

The Combined Effect of Botulinum Toxin Type A with a Biorevitalizing Treatment on Forehead Rejuvenation: A Case Series

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Abstract

Background: The forehead is particularly prone to repetitive facial expressions and hyperdynamic activity, resulting in deep wrinkles and a loss of elasticity and hydration. Although botulinum toxin type A (BoNTA) has been shown to reduce the appearance of wrinkles and allow patients to have a smoother and hence younger upper face, it cannot help to improve the other aspects that determine overall skin quality. **Objective:** This case series aims to evaluate the clinical efficacy of combining BoNTA injections with a biorevitalizing treatment (NCTF®135HA) on skin aging signs and quality using a split face approach. **Patients and Methods:** A total of eight patients from 30 to 55 years old were treated with botulinum toxin type A combined with NCTF®-135HA or alone. **Results:** At D60, clinical skin quality scoring showed that NCTF®135HA injection significantly reduced wrinkles and enhanced skin homogeneity, hydration, firmness, and radiance. The Global Aesthetic Improvement Scale (GAIS) by the evaluator at D60 reported mean scores of 2375 (much improved) on the side of the face treated with BoNTA + NCTF®-135HA compared to the side of the face without NCTF®135HA. According to patients, the NCTF®135HA injections resulted in a significantly better aesthetic improvement score on D60 (mean score of 2.5 compared to 0.125 without NCTF®135HA, p 0.001). **Conclusions:** Our findings show that combining a biorevitalizing treatment with a BoNTA injection can significantly improve the skin's overall appearance and decrease the wrinkle score when compared to the BoNTA injections alone. The results suggest that the combinatory strategy is effective, safe, and associated with a high level of patient satisfaction.

Keywords

BoNTA, Forehead Rejuvenation, Combining Treatment, Skin Biorevitalization

1. Introduction

Appeals for non-invasive aesthetic procedures are experiencing unprecedented interest in a society searching for eternal youth [1] [2].

Aging is a very complex multifactorial process affecting the skin but also the architecture (the skeleton) and the subcutaneous tissues (fat, muscles) [3] [4]. Skin aging is caused by intrinsic and extrinsic mechanisms [5]. Intrinsic aging is highly related to chronological age and genetic factors aggravated by free radicals and hormonal influences. Extrinsic aging is a distinct process caused by external factors such as UV exposure and the individual lifestyle (tobacco, pollution, nutrition) [6] [7] [8].

The forehead is a region particularly subjected to habitual facial expressions and hyperdynamic activity of underlying muscles (frown, puckering...), leading to the development of furrows in the glabella and frontalis areas and accentuation of these features due to a loss of elasticity and hydration and these repeated muscles contraction [9] [10]. Furthermore, this zone is an exposed area, especially following the COVID era, when people constantly wear masks [11].

A range of treatment options has been developed to reduce facial lines, including topical solutions, neuromodulators, fillers, and laser treatments [1] [12].

Botulinum toxin is a standard therapeutic option used to selectively target this area with hyperdynamic furrows by inducing transient and reversible paralysis of the treated muscles [13] [14] [15].

While botulinum toxin will specifically treat this type of wrinkle and allow the treated patient to obtain a relaxed, more rested, and therefore younger face, this technique won't achieve improvement of other features affecting the global skin quality of the face. In recent years, we observed a shift from a two-dimensional approach to an improved understanding and appreciation of the three-dimensional aspects of facial aging, including hydration, elasticity, and overall skin quality. New solutions are thus thought of and designed to achieve multiple improvements simultaneously, supporting the concomitant use of several techniques [16] [17] [18].

However, it is critical to understand how multiple aesthetic interventions can be combined safely and effectively [19]. However, the combined treatment option should have complementary effects on different skin parameters.

An anti-aging biorevitalizing treatment is a widely used technique intended to rejuvenate the skin using an intradermal multi-injection of an HA-based micro-filler or booster with a supporting component essential for the cellular environment [20] [21].

In this study, we chose to investigate the synergistic efficacy of NCTF®135HA (FILLMED Laboratories, France), a poly-revitalizing complex consisting of vitamins, amino acids, minerals, coenzymes, nucleic acids, and antioxidants, which support a non-cross-linked hyaluronic acid for its moisturizing and plumping properties. These will help recreate the ideal environment for fibroblasts, leading to an increase in collagen and elastin production for the restructuring of mature

skin and preventing future aging signs [22] [23] [24].

Considering that these two procedures are totally distinctive, we hypothesize that an aesthetic biorevitalizing treatment will perfect the botulinum toxin treatment on the forehead area by rehydrating the skin and stimulating collagen, which can help the muscle paralysis to induce the maximum efficacy for an anti-wrinkle objective. Moreover, there are no contraindications between the two injection techniques in the previous literature review, and many physicians use these two techniques synchronously in their daily activities.

While combining botulinum toxin with hyaluronic acid has been the focus of recent research [19] [25] [26], studies examining the benefits of combining multiple techniques on human skin are lacking, and the efficacy and safety of such a therapeutic strategy are poorly documented. Thus, this study aimed to demonstrate the rationale of a combinatory approach, suggesting that two techniques act better than a single treatment to recover facial aging and improve skin texture and quality.

In this study, we propose to study the synergistic effect of combining the NCTF®135HA biorevitalizing technique with botulinum toxin injections in the forehead.

2. Material and Methods

2.1. Patients

Eight patients from 30 to 55 years old (43-35-37-30-40-55-31-33 years old), all women, accepted to participate in this short experience. The median age was 38 years (range 30 - 55 years). All the patients were healthy, with no previous history of surgical or non-surgical procedures to improve skin quality on the forehead. To compare the efficacy of botulinum toxin alone or in combination with NCTF®135HA on the same patient, both sides of the forehead were treated with Botulinum toxin while only one side was injected with NCTF®135HA. Three injection sessions were planned at D0, D30 and D45 by NCTF®135HA while the Botulinum toxin injection was performed only at D15 (**Figure 1**).

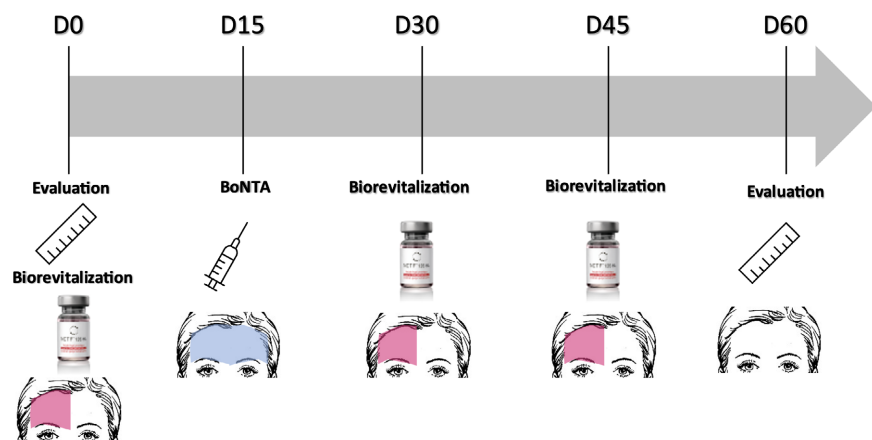


Figure 1. Injection schema with 3 biorevitalizing treatment and one BoNTA injection.

The patients agreed to have the biorevitalizing treatment on the non-treated side two months later by signing a consent form.

2.2. Procedure

The study was conducted over a period of 8 weeks. All eight patients underwent one session of botulinum toxin type A injections (Azzalure®, IPSEN, UK) combined with NCTF®135HA (side 1) or alone (side 2). An interval of 2 weeks was achieved between each session (Table 1).

The average procedure duration was 10 to 15 minutes, and no cosmetic care was carried out during the study.

2.3. Criteria for Efficacy Evaluation

The evaluator conducted a complete assessment of each patient. Various parameters were measured to determine treatment efficacy: clinical scoring of forehead wrinkles based on the Bazin Forehead Wrinkle Scale [27], skin radiance, skin hydration, skin firmness, and skin homogeneity by clinical scoring scale.

Patients were assessed at injection (baseline) and at D60 after treatment. At each evaluation, the physician evaluated wrinkle severity at maximum brow elevation using the five-point Bazin forehead wrinkle scale [27] (BFWS, 0 = no wrinkle, 1 = fine lines, 2 = slight wrinkles, 3 = moderately deep wrinkles, 4 = deep wrinkles, and 5 = very deep wrinkles) (Table 2).

Table 1. Treatments and timeline of the protocol.

	Procedure	D0	D15	D30	D45
SIDE 1	NCTF 135HA	+	-	+	+
	Botulinum toxin	-	+	-	-
SIDE 2	NCTF 135HA	-	-	-	-
	Botulinum toxin	-	+	-	-

Table 2. Bazin forehead wrinkle scale for women.

BAZIN FOREHEAD WRINKLE SCALE FOR WOMEN	
GRADE	DESCRIPTION
0	No wrinkle
1	Fine lines
2	Slight wrinkles
3	Moderately deep wrinkles
4	Deep wrinkles
5	Very deep wrinkles

The clinical scoring was performed on a 9-scale base scoring system (0 = none, 1 - 3 = light, 4 - 6 = moderate, 7 - 9 = important) for skin homogeneity, hydration, and firmness. In addition, clinical scoring of skin radiance was based on four scales scoring system as follows: 0 = very dull skin, 1 = dull skin, lacking radiance, 2 = slightly radiant skin, 3 = radiant skin, 4 = very radiant skin.

Wrinkle severity at maximum brow elevation was evaluated using the five-point Bazin forehead wrinkle scale (BFWS, 0 = no wrinkle, 1 = fine lines, 2 = slight wrinkles, 3 = moderately deep wrinkles, 4 = deep wrinkles, and 5 = very deep wrinkles) (Table 2, Figure 2).

Assessments of physician-reported and subject-reported appearance were conducted using the VISIA skin analysis system. Outcomes were assessed at D0 and D60. The satisfaction rate was evaluated based on the GAIS, a 7-point scale to measure the post-treatment improvement rate from “very much improved” to “very much worse” (Table 3). The improvement scale with reference to the pre-injection aging grade was assessed independently by both subjects and physician at D0 and D60. Assessments included visual evaluation and clinical scoring. All procedures were photographically documented.

2.4. Statistical Analysis

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

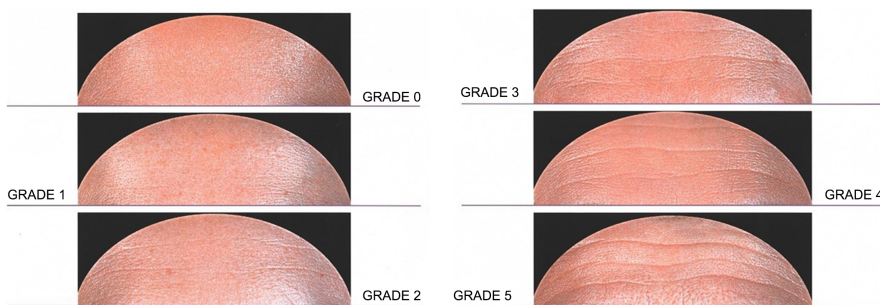


Figure 2. Bazin forehead wrinkle scale for females.

Table 3. GAIS (Global Aesthetic Improvement Scale) scoring.

GAIS (Global Aesthetic Improvement Scale) Scoring	
SCORE	GRADE
3	Very much improved
2	Much improved
1	Improved
0	No change
-1	Worse
-2	Much worse
-3	Very much worse

3. Results

3.1. Clinical Scoring of Forehead Wrinkles

The wrinkle scoring comparison showed a significant reduction in wrinkle severity at D60 compared to baseline (D0) in both groups. At D60, response rates (patients who scored 0 [none] or 1 [fine lines] on the BFWS) were 100% (8 patients) on the botulinum toxin + NCTF side and 50% (4 patients) on the botulinum toxin alone side (mean score of 0.375, $p < 0.001$ and 1.625, $p < 0.05$, respectively), *i.e.*, a decrease of 2 and 0.75 points respectively ($p < 0.01$), suggesting a greater efficacy of the addition of NCTF to the treatment compared to botulinum toxin alone. The results of wrinkles scoring are summarized in **Table 4** and **Figure 3**.

Table 4. Clinical scoring values at D0 and D60.

Evaluation	Treatment	Day	Mean	Sd	Comparison at baseline t-test (p-value)	Comparison d0 vs d60 t-test (p-value)	Comparison delta control (toxin) vs + nctf t-test (p-value)
Forehead Wrinkles	NCTF + BoNTA	D0	2.375	0.52	1	-	p = 0.004
		D60	0.375	0.52	-	2.04141E-06	
	BoNTA	D0	2.375	0.52	1	-	
		D60	1.625	0.74	-	0.034579201	
Skin Radiance	NCTF + BoNTA	D0	0.625	0.52	1	-	p < 0.001
		D60	2.75	0.46	-	5.40847E-07	
	BoNTA	D0	0.625	0.52	1	-	
		D60	0.75	0.46	-	0.618559951	
Skin Hydration	NCTF + BoNTA	D0	1.75	1.04	1	-	p < 0.001
		D60	6.75	1.16	-	3.06584E-07	
	BoNTA	D0	1.75	1.04	1	-	
		D60	1.75	1.04	-	1	
Skin Firmness	NCTF + BoNTA	D0	2	1.07	1	-	p < 0.001
		D60	7	0.76	-	3.56675E-08	
	BoNTA	D0	2	1.07	1	-	
		D60	2	1.07	-	1	
Skin Homogeneity	NCTF + BoNTA	D0	1.625	0.92	1	-	p < 0.001
		D60	6.125	0.99	-	1.92069E-07	
	BoNTA	D0	1.625	0.92	1	-	
		D60	1.75	0.71	-	0.764476762	

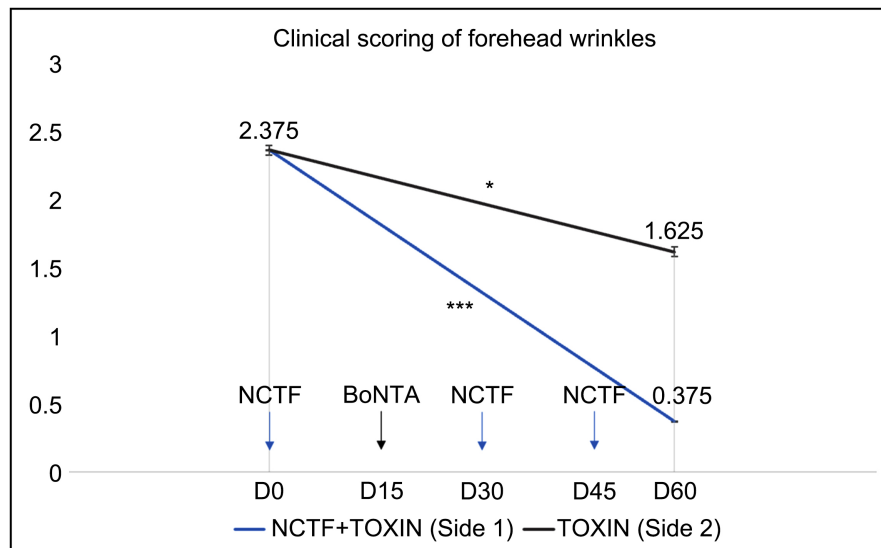


Figure 3. Evolution of mean forehead wrinkle score from D0 to D60 after 3 sessions of intradermal injections of NCTF 135HA and one injection of BoNTA or one injection of BoNTA alone. Significant: * $p < 0.05$, *** $p < 0.001$.

3.2. Clinical Scoring of Skin Quality

After objective consideration, as shown in **Table 4**, all patients presented an overall improvement in their facial features.

The mean hydration score increased significantly only on the face-side treated with botulinum toxin and NCTF®135HA from D0 to D60 (mean score 6.75 versus 1.75 respectively, $p < 0.001$) compared to botulinum toxin alone (1.75 versus 1.75, NS).

The mean homogeneity score also increased significantly on the side treated with the combination of botulinum toxin + NCTF®135HA compared to the side treated only with botulinum toxin (delta D60-D0 of 4.5 points on side one versus 0.125 point on side 2, $p < 0.001$) (**Table 4**, **Figure 4**).

Concerning the skin firmness, results showed no difference (delta = 0) before and after treatment with botulinum toxin alone. At the same time, we observed a delta of 5 points between D60 and baseline (D0) ($p < 0.001$) for the other side of the face treated with toxin + NCTF®135HA (**Table 4**, **Figure 4**).

Finally, the skin radiance evaluated by clinical scoring (scores 0 to 4, 0 corresponding to very dull skin and 4 corresponding to very radiant skin) showed a significant increase of the score for combined treatment at D60 compared to D0, D15, D30, and D60 ($p < 0.001$ for all study visits). This parameter was increased particularly by 2.125 points after 3 NCTF®135HA treatments + BoNTA, compared to botulinum toxin alone (an increase of 0.125 point) ($p < 0.001$) (**Table 4**, **Figure 4**).

3.3. GAIS Scoring

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

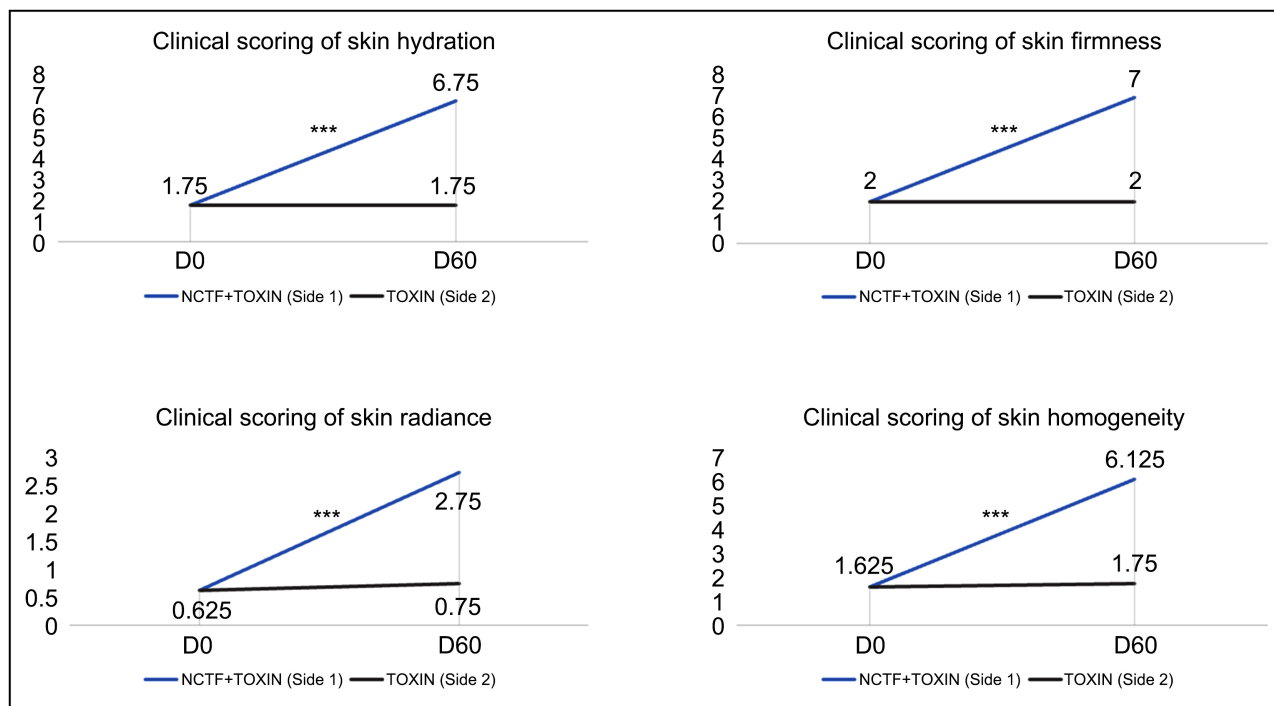


Figure 4. Evolution of mean skin hydration, skin firmness, skin radiance and skin homogeneity scores from D0 to D60 after 3 sessions of intradermal injections of NCTF 135HA and one injection of BoNTA or one injection of BoNTA alone. Significant: * $p < 0.05$, *** $p < 0.001$.

After objective examination, as shown in **Figure 5**, the evaluator reported mean scores on the GAIS of 2.375 (much improved) on the side of the face treated with botulinum toxin + NCTF*135HA compared to the side of the face treated with toxin alone (score of 0 (no change), $p < 0.001$).

On D60, patients reported a significantly greater aesthetic improvement score with combined treatment (mean score of 2.5 vs. 0.125 for toxin alone, $p < 0.001$).

Results showed that the outcome after botulinum toxin + NCTF was much improved in 4 patients (50%) and very much improved in the four other patients (50%) (total 100%). Interestingly, when observing the other side of the face (toxin alone), the outcome was deemed improved in only one patient (12.5%), and seven patients (87.5%) considered that their appearance was essentially the same as baseline (no changes).

4. Discussion

Skin aging is a very complex multifactorial process caused by intrinsic and extrinsic mechanisms and a variety of cellular impairments, including those of fibroblasts and keratinocytes.

In particular, the forehead is a zone prone to repeated facial expressions and hyperdynamic activity, which leads to the development of wrinkles and the prominence of these imperfections due to a loss of firmness and hydration [9] [10].

A variety of therapeutic alternatives have been developed to reduce forehead wrinkles and improve overall skin quality.

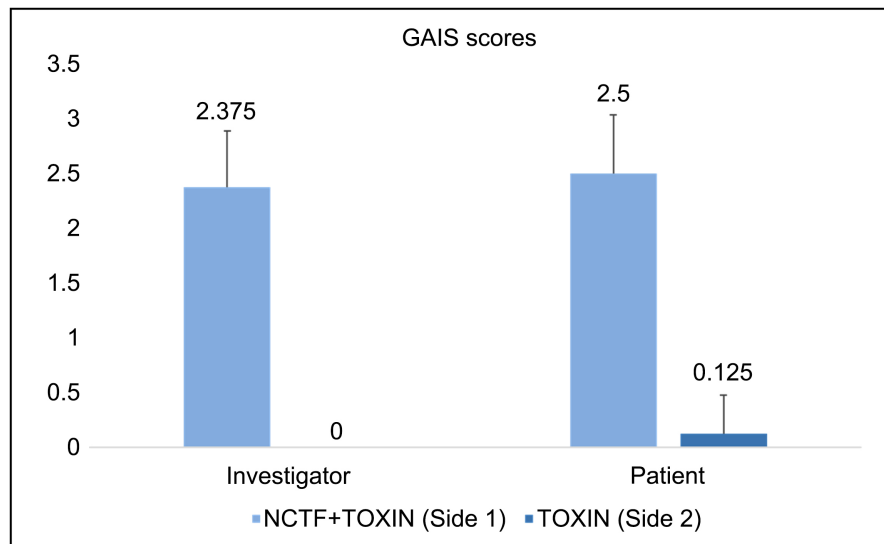


Figure 5. Investigator and patient Global Aesthetic Improvement Scale (GAIS) ratings at D60 after 3 sessions of intradermal injections of NCTF 135HA and one injection of BoNTA or one injection of BoNTA alone.

Botulinum toxin has been used in the field of ophthalmology for decades. In the last 20 years, its use has spread to many health domains, particularly in dermatology [14] [15]. It comprises seven different neurotoxins, although only toxins A and B are administered in therapeutic settings. Botulinum toxin A successfully improves facial lines, including forehead wrinkles [28]. However, as the results of the toxin are temporary and will decrease after several consecutive injections, recent research has focused on the combination of botulinum toxin and other therapeutic options, such as hyaluronic acid fillers [19] [25] [26], while studies on the benefits of combining other procedures on human skin, such as biorevitalizing treatment are lacking. Furthermore, the efficacy and safety of such a therapeutic strategy are rarely reported.

The polycomponent NCTF®135HA is a dermal microfiller based on non-cross-linked hyaluronic acid designed for skin revitalization and hydration, the filling of superficial wrinkles, and the re-plumping of mature or sagging skin [22] [23] [24].

This study aimed to evaluate the synergistic effects of combining botulinum toxin injections with a biorevitalizing treatment in the forehead.

The improvements in skin health observed in the current study are consistent with previous studies examining the efficacy of NCTF®135HA injections [22] [29].

The mean wrinkle score decreased significantly at D60 after three sessions of NCTF injections (at D0, D30, and D45) combined with one session of botulinum toxin injections at D15 compared to botulinum toxin injections alone.

Overall, results showed that this combination treatment resulted in a statistically significant increase in skin hydration, skin firmness, skin radiance, and skin homogeneity in patients with forehead wrinkles. The synergistic use of different

techniques (BoNTA + NCTF®135HA) is highly advantageous, has no adverse effects (both groups experienced similar rates of injection site bruising), and is correlated with a high level of patient satisfaction.

Altogether, these results demonstrate that the addition of NCTF to the combinatory approach significantly improves the skin's global aesthetic aspect and decreases wrinkles substantially compared to the patients who underwent botulinum toxin injections without the biorevitalization option.

Statement of Ethics

All procedures adopted in the present study were in respect to the ethical standards in the World Medical Association Declaration of Helsinki.

Written informed consent was obtained from the patients for publication of this case report and any accompanying images. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines.

Conflict of Interest Statement

Ambassador for Fillmed Laboratory, LPG Laboratory and MINT PDO Threads.

Author Contributions

Dr Philippe Hamida-Pisal conceived the presented idea, carried out the procedures and wrote the manuscript.

Data Availability Statement

All data reported in this case study are included in this manuscript and its online supplementary material. Further inquiries can be directed to the corresponding author.

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