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Research Article

The Efficacy and Safety of Touch-up Treatment with Hyaluronic Acid Filler for the Correction of Nasolabial Folds -

Kui Young Park[1#], Se YeongJeong[1,2#], JoonHyuk Suh[1], Sun Young Choi[1], EunJa Choi[1], BeomJoon Kim[1*], Myeung Nam Kim[1]

[1]*Department of Dermatology,Chung-AngUniversity College of Medicine, Seoul, South Korea*

[2]*Good Day Skin & Laser Clinic, Seoul, South Korea*

***Address for Correspondence:** BeomJoon Kim, M.D., Ph.D., Chief Professor, Department of Dermatology, Chung-Ang University Hospital, Chung-Ang University Collegeof Medicine, 224-1 Heukseok-dong, Dongjak-ku, Seoul 156-755, South Korea, Tel: 82-2-6299-1525; Fax: 82-2-823-1049; E-mail: beomjoon@unitel.co.kr

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ABSTRACT

Background: Many new brands of Hyaluronic acid (HA) fillers are being produced, and the longevity and safety are always major concern about HA fillers.

Objective: To evaluate the efficacy, tolerability, and safety of touch-up treatment of a HA filler, Elravie® deep line which is used for correcting nasolabial folds (NLFs).

Methods: The rheological property values of HA fillers were measured using a rheometer.A total of 50 subjects with visible NLFs were enrolled in this clinical study and were divided into test and control groups. All subjects were injected with same amount of HA in both NLFs and only the test group had touch-up treatment after 9 months of first injection. All participants were then reassessed for cosmetic changes using Wrinkle Severity Rating Scale (WSRS) and Global aesthetic improvement scale (GAIS).

Results: By month 9, the mean improvement in the WSRS of test group compared to control was not statistically significant. But on month 12, 15 and 18, the mean WSRS of test group compared to control were remarkably improved. GAIS of test group showed also significant high score since month 12, compared to control. The touch-up treatments of filler were well-tolerated and adverse reactions were mild and transient in most cases.

Conclusion: The touch-up of HA filler, which is performed before injected filler was not fully disappeared, is safe, effective and more satisfactory treatment for correcting NLFs.

KEYWORDS: hyaluronic acid, nasolabial folds

INTRODUCTION

Hyaluronic acid (HA) filler is becoming most popular choice as a temporary filler for facial augmentation. It is a safe, non-surgical procedure that conveniently softens facial lines and furrows. HA is a normal component of human skin, where it provides a low degree of immunogenicity, therefore it has the added benefit of not requiring skin testing before use [1].

Different commercial HA fillers are similar, but their physical characteristics and clinical outcomes can differ. Favorable physical properties of administered HA include ease of administration, resistance to deformation after application, acceptable persistence, biocompatibility, and reversibility with hyaluronidase [2,3], HA implantation is not permanent. Like natural HA, manufactured HA once injected into the skin will gradually break down and be absorbed by the body. In most cases, the augmentation usually lasts anywhere between 3-9 months. To maintain the initial results, repeat treatments or touch-up treatments will be necessary, but comparative research on the efficacy and safety of touch-up treatment is limited [4].

In this study, we compared the efficacy and safety of touch-up treatment with newly developed HA filler (Elrevie®, Huons, Korea) for correcting nasolabial folds.

MATERIALS AND METHODS

Subjects

This randomized, controlled study was conducted at single center in Seoul, South Korea. We included 50 healthy Korean subjects over the age of 20 with visibly moderate to severe NLFs of 3 to 4 points on the Wrinkle Severity Rating Scale (WSRS)[5]. All subjects voluntarily participated in the study and were able to freely terminate their participation at any time. 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 and Korea Good Clinical Practice. The study was approved by Chung Ang University Institutional Ethics Committee.

Materials

The Elravie® deep line used in the study is a transparent, colorless, viscoelastic gel containing HA at a concentration of 23 mg/mL. It was administered via sterile, 1.0-mL, pre-filled syringes with 28-gauge needles.

Rheology measurement

The rheological property of HA fillers can be described by a complex modulus G*, which is defined as the sum of storage modulus G' and loss modulus G", also known as elastic and viscous modulus, respectively. The storage modulus G' is often used to characterize the rigidity of a gel, and a stiffer material has a higher G' and a softer material has a lower G'. The G' and G" values were measured using a rheometer (Kinexus, Malvern, UK) for determining δ=G"/G'. All the measurements were performed using a 20-mm steel plate oscillating at a frequency between 0.1 Hz and 10 Hz. The presented values were obtained at the frequency of 1 Hz and were compared.

Treatment

The faces of all subjects were digitally photographed at rest upon every visit. Subjects were randomized using a computer-generated code to determine who would receive touch-up treatment 9 months after first injection. Evaluating investigators were blinded, but subjects and treating investigators were not, as implied by study design. The same amount of 1.0 mL for each NLF was injected for each subject.

Efficacy Measures

The primary efficacy measure was point improvement in baseline WSRS scores as determined by the blinded evaluating investigators. Secondary efficacy measures included changes in Global Aesthetic Improvement Scale (GAIS) scores measured through subject self-assessment and also by the treating investigators. Pretreatment photographs of each subject taken at the screening visit were reviewed during each visit to aid severity assessments as a control.

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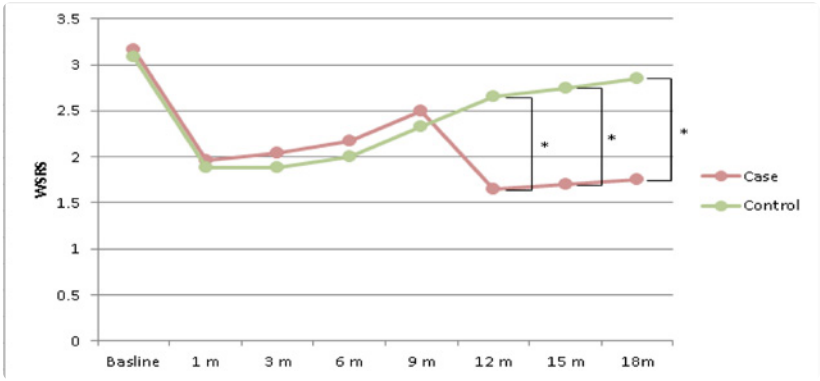

Figure 1: The change of Wrinkle Severity Rating Scale (WSRS) at baseline, 1, 3, 6, 9, 12, 15 and 18 month after the treatment with hyaluronic acid filler for the correction of nasolabial Folds. Statistical analysis showed significant difference since 12 months after first injection. *p<0.05.

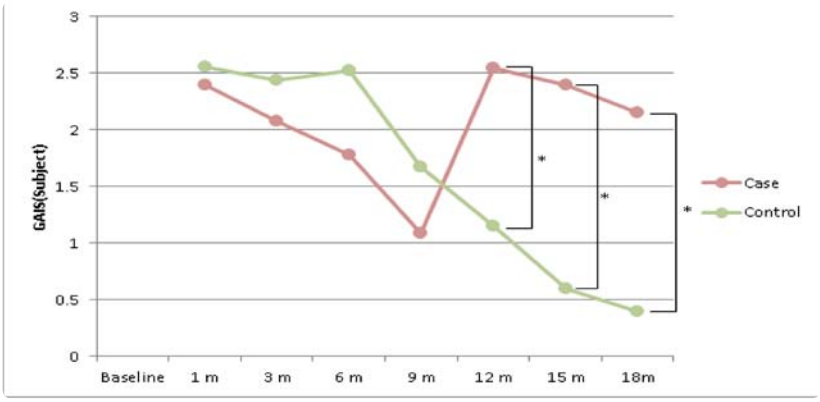

Figure 2: The change of Global Aesthetic Improvement Scale (GAIS), which is scored by subject, at baseline, 1, 3, 6, 9, 12, 15 and 18 month after the treatment with hyaluronic acid filler for the correction of nasolabial Folds. Statistical analysis showed significant difference since 12 months after first injection.*p<0.05.

Safety Measures

All abnormal reactions during this clinical test were documented.

Statistical Analysis

Inter-treatment differences were verified using Wilcoxon's signed rank test with a 5% significance level. A safety analysis of local injection site reactions and systemic adverse events was performed for both treatment groups using McNemar's test.

RESULTS

The rheological property of HA fillers was described in Table 1. A total of 50 subjects were randomized and treated with Elravie® deep line; 40 subjects completed this study with 18-months follow-up period. The baseline WSRS were 3.16±0.37 in experimental groups and 3.08±0.28 in control groups, respectively. Average values of WSRS differences between the experimental and control groups were evaluated by independent assessors on the 18 months after first injection and found to be 1.75±0.55 and 2.85±0.49 in the experimental and control groups, respectively. And this was statistically significant. The average value on the 9 months after first injection (just before touch-up) was 2.50±0.67 and 2.33±0.56 for experimental and control groups, respectively, and there was no statistical significance. The statistical significant difference between two groups was appearing since 12 months after first injection (Figure 1). Similarly, baseline GAIS rated by treating investigators and study subjects was not significantly different for the two groups, and then statistical significance was beginning to appear from 12 months after first injection (Figure 2,3). This demonstrates that all study subjects judged the severity of NLFs to be generally improved up to 9 months after the first injections of Elravie®, and the control groups was more improved 12 months after first injection. Representative photographs of the NLFs of a subject with touch-up taken before and after NLF correction are shown in Figure 4.

Adverse events (AEs) were actively elicited from all subjects in this study by asking about any redness, swelling, bruising, bleeding, and pain following filler treatments. Both treatments were well-tolerated and in most cases, AEs were mild and transient. Local reactions mostly disappeared within two weeks without any treatment, and there were no reports of serious local reactions or local reactions that required treatment (Table 2). The safety of touch-up group was not different from that of control groups.

DISCUSSION

Injecting fillers to correct wrinkles has become a standard therapeutic method in modern cosmetic practice. Due to the

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Table 1.The rheological property of HA filler(Elravie deep line®) G'

	G'(Pa) (1Hz)	G"(Pa) (1Hz)	G*(Pa) (1Hz)	η*(Pa s) (1Hz)	δ(°) (1Hz)	η(Pa s) (450s)	tanδ	Elasticity %
Elravie Deep Line®	265.1	33.89	267.2	42.63	7.29	1008.0	0.128	88.665

Table 2. Incidence of adverse events

Treatment	Adverse case (%)		95% Confidence interval		Adverse event (%)		Total
Touch up	5	20.00%	(4.3%,	35.7%)	6	24.00%	25
Control	5	20.00%	(4.3%,	35.7%)	6	24.00%	25
Total	10	20.00%	(8.9%,	31.1%)	12	24.00%	50

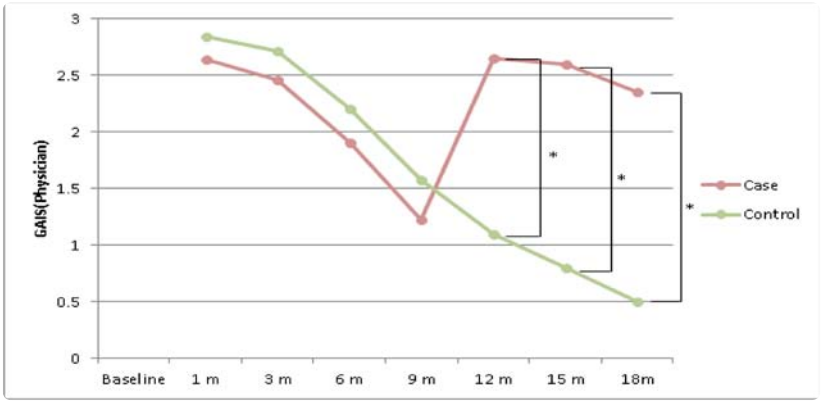

Figure 3: The change of Global Aesthetic Improvement Scale (GAIS), which is scored by physician, at baseline, 1, 3, 6, 9, 12, 15 and 18 month after the treatment with hyaluronic acid filler for the correction left nasolabial Folds. Statistical analysis showed significant difference since 12 months after first injection.*p<0.05.

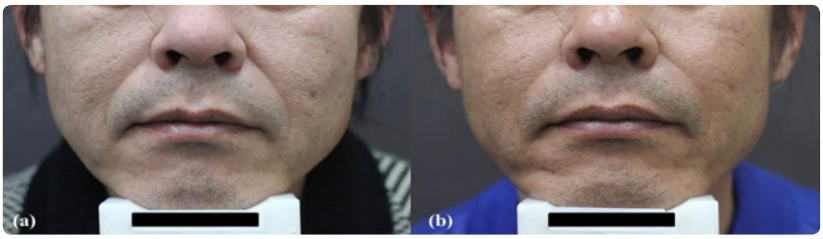

Figure 4: Representative photographs of the NLFs of a subject with touch-up taken before (a) and after (b) NLF correction.

increasing demand for filler injection, the market for dermal fillers has grown dramatically over the last several years. HA is currently the first-choice filler material for facial contouring via intradermal injection because HA fillers have several advantages over other fillers. Numerous studies have demonstrated that HA dermal fillers have better persistence than older collagen-containing products[6,7]. The favorable physical properties of HA include ease of administration, resistance to deformation after application, acceptable persistence, biocompatibility, and reversibility with hyaluronidase. HA can attract water to keep skin firm and moisturized. In addition, HA is a normal component of human skin and provides a low degree of immunogenicity [1-3,9].

As the filler market expands, many medical and pharmaceutical companies have begun manufacturing their own HA fillers. Elravie® belongs to the family of monophasic HA fillers. The Korean Food and Drug Administration approved Elravie® for correcting NLFs, and there is study of cosmetic results and safety profiles of Elravie® in the published literature[8]. The amount of time each patient gets from the fillers before needing a touch-up treatment varies by person; placement of product and frequency/timing of ongoing touch-ups. All these factors play a role in how long each filler lasts-from a few months to a few years. As with other advanced dermal fillers, many patients require less product and longer treatment intervals over time. In practice, patients and medical practitioners have reported needing less product and longer intervals between touch up treatments over time, if patients are diligent in returning for touch ups before the product has completely dissipated. Added longevity can be achieved from a touch-up while some filler is still present in the face, as this usually causes a response of additional collagen production from the skin. Whereas HA fillers usually last average 6-9 months, Elravie® with high quality cross-linking technology has been lasted over a year.

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So we decided a touch-up time to 9 month after first injection.

In this study, the mean improvement in the WSRS of test group compared to control was not statistically significant by month 9. But on month 12, 15 and 18, the mean WSRS of touch-up group compared to control was remarkably improved. GAIS of touch-up group showed also significant high score since month 12, compared to control. The fillers were well-tolerated and adverse reactions were mild and transient in most cases. There were no significant differences in local reactions to touch-up and control group. In this study, the touch-up injection of HA filler proved to be generally safe.

A careful review of filler material characteristics is needed to select fillers that enhance performance and safety. In addition, we could maximize cosmetic result and patient satisfaction through touch-up treatment of HA filler.

ACKNOWLEDGEMENTS

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