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ORIGINAL ARTICLE NON-SURGICAL AESTHETIC

Effects of Polynucleotide Dermal Filler in the Correction of Crow's Feet Using an Antera Three-Dimensional Camera

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Abstract

Background Dermal fillers are gaining interest for tissue enlargement and skin improvement. Among them, polynucleotides have demonstrated multiple skin beneficial effects. The effects of polynucleotide fillers were objectively evaluated using an Antera 3D camera, subjectively evaluated by participants and investigators.

Methods Thirty subjects with crow's feet were enrolled in the study. The subjects received polynucleotide filler for crow's feet. Crow's feet grading score (CFGS), global esthetic improvement scale (GAIS), and Antera 3D imaging results were evaluated.

Results Twenty-eight subjects (93.3%) completed the study. An improvement in CFGS compared with that at baseline ($p < 0.001$) was observed 18 weeks after the first injection of polynucleotides. Additionally, at the final visit, there were improvements in wrinkle, texture, pore, depression, and Hb values compared with those at baseline ($p < 0.05$). However, no significant difference in melanin level was detected between the initial and final visits.

Conclusions Improvements in wrinkles, pores, texture, depression, and Hb level after polynucleotide filler injection were verified by objective and subjective evaluations. To the best of our knowledge, this is the first report on the objective evaluation of polynucleotide fillers in crow's feet using the Antera 3D camera.

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Keywords Polynucleotide · Dermal filler · Crow's feet

Introduction

Wrinkles are a major beauty-related concern faced by middle-aged adults, resulting in a growing demand for procedures for softening or removing wrinkle [1]. Crow's feet are wrinkles spreading from the corner of the eyes and are naturally developed owing to the loss of collagen and elastic tissue in the skin with aging. The use of injectable agents has increased over recent years because of the demand for minimally invasive techniques and their simplicity. Recently, dermal fillers have received considerable interest in tissue enlargement and skin improvement [2]. Among them, hyaluronic acid (HA) has received the most attention. It is used in cosmetics because of its biocompatibility and stability [3, 4]. However, the use of HA fillers carry an inherent risk of hypersensitivity reactions [5] and can cause inflammation and elicit adverse effects

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including redness, edema, hematoma, and pain [6]. Therefore, various substances have been developed to replace HA fillers.

Recently, a new filler was synthesized using purified polynucleotide extracted from germ cells of salmon and other fish [7]. Polydeoxyribonucleotide has multiple beneficial biological activities in skin cells, including hypopigmentation, induction of mitochondrial biogenesis, and inhibition of collective tissue proteins [8]. In a clinical trial, efficacy outcome measures showed no significant differences between the polynucleotide filler and HA filler groups [9]. Presently, polynucleotide is widely used; however, only a few studies have conducted objective and subjective evaluations of its efficacy in the treatment of crow's feet.

In this clinical study, we evaluated the effects of polynucleotide fillers subjectively using CFGS, global esthetic improvement scale (GAIS), and objectively using an Antera 3D camera. The Antera 3D camera is a three-dimensional (3D) camera used to evaluate skin objective indicators and measure the texture and color of the skin by reconstructing 3D images. The Antera scoring system is a 3D imaging method that objectively presents images before and after treatment; the comparison results are accurate and avoid interference factors [10].

Materials and Methods

Participants

This study was conducted at Wonju Severance Christian Hospital, Wonju, Korea. It involved 30 healthy volunteers aged 19–60 years with crow's feet grading score (CFGS) of 2–4 points. The exclusion criteria were as follows: received facial rejuvenation therapy (e.g., botulinum toxin and filler), history of skin disorder, immune disease, currently pregnant, and lactating. All subjects voluntarily participated in the study and were allowed to discontinue at any time during the study. The subjects provided written informed consent for the publication and use of their images. Written informed consent was obtained from all participants after a full explanation of the risks and benefits of the procedure and the study protocol conformed to the guidelines of the Declaration of Helsinki. This study was approved by the institutional review board (IRB No.19-003) and ethics committee of Wonju Severance Christian Hospital.

Study Device

HP cell Vitaran I® (BR PHARM Co., Ltd., Wonju, Korea) is a transparent liquid consisting of polynucleotides (20 mg/mL). It was administered via a sterile 1.0-mL prefilled syringe with a 34-gauge needle.

Study Procedure

After screening the subjects, polynucleotide fillers were injected into the crow's feet site of all subjects. To confirm whether an acute allergic reaction occurred, a test injection was administered, and the subjects were monitored for any reactions for 2 min, before administering the main injection. A diary was provided to all subjects, and instructions were provided to record the occurrence of adverse effects during 2 weeks following the injection. The treatment was performed by the same investigator every 2 weeks, and a total of four treatments were administered. All subjects visited the study clinic at 2, 4, 6, 8, 10, and 18 weeks after the initial treatment. As the first treatment was the second clinic visit, it was recorded as v2, and according to the number of visits, visit at 8 weeks after the first treatment was recorded as v6, visit at 10 weeks as v7, and that at 18 weeks as v8 (Fig. 1). All treatments were performed using serial puncture techniques; 0.5 mL of the filler was injected at the corner of each eye, and the dose was altered based on the investigator's discretion. There was no control group in the present study.

Assessments

Clinical efficacy was measured using the crow's feet grading score (CFGS), global esthetic improvement scale (GAIS), and Antera 3D parameters. Antera 3D digital images were obtained at four different time points during resting muscular activity of both periocular areas.

The primary efficacy measure was the mean Antera 3D evaluation scores for wrinkle, texture, pore, depression, melanin, and hemoglobin level, which were processed using Antera Pro® (v2.8.6; Miravex Limited, Dublin, Ireland). The secondary efficacy measures were the mean improvement in CFGS at 18 weeks compared with that at baseline, determined by blinded evaluators and the changes in GAIS (1 = very much improved, 2 = much improved, 3 = improved, 4 = no change, 5 = worsened), evaluated by the subjects themselves (self-assessment) and the investigators over 18 weeks. Antera Pro® was used to analyze images before the first procedure and after the first procedure at 8, 10, and 18 weeks. A small filter appropriate for analyzing fine wrinkles from 0.5 to 1 mm in size was used for wrinkle assessment [11].

Safety

The incidence of the following adverse events were evaluated at each visit: erythema, edema, itching, stinging

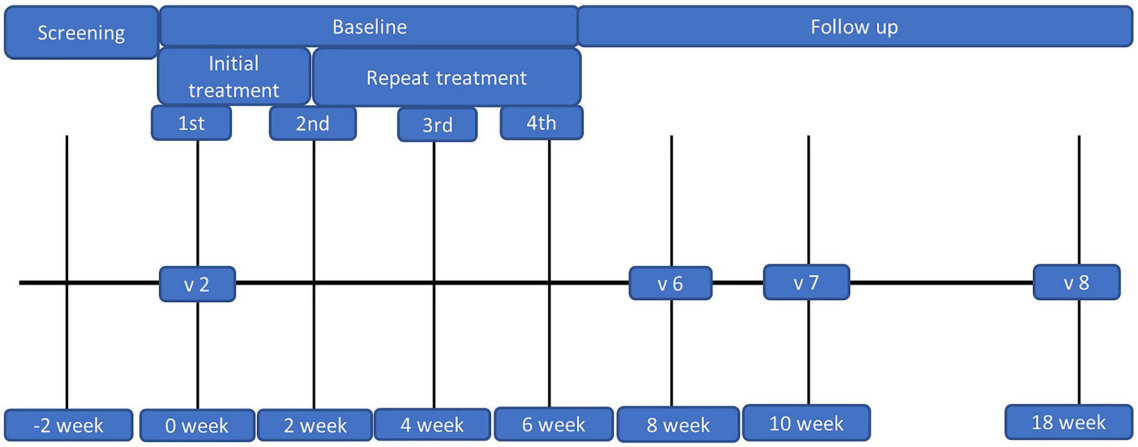

Fig. 1 Study flowchart

sensation, and tightness. Safety was assessed using laboratory findings and physical examinations during the study. All adverse events that occurred during the entire surveillance period were reported, regardless of their causal relationship with the study drug.

Statistical Analysis

Statistical comparisons before and after treatment (each visit) were performed by Wilcoxon signed-rank test using R software version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria). Data are presented as mean and standard deviation (SD). Statistical significance was set at $p < 0.05$.

Results

Patient Disposition and Baseline Characteristics

In this study, we enrolled 30 subjects, 27 women, and 3 men. All subjects were evaluated for safety after each procedure. However, two subjects dropped out of the study, and hence, 28 subjects were included in the evaluation of treatment efficacy. The mean age of the subjects was 55.71 years.

Subjective Assessment of Crow's Feet Improvement

The average CFGS was 2.77 ± 0.85 at 0 week (v2), 1.96 ±0.79 at 8 weeks (v6), 1.71 ± 0.71 at 10 weeks (v7), and 1.84 ± 0.78 at 18 weeks (v8). The CFGS score at v6 ($p < 0.001$), v7 ($p < 0.001$), and v8 ($p < 0.001$) was significantly different from that at v2.

The GAIS scores were determined by the investigator or were self-assessed by the study subjects. The average GAIS scores determined by the observer were 2.68 ± 0.47 at v6, 2.21 ± 0.62 at v7, and 1.48 ± 0.50 at v8. The average GAIS scored determined by the subjects were 2.34 ± 0.84 at v6, 2.43 ± 0.85 at v7, and 2.30 ± 0.85 at v8 (Fig. 2, Table 1).

Objective Assessment of Crow's Feet Improvement Using the Antera 3D Camera

The Antera scores for wrinkle improved from 19.39 ± 7.84 at v2 to 16.02 ± 5.78 at v6, 15.72 ± 5.52 at v7, and 17.21 ± 5.69 at v8. The Antera scores for wrinkle improvement at v6, v7, and v8 ($p < 0.001$) were significantly different from those at v2.

The Antera scores for texture improved from 20.70 ± 9.15 at v2 to 16.59 ± 6.76 at v6, 16.23 ± 6.24 at v7, and 17.91 ± 6.53 at v8. The Antera scores for texture improvement were significantly different at v6, v7, and v8 ($p < 0.001$) compared to those at v2.

The Antera scores for depression improved from 1.19 ± 0.65 at v2 to 0.91 ± 0.48 at v6, 0.88 ± 0.47 at v7, and 1.01 ± 0.47 at v8. The Antera scores for improvement in depression at v6, v7, and v8 ($p < 0.001$) were significantly different from those at v2.

The Antera scores for pore improved from 0.32 ± 0.15 at v2 to 0.23 ± 0.12 at v6, 0.24 ± 0.13 at v7, and 0.27 ± 0.12 at v8. The Antera scores for pore improvement at v6, v7, and v8 ($p < 0.001$) were significantly different from those at v2.

The Antera scores for melanin level were 0.61 ± 0.08 at v2, 0.60 ± 0.08 at v6, 0.59 ± 0.07 at v7, and 0.61 ± 0.07 at v8. The Antera scores for melanin level at v6 ($p = 0.022$), v7 ($p = 0.002$) were significantly different from those at v2. However, the scores at v8 ($p = 0.968$) were not significantly different from those at v2.

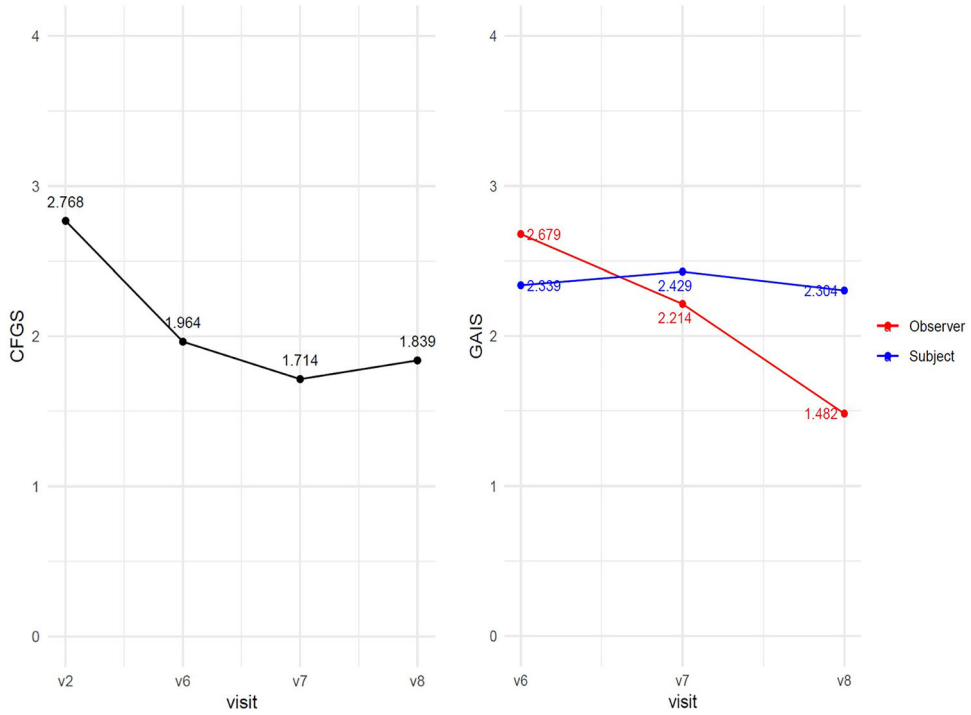

Fig. 2 Mean changes in crow's feet grading scale (CFGS) and global esthetic improvement scale (GAIS)

Table 1 Measurement of crow's feet using the crow's feet grading scale, global esthetic improvement scale, and Antera 3D camera

		v2	v6	v7	v8
CFGS		2.77 ± 0.85	1.96 ± 0.79	1.71 ± 0.71	1.84 ± 0.78
		Ref	< 0.001*	< 0.001*	< 0.001*
GAIS	Observer	Ref	2.68 ± 0.47	2.21 ± 0.62	1.48±0.50
	Subject	Ref	2.34 ± 0.84	2.43 ± 0.85	2.30±0.85
Wrinkle		19.39 ± 7.84	16.02 ± 5.78	15.72 ± 5.52	17.21 ± 5.69
		Ref	< 0.001*	< 0.001*	< 0.001*
Texture		20.70 ± 9.15	16.59 ± 6.76	16.23 ± 6.24	17.91 ± 6.53
		Ref	< 0.001*	< 0.001*	< 0.001*
Depression		1.19 ± 0.65	0.91 ± 0.48	0.88 ± 0.47	1.01 ± 0.47
		Ref	< 0.001*	< 0.001*	< 0.001*
Pore		0.32 ± 0.15	0.23 ± 0.12	0.24 ± 0.13	0.27 ± 0.12
		Ref	< 0.001*	< 0.001*	< 0.001*
Melanin		0.61 ± 0.08	0.60 ± 0.08	0.59 ± 0.07	0.61 ± 0.07
		Ref	0.022*	0.002*	0.968
Hemoglobin		0.89 ± 0.14	0.93 ± 0.17	0.90 ± 0.16	0.85 ± 0.17
		Ref	0.018*	0.359	0.015*

Continuous values are described as mean ± standard deviation

v2, 2nd visit; v6, 6th visit; v7, 7th visit; v8, 8th visit; CFGS Crow's feet grading scale; GAIS Global esthetic improvement scale

*Indicates p value less than 0.05. p value was measured based on Wilcoxon rank-sum test, and represents the statistical difference compared with that of v2

The Antera scores for hemoglobin level were 0.89 ± 0.14 at v2, 0.93 ± 0.17 at v6, 0.90 ± 0.16 at v7, and 0.85 ± 0.17 at v8. The Antera scores for hemoglobin level at v6 (p = 0.018) and v8 (p = 0.015) were significantly different from those at v2. However, the scores at v7 (p = 0.359) was not significantly different from those at v2 (Fig. 3, Table 1).

Figure 4 shows the photographs of crow's feet at baseline (v2) and 18 weeks (v8) after the first treatment with polynucleotide filler. Figure 5 shows the Antera 3D images

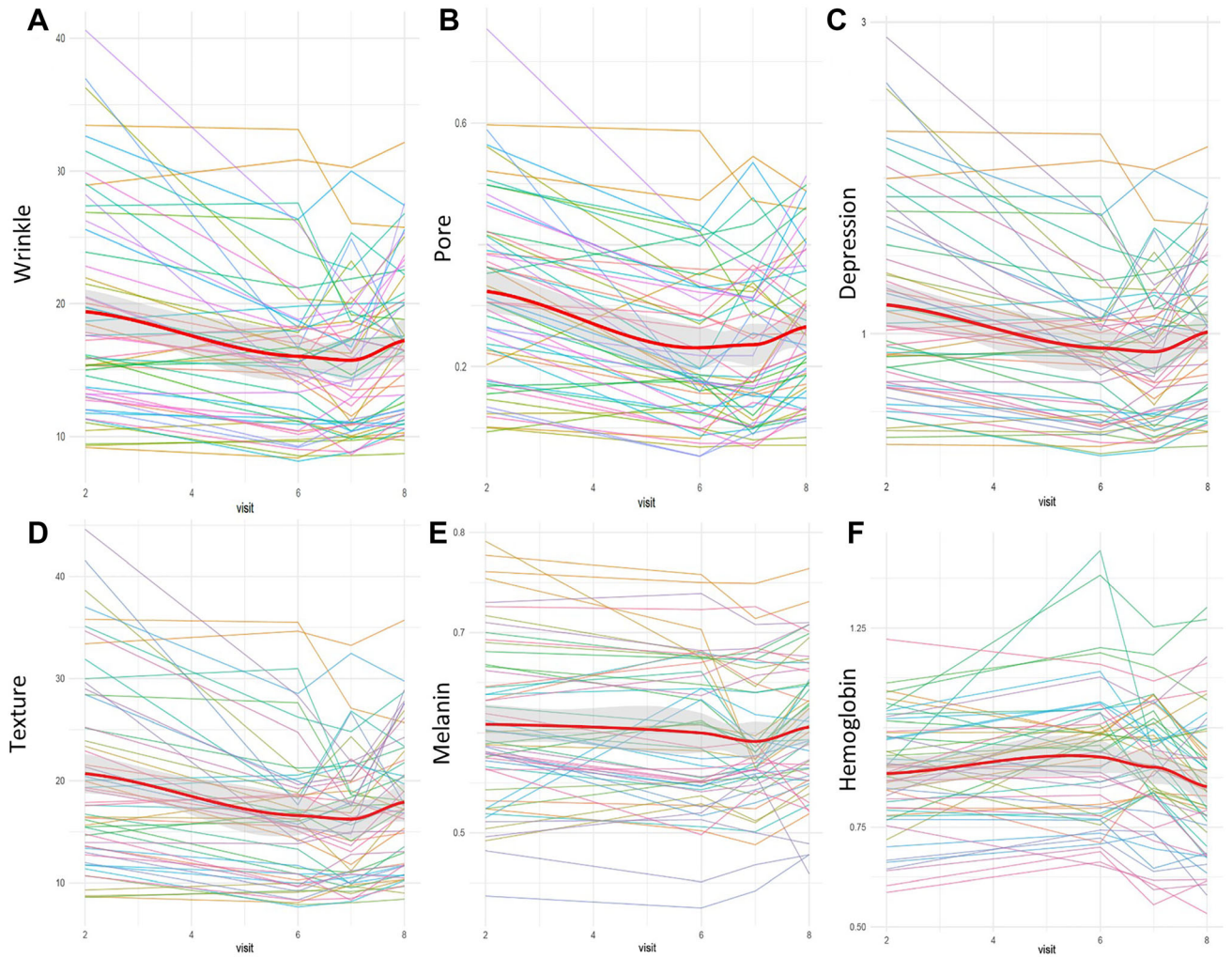

Fig. 3 Changes in the score of wrinkle **a**, pore **b**, depression **c**, texture **d**, melanin level **e**, and hemoglobin level **f** evaluated using Antera Pro®

of the crow's feet at baseline and 18 weeks after the first procedure.

Safety

In general, the polynucleotide fillers were well tolerated. No severe adverse effects were reported by the subjects and no persistent skin problems occurred during the study. Transient edema in the injection site (71.42%) was the most common adverse effect, followed by erythema (10.71%) and itching (3.57%).

Discussion

Several clinical studies have described the therapeutic use of polynucleotides in skin regeneration and wound healing [12–15]. Polynucleotide fillers can facilitate more favorable physiological conditions for the growth of cells in the skin, assist in increasing the production of amorphous extracellular matrix components and fibrillar substances, reduce fine wrinkles, and improve skin turgidity, elasticity, and tonicity [9]. Additionally, the current trend is gradually changing to regenerating skin by stimulating cellular components (such as fibroblasts) rather than injecting synthetic components (e.g., collagen, hyaluronic acid, and glycoprotein). Polynucleotides have been demonstrated to have multiple beneficial biological activities, including hypopigmentation, induction of mitochondrial biogenesis, and inhibition of collective tissue proteins, in skin cells in vitro [8]. Therefore, in recent years, many fillers containing polynucleotides have been studied. Jeong et al. confirmed the findings of a study that verified polynucleotide fillers as clinically effective based on subjective evaluation indicators, CFGS and GAIS scores [16]. However, as only a few studies have compared the clinical effects and carried out objective evaluations, we studied the efficacy using the Antera 3D camera. The results of this

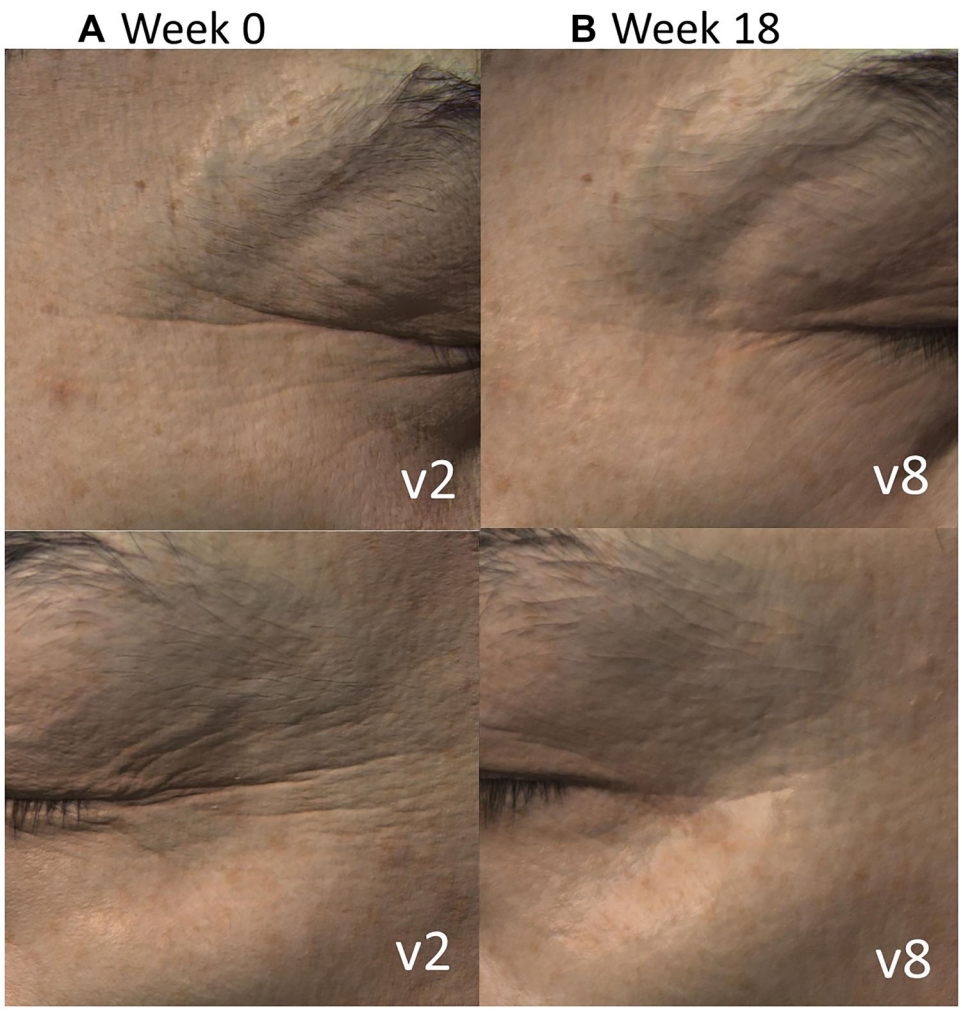

Fig. 4 Photograph of crow's feet at baseline (v2, left) and 18 weeks after first treatment of polynucleotide filler (right)

study objectively showed improvements in wrinkles, texture, pores, and depression. The improvements in wrinkles, texture, pores, and depression could be attributed to the effect of polynucleotides on collagenogenesis and mitochondrial function through the inhibition of matrix metalloproteinases-1 gene expression and elastase enzyme activity. Additionally, there was a significant difference in the melanin level up to v7. It was confirmed that there was effective skin tone improvement via the inhibition of melanogenesis. These results are consistent with those of previous studies [8, 17, 18]. However, it did not last longer than 3 months. This may be due to the small sample size; and therefore, further evaluation is required.

When comparing the Antera scores, the overall value of v7 showed the best result. The difference in the mean value (wrinkle, texture, pore, depression, and melanin level) at v7 seems to be the best, considering the cumulative effect of the addition of polynucleotides filler at v6, but there was no significant difference between v7 and v6. In addition, during the post-procedural evaluation, the average value (wrinkle, texture, pore, depression, and melanin level) at v8 was the worst. Considering that the time point v8 is 3 months after the last procedure, it can be considered that the polynucleotide filler did not maintain a consistent effect beyond 3 months. However, it is clear that even after 3 months post treatment, the filler is more effective than before treatment. In this study, as measurements were not made at v3, v4, and v5, it was not possible to determine the exact time of maximal effect of the polynucleotide filler, and it is necessary to investigate this in future.

The advantage of polynucleotide filler is that there are no major adverse effects unlike other permanent or HA fillers [19–21]. The disadvantage of polynucleotide filler is that it has less volumizing effect and durability than HA fillers [9, 16]. As localized swelling occurs immediately after injection, subjects may experience temporary discomfort in daily life.

A limitation of this study is that a split-face study design was not implemented. In addition, the sample size used in the study was small. Nevertheless, objective and statistically significant results were obtained in this study.

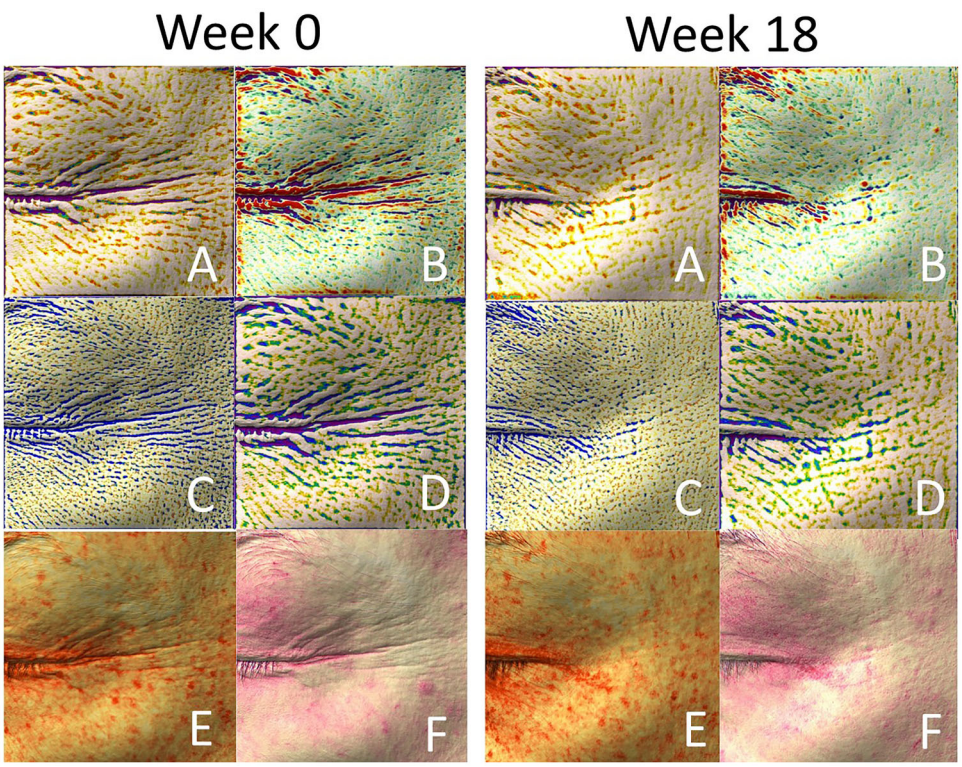

Fig. 5 Antera 3D image of crow's feet at baseline (v2, left) and 18 weeks after first treatment of polynucleotide filler (right). **a**: wrinkle, **b**: texture, **c**: pore, **d**: depression, **e**: melanin level, **f**: hemoglobin level

Conclusions

In addition to improving crow's feet around the eyes, polynucleotide filler was observed to facilitate the improvement of pores, texture, and skin tone. Such activities are considered to enhance skin quality as well as wrinkles, in shallow wrinkles, such as around the eyes. Nevertheless, further prospective, larger, randomized, and controlled investigations are required to confirm our findings and to optimize polynucleotide filler injection in patient with severe crow's feet wrinkles for enhanced results.

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Funding The all authors declare no potential conflict of interest relevant to this study.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent The subjects provided written informed consent for the publication and use of their images.

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