JAMA Facial Plastic Surgery | Original Investigation

Assessment of Long-term Outcomes of Soft-Tissue Augmentation by Injecting Fibroblasts Suspended in Hyaluronic Acid Filler

Kyung-Chul Moon, MD, PhD; Ki-Bum Kim, MD; Seung-Kyu Han, MD, PhD; Seong-Ho Jeong, MD, PhD; Eun-Sang Dhong, MD, PhD

IMPORTANCE In previous studies, this group has reported that cultured human fibroblasts suspended in hyaluronic acid (HA) filler might have potential use as a long-lasting injectable soft-tissue filler. However, the data were insufficient to determine the long-term outcomes.

OBJECTIVE To evaluate the long-term outcomes of cultured human fibroblasts suspended in HA filler used for soft-tissue augmentation.

DESIGN, SETTING, AND PARTICIPANTS A long-term case series study was performed. Between January 2010 and December 2013, a total of 38 patients were treated with fibroblast-HA filler mixture to augment nasal dorsa, nasolabial folds, and cheek depressions. Of these 38 patients, patients with follow-up period of greater than 3 years were included in this study. A total of 22 patients met the inclusion criteria.

MAIN OUTCOMES AND MEASURES Subjective assessment was performed to evaluate degree and time of resorption, improvement, satisfaction, softness of injection sites, and willingness to recommend this treatment to others. Objective assessment was carried out with patients' photographs. Safety and tolerability were also evaluated for this treatment.

RESULTS Of the 22 patients included in this study, 19 were women; mean (SD) patient age was 43 (15) years. All 22 patients experienced improvement following the treatment. Twenty (91%) patients were satisfied with the treatment. Nineteen patients (86%) considered that the injection site was as soft as it was before treatment. Patients' mean (SD) grading of improvement, satisfaction, and softness were 4.50 (0.51) (95% CI, 4.27-4.73), 4.14 (0.71) (95% CI, 3.82-4.45), and 4.82 (0.50) (95% CI, 4.59-5.00) at the last visit, respectively. Objective assessment demonstrated postoperative improvement in all patients: a rating of "much improved" was given to 7 patients (32%) by investigator 1; 8 patients (36%) by investigator 2; and 12 patients (55%) the injecting physician. This treatment was well tolerated; no adverse event was recorded for any patient.

CONCLUSIONS AND RELEVANCE Injection of cultured human fibroblasts suspended in HA filler might be successful for long-term soft-tissue augmentation. To our knowledge, this study represents the longest follow-up study of soft-tissue augmentation with a fibroblast-HA filler mixture to date.

LEVEL OF EVIDENCE 4.

JAMA Facial Plast Surg. doi:10.1001/jamafacial.2018.2127
Published online March 28, 2019.

Author Affiliations: Department of Plastic Surgery, Korea University Guro Hospital, Seoul, South Korea.

Corresponding Author: Seung-Kyu Han, MD, PhD, Department of Plastic Surgery, Korea University Guro Hospital, 148 Guro-Dong, Guro-Ku, 152-703, Seoul, Republic of Korea (pshan@kumc.or.kr).

Dermis, fat, and dermis-fat grafts have long been used for soft-tissue augmentation to correct facial wrinkles or skin contour defects. As increasing numbers of patients seek aesthetic improvement through minimally invasive procedures, the demand for effective and durable soft-tissue fillers to correct facial wrinkles or augment soft tissues has grown dramatically. To meet these demands, various commercially available soft-tissue filler products based on hyaluronic acid (HA) have been widely used.[1-3] They have a low likelihood of eliciting allergic reactions, and they require no skin testing. In addition, HA-based fillers can be stored at room temperature and unlike collagen, they have no risk of transmitting bovine spongiform encephalopathy.[4,5] Although HA fillers have been shown to be relatively safe and convenient to use, their variable degrees of resorption require repeated injections.[6]

To overcome these drawbacks, this group hypothesized that adding cultured human fibroblasts to HA filler might result in longer correction duration than that achieved using HA filler alone. The HA filler was expected to provide a dramatic early fill, while fibroblasts added to the filler could form extracellular matrices, leading to longer correction effect. However, commercial HA fillers were originally developed as filling materials of skin and soft tissue, not as cell carriers or suitable scaffolds.[7] In 2003, our research group conducted an animal study to evaluate the feasibility of using a commercial HA filler combined with cultured human dermal fibroblasts to enhance the longevity of injected bioimplants.[8,9] Those results demonstrated that HA filler mixed with cultured human dermal fibroblasts could produce human dermal matrices successfully with extended in vivo stability. Therefore, it might have potential as a living graft for long-lasting soft-tissue filler.[8,9]

Based on the results of our experimental study, a clinical pilot study was undertaken in 2003 to evaluate the clinical outcome of this method, particularly for augmentation rhinoplasty cases.[10] This method was well tolerated, all the patients were satisfied with the achieved long-term result, and no complications occurred.[10] However, the pilot study only included 6 patients with a follow-up period of 12 months. The number of patients and the follow-up period might not have been sufficient to determine the long-term outcomes of this treatment.

Therefore, the objective of this study was to evaluate the long-term outcomes of using cultured dermal fibroblasts seeded in HA filler as an injectable for soft-tissue augmentation.

Key Points

Question What are the long-term outcomes after using cultured fibroblasts seeded in hyaluronic acid filler for soft-tissue augmentation?

Findings In this case series with a follow-up period of greater than 3 years, soft-tissue augmentation with cultured fibroblasts seeded in hyaluronic acid filler was associated with positive outcomes for up to 6 years. All patients were improved following the treatment, and 91% of patients were satisfied with the treatment.

Meaning Cultured fibroblasts seeded in hyaluronic acid filler might be used as an injectable to sustain soft-tissue augmentation in the long term.

Methods

Techniques

Autologous Dermal Fibroblast Culture

A skin biopsy (approximately 1 cm^2) was performed in the groin area of each patient. Donor sites were closed by primary repair. The harvested skin was sent to a commercial laboratory (S Biomedics) for fibroblast culture. As instructed in the manual provided by the manufacturer, the skin was deepithelialized and minced. Healthy fibroblasts were extruded from minced skin and cultured in Dulbecco modified Eagle medium (Gibco), which contained 10% fetal bovine serum (Gibco). Cell density was measured with a hemocytometer, and cell viability was assessed using trypan blue dye exclusion assay. Six to 8 passages of cells were used for this study. To obtain sufficient fibroblasts (2×10^7 to 4×10^7 cells) for injection, 42 to 56 days were required. A series of additional efficacy release tests were performed on the final product, including confirmation of cell count and assessment of cell viability. In addition, fibroblasts were subjected to a series of quality controls to ensure their purity, safety, and potency and were approved by the Food and Drug Administration of Korea. These fibroblasts were packaged in a single-use vial intended for injection and shipped overnight to the treatment center at a temperature of 2°C to 8°C for administration within 24 hours.

Preparation and Injection of Fibroblast-HA Filler Mixture

Twenty million cultured fibroblasts were suspended in 1.0 mL of HA filler with moderate viscosity (Restylane; Q-Med). These fibroblasts in a single-use vial were warmed to body temperature for 5 to 10-minutes. Subsequently, fibroblasts and HA filler were placed into a 50-mL centrifuge tube under sterile conditions. The HA filler was gently stirred and mixed with fibroblasts in 1 direction to prevent cellular damage. Once mixed, the fibroblast-HA filler mixture was loaded into a 1- to 5-cc syringe immediately prior to injection.[10,11]

The desired shape and volume of the area to be augmented were decided by the patient. After preparing the skin around the injection site with common antiseptic solutions, the fibroblast-HA filler mixture was injected into intradermal, subdermal, and subcutaneous layers using 23-gauge and/or 26-gauge needles, depending on location and skin thickness. Immediate molding was performed with finger pressure to prevent possible uneven beading of the bioimplant. When the patient was satisfied with the augmentation, an additional volume was injected to achieve an overcorrection of 20% to 30%.

Table. Results of Improvement Grading Assessed by Independent Evaluators and the Injecting Physician

	Patients, No. (%)		
Characteristic	Investigator 1	Investigator 2	Injecting Physician
Much improved	7 (32)	8 (36)	12 (55)
Slightly improved	15 (68)	14 (64)	10 (46)
No change	0	0	0
Slightly worse	0	0	0
Much worse	0	0	0
Total	22 (100)	22 (100)	22 (100)

Patients

This was a case series from 1 center in Korea. The study protocol was approved by institutional review board of Korea University Guro Hospital (No. 2018GR0018). Between January 2010 and December 2013, a total of 38 patients (aged 22-72 years, 30 women, 8 men) were treated with fibroblast-HA filler mixture to augment nasal dorsum, nasolabial folds, and cheek depression. Of these 38 patients, patients with follow-up period of greater than 3 years were included in this study. Patients who had additional procedures were excluded to eliminate confounding events. A total of 22 patients met the inclusion criteria. Follow-up visits were conducted at 2 weeks and every 3 to 6 months after the injection. Mean (SD) follow-up length for these 22 patients was 49.2 (3.0) months (range, 3-6 years).

Subjective evaluation was performed through self-assessment by the patients. A questionnaire was designed to evaluate the following parameters: degree and time of resorption, improvement, satisfaction, softness of injection site, and willingness to recommend this treatment to others. Improvement measure was based on the Assessment of Aesthetic Improvement Scale (AAIS) in a 5-grade Likert scale: much worse, 1; worse, 2; no change, 3; improved, 4; and much improved, 5. Evaluation of satisfaction level also used a 5-grade Likert scale ranging from 5 (very satisfied) to 1 (very unsatisfied). Softness of injection site was measured on a 5-grade Likert scale, ranging from 5 (soft as before) to 1 (very hard). Lastly, patients were required to indicate whether they would recommend the treatment to others.

The AAIS was also used as an objective assessment tool to assess patient outcome. Photographs of the patients taken at pretreatment, follow-ups, and the last visit were reviewed. The assessment was performed by an injecting physician and 2 independent evaluating investigators (plastic surgeons) for baseline visit and the last visit.

Evaluation of safety and tolerability of the treatment was based on each follow-up visit and the last visit and was conducted by asking the patients about any adverse events or symptoms that might have occurred at the injection area.

Statistical Analyses

Data are presented as mean (SD) values. A 1-sample *t* test was used for statistical analyses of outcome data with 95% confidence intervals (CIs). A $P < .05$ was considered statistically significant. All statistical analyses were performed using SPSS for Windows, version 12.0 (SPSS Inc).

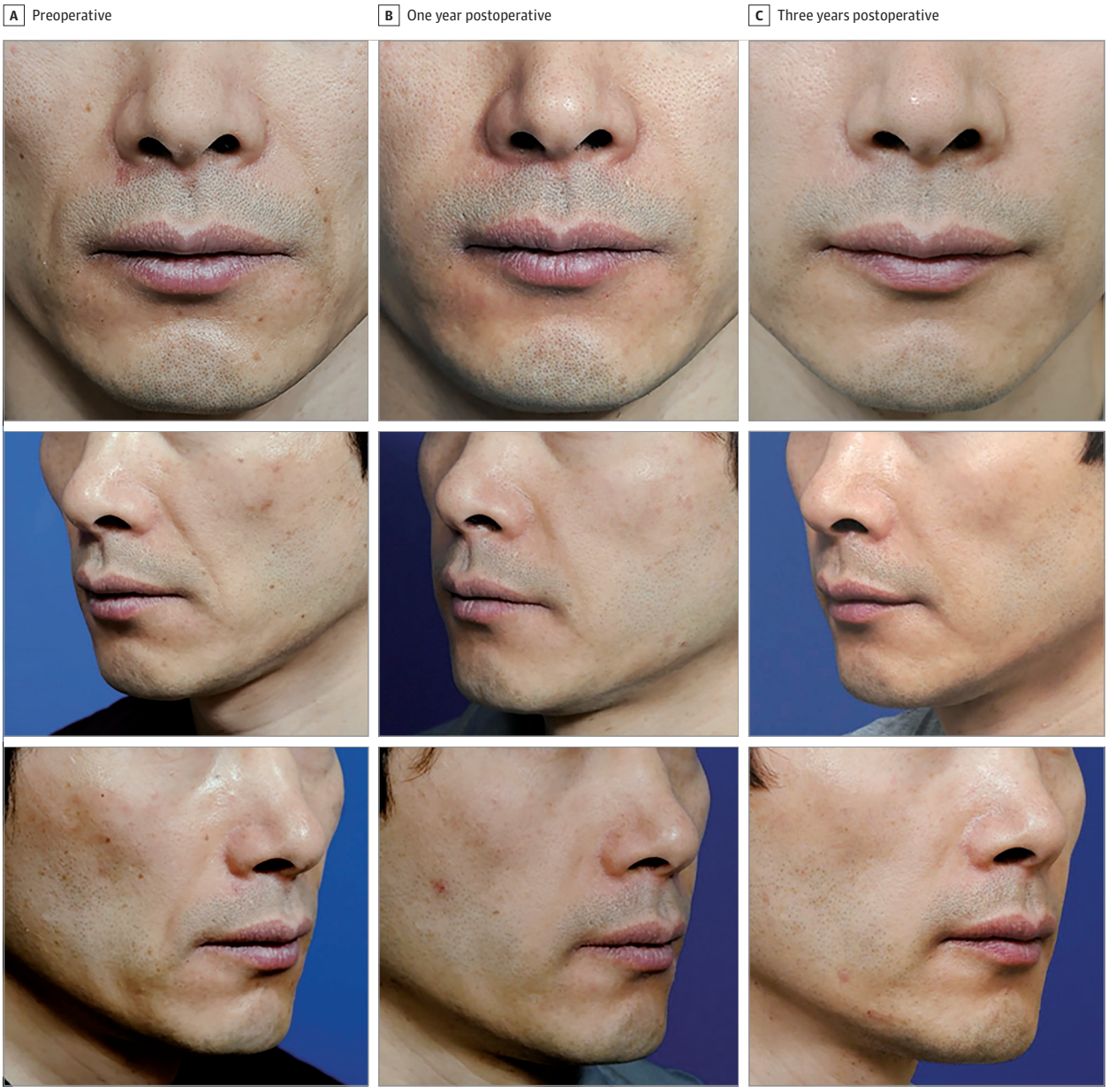
Results

For augmentation of the nasal dorsum (20 cases), 20 million cultured fibroblasts were suspended in 1.0 mL of HA filler with moderate viscosity. The mean (SD) injection volume of the fibroblast-HA filler mixture per nose was 0.82 (0.25) mL (range, 0.3-1.0 mL). One patient who had been initially treated for nasal dorsal augmentation with 0.5 mL received a second treatment with 0.5 mL 1 year later. For correction of deep nasolabial folds and depressed cheeks, 40 million fibroblasts seeded in 3 mL of HA filler and 40 million fibroblasts seeded in 4 mL of HA filler were injected, respectively.

All patients showed mild erythema at the injection site immediately after the procedure. However, this completely resolved within 1 to 6 days. Patients reported that the volume of the injected implant appeared to diminish during the early postoperative period. Three patients felt that volume reduced over the first 1 month, while 4, 13, and 2 patients reported that the volume decreased over 2, 3, and 6 months, respectively. All patients reported that the augmentation outcome was well maintained after this initial period. The amount of volume reduction was reported to be 10% to 20% in 2 patients, 20% to 30% in 9 patients, 30% to 40% in 8 patients, 40% to 50% in 2 patients, and greater than 50% in 1 patient. Patients' mean (SD) grading of improvement, satisfaction, and softness were 4.50 (0.51) (95% CI, 4.27-4.73), 4.14 (0.71) (95% CI, 3.82-4.45), and 4.82 (0.50) (95% CI, 4.59-5.00) at the last visit, respectively. Two (9%) patients who were not satisfied reported that, although there was some improvement with treatment, they desired more substantial change. Twenty (91%) patients answered that they would recommend the treatment to others.

Independent evaluators and the injecting physician concluded that improvement was achieved in all patients, consistent with patients' self-assessment (**Table** and **Figures 1**, **2**, and **3**). The study treatment was well tolerated. No adverse event was recorded in any patient during the follow-up period. No patients experienced an allergic reaction, infection, rejection, hematoma, granuloma, or nodule distorting the shape, migration, or extrusion of the product.

Figure 1. Correction of Deep Nasolabial Folds With Fibroblast-HA Filler Mixture



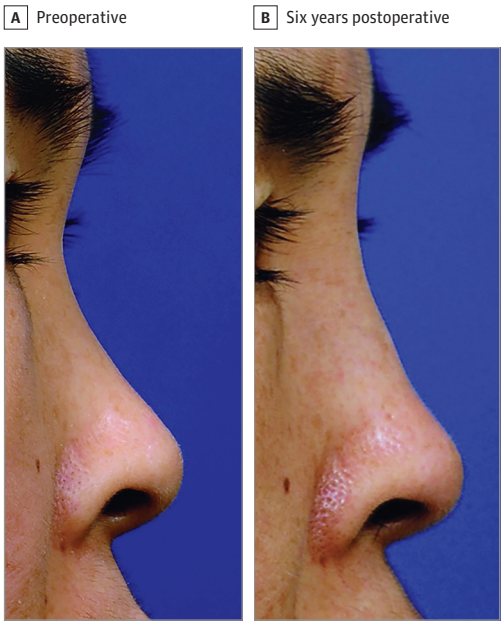
A, Preoperative view. B, One year after the injection. C, Three years after the injection.

Discussion

To sustain HA's augmentation outcome, a strategy using autologous cultured fibroblast injection has been developed, and various studies have been conducted to verify its successful use for soft-tissue augmentation.[12-15] This technique provides long-term aesthetic improvement and appears to show continuing positive outcomes for many months to years. However, injection of fibroblasts alone without filler might not be sufficient to achieve the high levels of filling success in cases requiring fairly extensive soft-tissue augmentation, such as augmentation rhinoplasty or correcting nasolabial folds. For example, treatment using a new commercial drug that contains autologous cultured fibroblasts requires 3 treatment sessions every 3 to 6 weeks to correct nasolabial folds.[16]

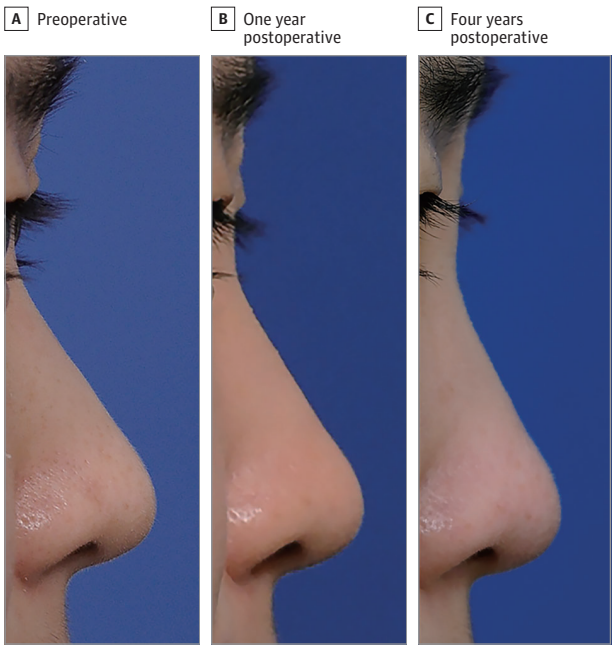
Results of this study showed that use of the fibroblast-HA filler mixture could sustain the outcome of soft-tissue augmentation up to 6 years after 1 session without touch-ups. Overall, this study demonstrates that fibroblast-HA filler mixture appears to have high patient satisfaction. Nineteen (86%) patients considered the injection site to be as soft as before treatment, and areas injected with fibroblast-HA filler mixture appeared to blend into surrounding tissues smoothly on palpation. Most patients included in this study were treated for the nose. Fifteen patients were treated for nasal dorsal

Figure 2. Nasal Dorsal Augmentation With Fibroblast-HA Filler Mixture



A, Preoperative view. B, Six years after the injection.

Figure 3. Nasal Dorsal Augmentation With Fibroblast-HA Filler Mixture



A patient who had been initially treated with fibroblast-HA filler mixture and received a second treatment 1 year later. A, Preoperative view. B, One year after the initial injection (before the additional injection). C, Four years after the initial injection (3 years after the additional injection).

augmentation. Of these patients, 13 (87%) were satisfied with the treatment. Five patients were treated for asymmetry of the nasal dorsum caused by nasal trauma. These patients had been offered secondary surgery or correction by fibroblast-HA filler mixture before treatment. None of these patients wished to undergo a secondary rhinoplasty surgery. All patients in this group were satisfied with the treatment.

As a qualitative assessment tool, the AAIS was used to assess improvement of treatment in this study. This validated 5-grade Likert scale originally designed for patients undergoing aesthetic facial procedures could measure both subjective and objective improvement.[17] Therefore, the AAIS has been commonly used and recognized as the primary assessment tool following aesthetic facial procedures.[2,3,18,19] In addition, the AAIS is a useful tool to assess improvement at different facial injection sites for soft-tissue augmentation.[2]

To our knowledge, there have been no studies of patients undergoing injection of autologous cells suspended in HA fillers for soft-tissue augmentation. Instead, a number of recent studies have assessed outcomes of patients by the AAIS after monotherapy using biocompatible materials, including autologous cells,[16,20] HA filler,[2,3,18,19] or microfat grafting.[21] However, the follow-up periods were mostly less than 12 months. A number of studies have addressed the long-term outcomes beyond 12 months.[17,19] Liew et al[17] have reported that 97% of patients showed greater than 1 increased grade of the AAIS from baseline after HA filler injection for soft-tissue augmentation during a maximum follow-up period of 14 months.. In addition, 1 study was conducted to verify the long-term outcomes of microfat grafting based on the AAIS for soft-tissue augmentation. Kao et al[22] recorded long-term outcomes for an average follow-up period of 19 months and 63% of patients showed greater than 1 grade increase in the AAIS from baseline. Although these studies addressed long-term outcomes, the follow-up periods were only 14 to 19 months.

The present study evaluated long-term outcomes for a minimum follow-up period of 36 months. All patients (100%) rated themselves as being improved after the treatment for a maximum follow-up period of 72 months. This may provide stronger support for the patient-perceived benefit of using fibroblast-HA filler mixture with much longer follow-up periods than other similar injection studies.

In an in vivo study by Solakoglu et al,[23] morphologic and morphometric analyses suggested that fibroblast-HA filler mixture has greater longevity than solitary HA and leads to additional synthesis of extracellular components in connective tissue. The average thickness of the dermis layer significantly increased at the injection site of fibroblast-HA filler mixture in the eighth month. They also demonstrated that elaunin and oxytalan components, precursors of elastin protein, were more numerous in the injection site of fibroblast-HA filler mixture at both 4 and 8 months.

The present study suggests that injected fibroblasts mixed in HA filler could survive and produce human dermal matrices successfully in the body. Our research group has also carried out a study to track injected fibroblasts in HA filler to determine if they remain at the injection site or move to other locations.[8] Human fibroblasts labeled with fluorescence dye were suspended in HA filler and injected into the back of nude mice. The results demonstrated that fluorescence signals of the fibroblasts were visible only at the injection sites without dispersing to other sites.[9] In addition, 4 weeks after injection,

28.1% of the fluorescence signals were still present at the injection site. However, direct-cell labeling was used in that study, resulting in decreased numbers of labels per individual cell, since the label could have been diluted when cells were divided. Therefore, the fluorescence intensity could not exactly quantify the viable cell number, and more than 28.1% of the fibroblasts might have remained at the injection site.

In addition, our research group[7] performed a study to determine optimal characteristics of HA filler combined with cultured human dermal fibroblasts to enhance the maximum viability of injected cells. The results demonstrated that HA-based filler with moderate viscosity (2 million-4 million centipoises) was superior to filler with low (600 thousand-800 thousand centipoises) or high (8 million-12 million centipoises) viscosities in terms of viability of human fibroblasts. The shape of particles (round or irregular) does not affect the viability of these injected fibroblasts.[7]

The exact mechanism of fibroblast survival in HA filler remains unknown. Angiogenesis, a biological mechanism for the formation of new capillaries, is fundamental to fibroblast survival in HA filler. In a previous study, increased vascular structures were observed at the injection site 8 months after injection with a fibroblast and HA filler mixture.[23] In addition to an increase in the number of blood vessels, colonization of macrophages associated with capillaries were observed with an electron microscope. This previous study demonstrated increased angiogenesis at the injection site of the fibroblast-HA filler mixture. Angiogenesis might increase the diffusion of nutrients and oxygen that are essential to fibroblast survival. However, further studies are needed to assess the mechanism of long-term fibroblast survival in HA filler.

An important consideration regarding all dermal fillers is the potential for adverse events. The fibroblast-HA filler mixture has an acceptable patient safety profile. In the present study, this treatment was generally well tolerated and adverse events were not observed. Mild erythema was encountered following the procedures. However, this was temporary and had no serious consequences. None of the patients experienced an allergic reaction. Delayed complication of lump formation was not noted.

The injection of fibroblast-HA filler mixture has many advantages. It can be performed at an outpatient clinic; it provides successful long-term outcomes, is a minimally invasive procedure, and demonstrates minimal donor site morbidity. Additionally,, it can minimize communication errors between the physician and patient because patients immediately notice the outcome. Furthermore, patients are psychologically comfortable because autogenic tissue is applied.

Limitations

Despite promising results, the present study has limitations inherent to retrospective studies. For example, an injecting physician and 2 independent evaluating investigators were aware of treatment protocols. However, this was unavoidable because they were required to assess the improvement from baseline. Therefore, a further blinded study with a large sample size is required to establish the long-term effect of a fibroblast-HA filler mixture with certainty, although it is very difficult to design a prospective blinded randomized clinical trial to evaluate the outcomes for as long as 6 years.

Conclusions

Tissue engineering is a relatively novel field that combines cell elements with biodegradable polymer scaffolds to create new tissue for repair or replacement. Although further investigation is needed to determine the ultimate value of this method, the present study demonstrates that cultured human dermal fibroblasts suspended in HA filler might be a suitable long-lasting, injectable material for soft-tissue augmentation. Injecting cultured human fibroblasts suspended in HA filler might be successful for long-term soft-tissue augmentation.

ARTICLE INFORMATION

Accepted for Publication: Nobember 3, 2018.

Published Online: March 28, 2019. doi:10.1001/jamafacial.2018.2127

Author Contributions: Dr Moon had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Han, Dhong.
Acquisition, analysis, or interpretation of data: Moon, Kim, Han, Jeong.
Drafting of the manuscript: Moon, Han, Dhong.
Critical revision of the manuscript for important intellectual content: Moon, Kim, Han, Jeong.
Statistical analysis: Moon, Han.
Administrative, technical, or material support: Moon, Kim, Han, Jeong.
Study supervision: Han, Dhong.

Additional Contributions: We thank the patients pictured in Figures 1, 2, and 3 for granting permission to publish this information.

Conflict of Interest Disclosures: None reported.

REFERENCES

1. Hall MB, Roy S, Buckingham ED. Novel use of a volumizing hyaluronic acid filler for treatment of infraorbital hollows. *JAMA Facial Plast Surg*. 2018;20(5):367-372. doi:10.1001/jamafacial.2018.0230

2. Wilson MV, Fabi SG, Greene R. Correction of age-related midface volume loss with low-volume hyaluronic acid filler. *JAMA Facial Plast Surg*. 2017;19(2):88-93. doi:10.1001/jamafacial.2016.1274

3. Ho D, Jagdeo J. Safety and efficacy of a volumizing hyaluronic acid filler for treatment of HIV-associated facial lipoatrophy. *JAMA Dermatol*. 2017;153(1):61-65. doi:10.1001/jamadermatol.2016.3827

4. Duranti F, Salti G, Bovani B, Calandra M, Rosati ML. Injectable hyaluronic acid gel for soft tissue augmentation. A clinical and histological study. *Dermatol Surg*. 1998;24(12):1317-1325. doi:10.1111/j.1524-4725.1998.tb00007.x

5. Fagien S, Klein AW. A brief overview and history of temporary fillers: evolution, advantages, and limitations. *Plast Reconstr Surg*. 2007;120(6)(suppl):8S-16S. doi:10.1097/01.prs.0000248788.97350.18

6. Smith SR, Jones D, Thomas JA, Murphy DK, Beddingfield FC III. Duration of wrinkle correction following repeat treatment with Juvéderm hyaluronic acid fillers. *Arch Dermatol Res*. 2010;302(10):757-762. doi:10.1007/s00403-010-1086-8

7. Kim DY, Namgoong S, Han SK, et al. Optimal viscosity and particle shape of hyaluronic acid filler as a scaffold for human fibroblasts. *J Craniofac Surg*. 2015;26(5):1534-1538. doi:10.1097/SCS.0000000000001833

8. Yoon ES, Han SK, Kim WK. Advantages of the presence of living dermal fibroblasts within restylane for soft tissue augmentation. *Ann Plast Surg*. 2003;51(6):587-592. doi:10.1097/01.sap.0000096424.23397.2a

9. You HJ, Namgoong S, Rhee SM, Han SK. Tracking and increasing viability of topically injected fibroblasts suspended in hyaluronic acid filler. *J Craniofac Surg*. 2016;27(2):521-525. doi:10.1097/SCS.0000000000002518

10. Han SK, Shin SH, Kang HJ, Kim WK. Augmentation rhinoplasty using injectable tissue-engineered soft tissue: a pilot study. *Ann Plast Surg*. 2006;56(3):251-255. doi:10.1097/01.sap.0000198549.64341.17

11. Rhee SM, You HJ, Han SK. Injectable tissue-engineered soft tissue for tissue augmentation. *J Korean Med Sci*. 2014;29(suppl 3):S170-S175. doi:10.3346/jkms.2014.29.S3.S170

12. Lowe NJ, Lowe PL, St Clair Roberts J. A phase IIa open-label dose-escalation pilot study using allogeneic human dermal fibroblasts for nasolabial folds. *Dermatol Surg*. 2010;36(10):1578-1585. doi:10.1111/j.1524-4725.2010.01686.x

13. Watson D, Keller GS, Lacombe V, Fodor PB, Rawnsley J, Lask GP. Autologous fibroblasts for treatment of facial rhytids and dermal depressions: a pilot study. *Arch Facial Plast Surg*. 1999;1(3):165-170. doi:10.1001/archfaci.1.3.165

14. Weiss RA, Weiss MA, Beasley KL, Munavalli G. Autologous cultured fibroblast injection for facial contour deformities: a prospective, placebo-controlled, Phase III clinical trial. *Dermatol Surg*. 2007;33(3):263-268.

15. Boss WK Jr, Usal H, Chernoff G, Keller GS, Lask GP, Fodor PB. Autologous cultured fibroblasts as cellular therapy in plastic surgery. *Clin Plast Surg*. 2000;27(4):613-626.

16. Smith SR, Munavalli G, Weiss R, Maslowski JM, Hennegan KP, Novak JM. A multicenter, double-blind, placebo-controlled trial of autologous fibroblast therapy for the treatment of nasolabial fold wrinkles. *Dermatol Surg*. 2012;38(7 Pt 2):1234-1243. doi:10.1111/j.1524-4725.2012.02349.x

17. Liew S, Scamp T, de Maio M, et al. Efficacy and safety of a hyaluronic acid filler to correct aesthetically detracting or deficient features of the asian nose: a prospective, open-label, long-term study. *Aesthet Surg J*. 2016;36(7):760-772. doi:10.1093/asj/sjw079

18. Weiss RA, Moradi A, Bank D, et al. Effectiveness and safety of large gel particle hyaluronic acid with lidocaine for correction of midface volume deficit or contour deficiency. *Dermatol Surg*. 2016;42(6):699-709. doi:10.1097/DSS.0000000000000771

19. Schuster B. Injection rhinoplasty with hyaluronic acid and calcium hydroxyapatite: a retrospective survey investigating outcome and complication rates. *Facial Plast Surg*. 2015;31(3):301-307. doi:10.1055/s-0035-1555628

20. Moon KC, Lee HS, Han SK, Chung HY. Correcting nasojugal groove with autologous cultured fibroblast injection: a pilot study. *Aesthetic Plast Surg*. 2018;42(3):815-824. doi:10.1007/s00266-017-1044-3

21. Hu X, Xue Z, Qi H, Chen B. Comparative study of autologous fat vs hyaluronic acid in correction of the nasolabial folds. *J Cosmet Dermatol*. 2017;16(4):e1-e8. doi:10.1111/jocd.12333

22. Kao WP, Lin YN, Lin TY, et al. Microautologous fat transplantation for primary augmentation rhinoplasty: long-term monitoring of 198 asian patients. *Aesthet Surg J*. 2016;36(6):648-656. doi:10.1093/asj/sjv253

23. Solakoglu S, Tiryaki T, Ciloglu SE. The effect of cultured autologous fibroblasts on longevity of cross-linked hyaluronic acid used as a filler. *Aesthet Surg J*. 2008;28(4):412-416. doi:10.1016/j.asj.2008.04.008