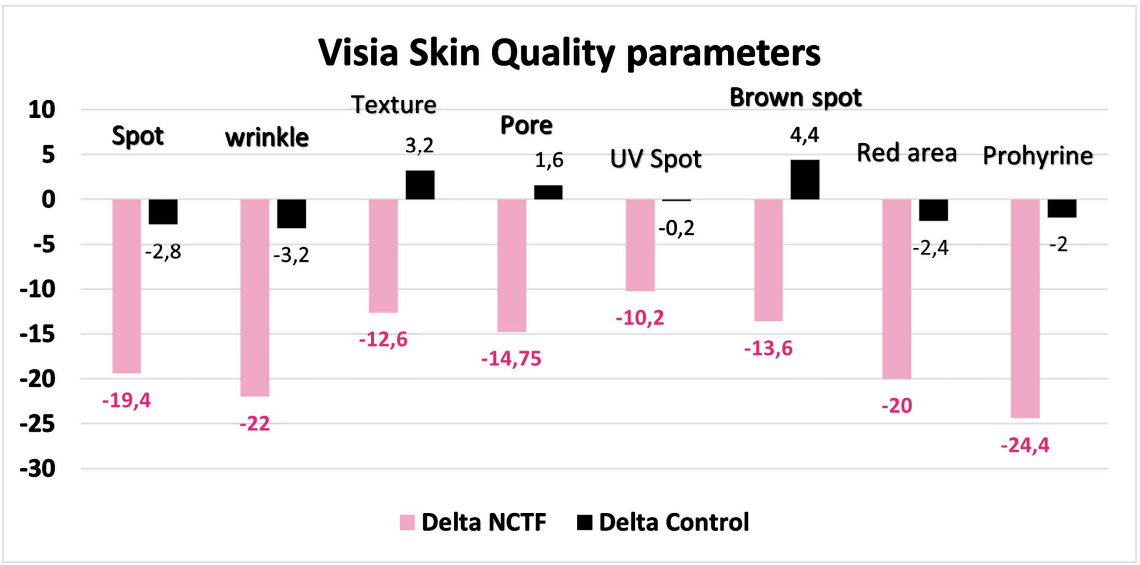
3.3. VISIA® Skin Analysis Results

Photo analysis using the VISIA® Skin Analysis system (Canfield Scientific, USA) revealed greater improvements in several skin quality parameters on the side treated with BoNTA + NCTF®135HA compared with the BoNTA-only side (Figure 5).



Changes in clinical skin quality scores between baseline (D0) and D60 for the side treated with BoNTA + NCTF®135HA and the BoNTA-only side. (a) Skin radiance score; (b) Skin hydration score; (c) Skin firmness score; (d) Skin homogeneity score. Greater improvements were observed on the side treated with the combined approach.

Figure 4. Clinical scoring of skin quality parameters.



Changes in VISIA® skin analysis parameters between baseline and follow-up for the side treated with BoNTA + NCTF®135HA compared with BoNTA alone. Parameters evaluated included spots, wrinkles, texture, pores, UV spots, brown spots, red areas, and porphyrins. Negative values represent improvement (reduction in the parameter score). Greater improvements were observed on the side treated with the combined approach.

Figure 5. VISIA® skin quality parameters.

The Spot parameter, reflecting the quantification of skin discolorations and

pigment irregularities, showed a marked reduction on the combined-treatment side (Δ = −19.4) compared with a smaller reduction on the BoNTA-only side (Δ = −2.8). This difference between treatments was statistically significant (p = 0.02), indicating improved overall skin uniformity with the addition of NCTF®135HA.

The Wrinkle parameter also showed a greater decrease on the combined-treatment side (Δ = −22.0) compared with the BoNTA-only side (Δ = −3.2) (p = 0.07).

Similarly, skin texture improved on the side treated with BoNTA + NCTF®135HA (Δ = −12.6), whereas no improvement was observed on the BoNTA-only side, where the parameter slightly increased (Δ = +3.2). This difference between treatments was statistically significant (p = 0.003).

Additional VISIA® parameters showed a similar trend. The Pore parameter slightly increased on the BoNTA-only side while remaining stable or improving on the combined-treatment side. UV spot counts decreased on the BoNTA + NCTF®135HA side, whereas minimal changes were observed with BoNTA alone. Brown spots showed an increase on the BoNTA-only side but remained more stable on the combined-treatment side. Red areas and porphyrins decreased more markedly on the combined-treatment side compared with the BoNTA-only side.

Standardized VISIA® photographic overlays corroborated these quantitative findings. A visible reduction in pigmented spot density, wrinkle mapping intensity, and surface irregularities was observed on the BoNTA + NCTF®135HA-treated side, whereas minimal changes were detected on the BoNTA-only side.

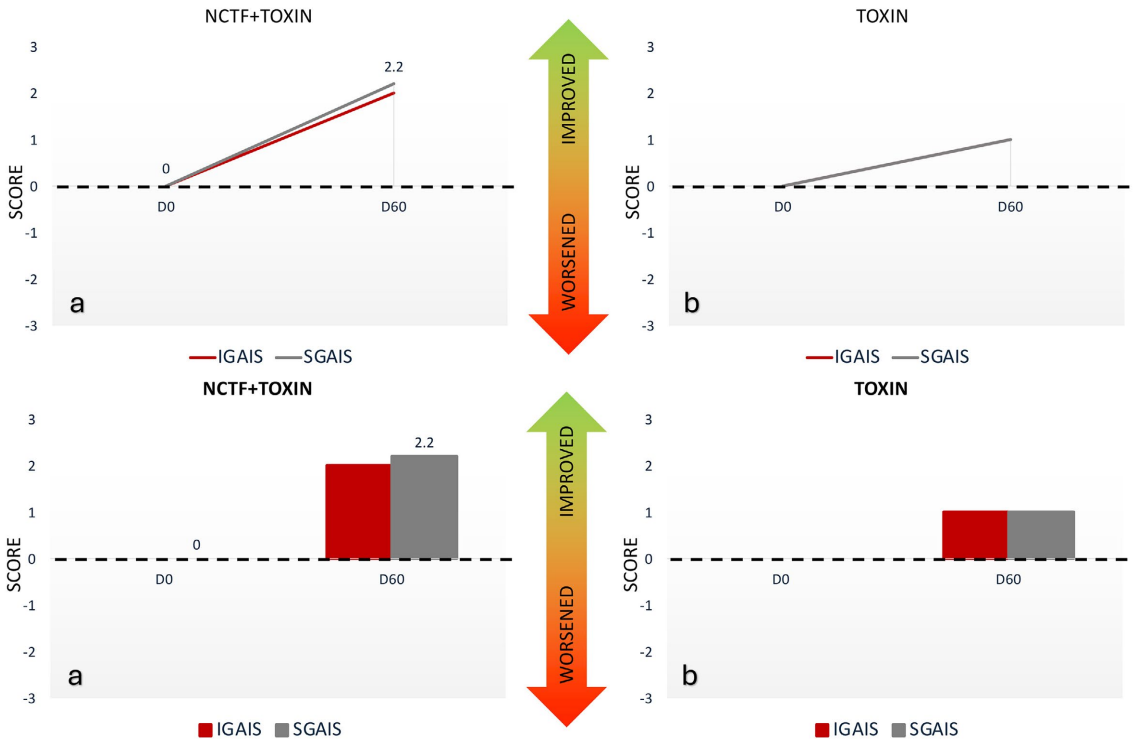
Representative standardized clinical photographs and VISIA® imaging overlays from two participants are presented in Supplementary **Figure S1**. These images illustrate the changes observed between baseline and follow-up, including a visible reduction in pigmented spots, wrinkle mapping intensity, and surface irregularities on the side treated with BoNTA + NCTF®135HA. These visual observations are consistent with the quantitative improvements measured by VISIA® analysis.

3.4. GAIS Scoring

Treatment efficacy was assessed using the Global Aesthetic Improvement Scale (GAIS) by both the physician and the participants at D60.

As shown in **Figure 6(a)**, the physician reported greater aesthetic improvement on the side treated with BoNTA + NCTF®135HA, with a mean GAIS score of 2 (much improved) compared with 1 (improved) on the BoNTA-only side. However, this difference did not reach statistical significance.

Patient-reported outcomes showed a significantly greater perceived aesthetic improvement with the combined treatment. At D60, the mean GAIS score reported by participants was 2.2 for the BoNTA + NCTF®135HA side versus 1 for the BoNTA-only side (p = 0.0003) (**Figure 6(b)**).



Assessment of aesthetic improvement at D60 using the Global Aesthetic Improvement Scale (GAIS). (a) Physician-reported GAIS scores comparing BoNTA + NCTF®135HA and BoNTA alone; (b) Patient-reported GAIS scores showing greater perceived improvement on the side treated with the combined approach.

Figure 6. Global Aesthetic Improvement Scale (GAIS) evaluation.

3.5. Safety and Tolerability

The treatment protocol was well tolerated by all participants, with no reports of systemic adverse events or functional impairments. Specifically, there were no documented cases of ptosis, facial asymmetry, muscle weakness, or dysphagia on either the treated or control sides. Regarding local injection-site reactions, the safety profile was favorable: only one patient experienced mild ecchymosis at two injection points in the periorbital region. This bruising was localized, did not require medical intervention, and resolved spontaneously within five days. No significant differences in pain levels were reported between the BoNTA-only side and the combined treatment side.

4. Discussion

Aging of the face and neck is multifactorial and results from combined changes in skin quality, including hydration, texture, and dyschromia, together with alterations in deeper structures such as muscle activity [25]-[27]. In this exploratory split-face and split-neck case series, adding NCTF®135HA to BoNTA injections led to greater improvement in crow's feet and neck wrinkle scores compared with BoNTA alone on the contralateral side. Improvements in radiance and hydration were more pronounced and reached statistical significance on the side treated

with the combined approach. Instrumental assessment using VISIA® confirmed these findings. Significant improvements in spot and texture parameters were detected on the BoNTA + NCTF®135HA side, whereas no significant changes were observed with BoNTA alone. Patient-reported outcomes assessed with GAIS at D60 also favored the combined treatment. Together, these results suggest that treating both muscle activity and dermal quality provides better short-term aesthetic outcomes than neuromodulation alone.

Our findings are consistent with previous studies supporting multimodal strategies for neck rejuvenation. Jeon *et al.* reported improvement in horizontal neck wrinkles using a combination of energy-based treatment, hyaluronic acid, and BoNTA. Their results support the idea that targeting several mechanisms of aging enhances clinical outcomes [28]. Similarly, Li *et al.* showed that non-crosslinked hyaluronic acid combined with mesotherapy improved moderate-to-severe horizontal neck lines and achieved higher patient satisfaction compared with BoNTA alone. Their results emphasize the importance of improving dermal quality in addition to reducing muscle contraction [29].

Superficial injection techniques using BoNTA have also been described for improving fine wrinkles and skin surface appearance. In particular, the microbotox (mesobotox) technique described for the lower face and neck involves highly diluted toxin delivered intradermally or at the dermal-subdermal junction, aiming to improve fine rhytides, skin texture, and overall skin quality in addition to reducing muscular hyperactivity. This approach highlights that neuromodulation may exert effects beyond pure muscle relaxation, supporting combined strategies targeting both dynamic and dermal components of aging [30].

Pisal *et al.* conducted a split-face case series in which BoNTA was injected alone on one side and combined with a biorevitalizing hyaluronic acid solution on the other side. They found that the combined approach produced greater clinical improvement in wrinkle severity, skin texture, and patient satisfaction compared with BoNTA alone. This study provides direct clinical evidence supporting the benefit of combining neuromodulation with dermal quality enhancement. These approaches aim to improve skin texture in addition to muscle relaxation, reflecting a broader shift toward strategies that simultaneously address dynamic wrinkles and dermal quality.

In line with these observations, recent clinical evidence has shown that intradermal botulinum toxin techniques in the lower face and neck significantly improve skin smoothness and fine lines while maintaining natural muscular function [31] [32]. These findings further support the rationale for addressing superficial skin quality in addition to muscle activity.

The effects observed with NCTF®135HA are supported by previous clinical and histological studies. Polycomponent mesotherapy formulations and non-crosslinked hyaluronic acid have been shown to improve dermal hydration, stimulate fibroblast activity, and promote collagen synthesis [14]-[16]. Reinforcing the dermal microenvironment may enhance cellular function in aged skin, which can

translate into improved texture and radiance. Randomized controlled studies have demonstrated that NCTF®135HA improves superficial wrinkles and overall skin quality [33]. In our study, the improvements in hydration, radiance, and VISIA® texture parameters are consistent with these mechanisms.

This study has several strengths. The split-side design allowed each patient to serve as her own control, reducing interindividual variability. This design is particularly useful in small exploratory studies. In addition, outcomes were assessed using complementary methods, including clinical wrinkle scoring, skin quality evaluation, VISIA® imaging, and GAIS. The consistency of results across subjective and objective measures strengthens the internal coherence of the findings.

This exploratory study has limitations that should be acknowledged. The sample size was limited and follow-up was restricted to 60 days, reflecting short-term outcomes. The study was not blinded, and external factors were not strictly standardized. Although VISIA® provides objective quantitative imaging, it does not directly assess histological changes.

Within the limitations of this exploratory case series, the combination of NCTF®135HA and BoNTA resulted in greater improvement in wrinkle severity and skin quality parameters than BoNTA alone over 60 days. These findings support the rationale for a multimodal approach to neck rejuvenation that targets both muscular activity and dermal quality. Larger randomized controlled studies with longer follow-up and blinded assessments are needed to confirm these results and to better define the durability and optimal indications of this combination strategy.

Statement of Ethics

This investigator-initiated exploratory case series was conducted in accordance with the ethical principles of the Declaration of Helsinki (World Medical Association, 1964, and its subsequent amendments). All procedures were performed as part of routine clinical practice at the study site. No potentially identifiable personal information is disclosed in this report. Written informed consent was obtained from all participants prior to any study-related procedures. Formal ethics committee review was not sought.

Conflicts of Interest

RK, HI, and FF are employees of Fillmed. The other authors declare no conflicts of interest.

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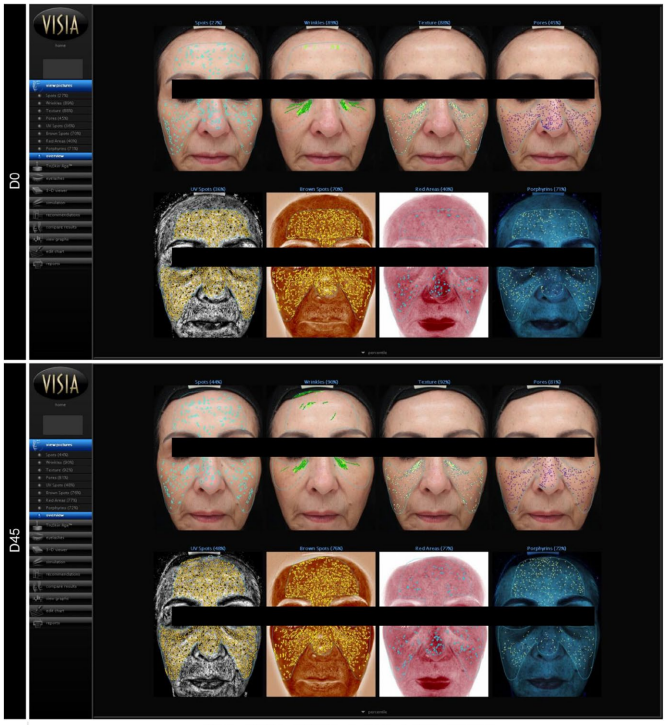
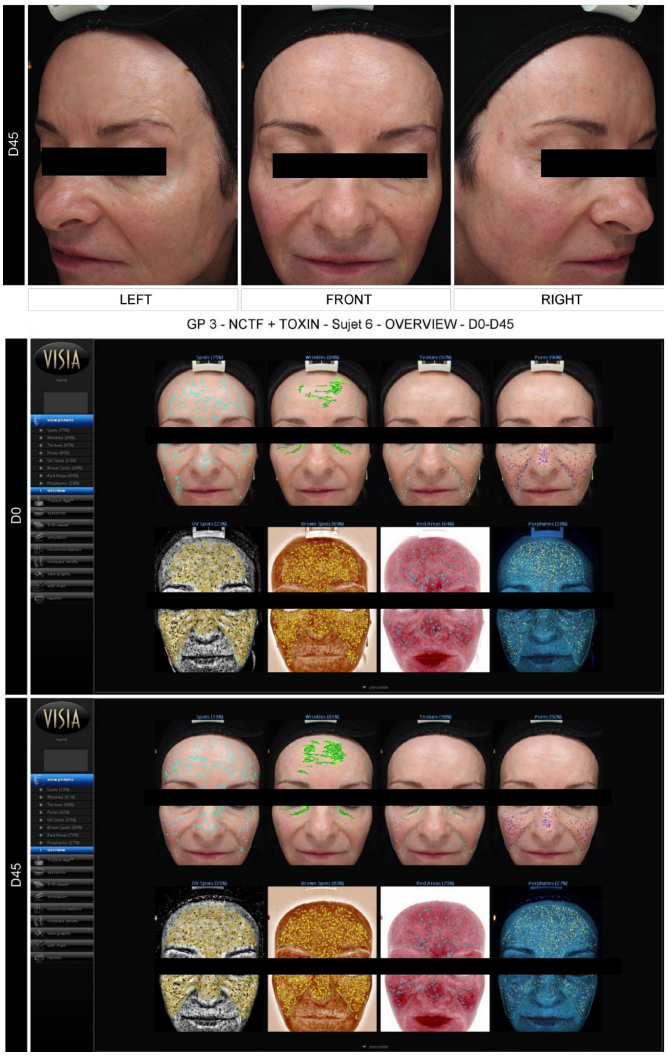
Supplementary Materials

GP 3 - NCTF + TOXIN - Sujet 3 - L-F-R - D0-D45

GP 3 - NCTF + TOXIN - Sujet 3 - OVERVIEW - D0-D45



GP 3 - NCTF + TOXIN - Sujet 6 - L-F-R - D0-D45



Representative images from two participants illustrating treatment outcomes. For both subjects, the right side corresponds to the BoNTA + NCTF®135HA-treated side. Standardized clinical photographs (left, frontal, and right views) and VISIA® imaging overlays obtained at baseline (D0) and follow-up (D45) show visible improvement in skin appearance, including reductions in pigmented spots, wrinkle mapping intensity, and surface irregularities on the side treated with BoNTA + NCTF®135HA.

Figure S1. Representative clinical photographs and VISIA® imaging.