Effect of Multisyringe Hyaluronic Acid Facial Rejuvenation on Perceived Age

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BACKGROUND The objective of aesthetic treatments is to create a more youthful appearance. Most injectable fillers are indicated for the reduction of nasolabial folds, but the current aesthetic movement is toward volume replacement in multiple areas, known as global fillers or liquid face-lift.

OBJECTIVES To quantify the degree of perceived age reduction from multisyringe hyaluronic acid treatment.

MATERIALS AND METHODS Ten women were treated with 6 to 8 mL of hyaluronic acid. Exclusion criteria were no laser for 6 months and no hyaluronic acid fillers for 6 months or semipermanent fillers for 1 year. High-resolution photographs were taken in identical lighting and position before and 2 and 4 weeks after treatment. Three blinded dermatologists rated patients' ages before and after from photographs.

RESULTS The dermatologists reported an average of 6.1 to 7.3 years of reduction in apparent age at 2 and 4 weeks, respectively. The patients perceived a decrease in apparent age of 7.8 and 9 years.

CONCLUSION Multisyringe injection of hyaluronic acid filler into the aging face results in a reduction of apparent age from 6.1 to 9 years after 2 to 4 weeks. Full-face correction with hyaluronic acid is an important procedure in the armamentarium of anti-aging techniques.

Statistical analysis support and the syringes of Restylane and Perlane were provided by Medicis. Drs. Taub, Gold, and Jacob are consultants to Medicis. Drs. Taub and Jacob are consultants to Allergan.

Patients seek out most aesthetic procedures to look younger. Aesthetic physicians have realized that volume deficits contribute just as much, if not more, to the aging face than skin laxity. The introduction of collagen stimulatory fillers such as poly-L-lactic acid for correction of human immunodeficiency virus (HIV)-induced lipoatrophy and aging has led to further appreciation of volumetric considerations. This technique, called global fillers, "liquid face-lift," or optimal volume correction, is new in the anti-aging panoply of options. Fat auto transplantation is another method of volume replacement. Hyaluronic acids are the most commonly used fillers worldwide and have an excellent safety record as well as reversibility and are readily available. Hyaluronic acid fillers have been focused primarily on the reduction of specific folds and wrinkles. This study was undertaken to determine whether multisyringe facial injection of hyaluronic acid could yield quantifiable reduction in apparent age.

Methods

Ten female patients aged 42 to 59 (mean 49) were recruited for a single-center (Advanced Dermatology, SKINQRI, LLC) prospective study.

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Treatment inclusion criteria were moderate to severe volume loss of the face, aged 40 to 60, be able to give proper informed consent in writing, and be willing to follow the treatment schedule and perform all necessary precautions and instructions. Exclusion criteria were pregnant or nursing; hyaluronic acid or collagen injections of the face in the previous 6 months; calcium hydroxylapatite injections in the previous 12 months; poly-L-lactic acid injections in the previous 3 years; facial surgery, tissue tightening, or laser treatments in the previous 6 months; history of keloid or scar formation; unwillingness to refrain from excess sun exposure or tanning beds during the healing process; and taking any medications or supplements that would increase the potential for bruising (if aspirin was discontinued for 10 days prior to procedure with primary care physician's permission, then participation was allowed).

One of the authors (AFT) administered a single injectable treatment using 6 to 9 mL per patient of nonanimal hyaluronic acid (Perlane and Restylane, Medicis Corporation, Scottsdale, AZ) into the malar and in some patients the medial cheek, tear trough, melolabial fold, nasolabial fold, lips (vermilion border, body and upper lip rhytides if present), and chin. No touch-up or alteration of treatment was allowed within the 4-week study period.

Standardized frontal and 45° angle photographs at various illuminations were taken before treatment and at 2 and 4 weeks using the VISIA CR system (Canfield Scientific, Fairfield, NJ).

Three blinded cosmetic dermatologist reviewers (DS, MG, CJ) assessed age at baseline, week 2, and week 4 in photographs. The patients also rated themselves as to how old they thought they looked before the treatment and at 2 and 4 weeks after the treatment. The blinded reviewers rated 36 images, whereas the patients looked only at their own photographs. All were of the lower two-thirds of the face (the upper third was not treated) and included a frontal view and two side views at 45° angles. These images were scrambled such that there was no indication of which photos were before and after. Each blinded reviewer was instructed to look at each image and spend no more than 30 seconds rating the subject's age. They were also instructed not to compare photos or change any age rating after 30 seconds. Eight of 36 images viewed were not study subjects. They did not know which patients were study subjects and which were not.

The median change in perceived age from baseline of the three blinded reviewers was calculated for each subject, as well as the assessment of the treating physician and the patient and used for analysis. One-sample *t*-tests were used to determine whether the change from baseline was significantly different from 0 (assessed at $\alpha = 0.05$).

Results

All 10 patients completed their treatment and at least one of the two follow-up sessions.

There were no adverse events other than temporary swelling, bruising, redness, and discomfort.

The median change in perceived age of the patient at 2 weeks was 6.1 years for the blinded reviewers and 9 years for the patients. The median change in perceived age at 4 weeks was 7.3 years for the blinded reviewers and 7.8 years for the patients. All of the changes for each group and each time point were statistically significant, as shown in Table 1. The age reduction over the 2 to 4 weeks according to a graph depiction is demonstrated in Figure 1. Figures 2–4 show representative before and after photographs of the patients.

Discussion

This study demonstrates that multiple-syringe hyaluronic acid treatment of the aging face can result in a statistically significant decrease in perceived age of 6.1 to 9.0 years in a 2- to 4-week period.

TABLE 1. Change in Perceived Age from Baseline

	Week 2	*Week 4*
Blinded reviewers*		
N	10	8
Mean (SD)	−6.1 (3.2)	−7.3 (3.2)
p-value	.005	.005
Patient		
N	9	5
Mean (SD)	−9.0 (1.7)	−7.8 (2.6)
p-value	.012	.003

*The median value for the three blinded reviewers was used in the analyses.

There are no definitive measuring systems that correllate certain features with numerical aging. There are many descriptors of features of aging such as hollowing of the infraorbital area, ptosis of the cheek mound, nasolabial folds, elongation of the distance from the base of the nasal columella to the vermilion border, perioral rhytides, brow ptosis, jowling, skin dryness, and wrinkles. There are many ways to visually appreciate aging changes of the face, such as in motion or at rest, from various angles, and with shadow or without. The study purposefully did not give criteria for evaluating a patient's age. How do we know by looking that someone is 50 or 70? Although we can debate the individual contributions of each of these components to an individual's appearance, we all develop a certain immediate impression of people based on many visual clues, a type of gestalt. The hypothesis of this study was that, by significantly altering five areas of wrinkles and volume loss in the aging face (the tear trough and infraorbital hollows, cheek ptosis, nasolabial folds, marionette areas, and perioral area including lip enhancement), one could find a consistent reduction in the apparent age of the individual. The study was not meant to determine which areas may have contributed most to this reduction. It is possible that this reduction in apparent age could have been achieved with a smaller volume of product. Perhaps with a keener analysis of each person's features, only those portions that contributed most to their aging appearance could have been injected and achieved the same results as those with the higher volume of filler.

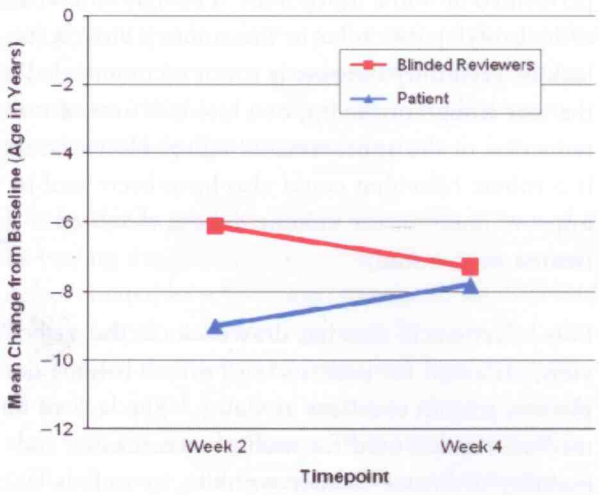

Figure 1. Graph of data of change in apparent age 2 and 4 weeks after treatment with hyaluronic acid injections.

Despite the recognition of cosmetic dermatologists and plastic surgeons that restoring volume plays a central role in facial rejuvenation, as well as the fact that it is a central theme in the literature and on the podium at international cosmetic meetings,[1] use of one to two syringes of hyaluronic acid filler per patient dominates the day-to-day practice of fillers in the United States. The main reason for this is ostensibly economic; multisyringe treatments are expensive. Although hyaluronic acid is the most commonly used filler in the United States and the world,[2] most full-face volume replacement augmentations are performed with semipermanent fillers, because of the prevailing idea that it is not economically viable for a patient to return every 6 to 8 months for retreatment of large quantities of filler. Yet most experienced injectors will tell you that they notice a decrease over time in the amount of hyaluronic acid filler necessary to retain optimal correction if regular, usually smaller, volume maintenance procedures are undertaken. Two studies have recently given an objective boost to this "hunch." The first is a study that fibroblastic stimulation of collagen production was demonstrated after hyaluronic acid injections.[3] The second, a recent clinical trial of nasolabial folds injected with nonanimal, stabilized hyaluronic acid, showed that, when full correction was achieved at 2 weeks and

Figure 2. Before and 2 weeks after injection of three syringes of cross-linked hylauronic acid 20 mg/mL of standard particle size and three syringes of same with 750- to 1,000-μm particle size.

retreatment was performed at 4.5 or 9 months with only half the original amount of filler, full correction was still present at 18 months.[4] These studies lead to the hypothesis that full-face hyaluronic acid might not be so "temporary," in the sense that, with regularly scheduled maintenance with lower volumes of material, optimal correction could persist for at least 1.5 years.

The two main intermediate fillers that have been used for facial volume correction in the United States are hydroxylapatite and poly-L-lactic acid. Hydroxylapatite is considered an intermediate filler because of its reported average longevity of 10 to 14 months,[5] although hydroxylapatite, too, may require periodic touch-ups;[6] in a study of 75 patients with injections into nasolabial folds, 38 required a "touch-up" at 2 to 3 months to sustain 12 months of correction. In addition, there is also a reduction of visible benefit at the 4- to 8-week window because of the gap between the resorption of the carboxymethyl cellulose gel carrier and the peak of collagen stimulation. In a 30-month study to sustain full correction in HIV lipoatrophy cases,[7] reinjection was performed at 6 and 18 months. The main drawback of hydroxylapatite filler in the author's view is its lack of versatility because it is not recommended in the tear trough or the lip, two essential areas for the reduction of the appearance of aging. However, this is a robust filler that could also have been used to improve many of the volume deficits that were treated in this study.

Poly-L-lactic acid also has drawbacks in the author's view, although for patients with severe volume depletion, it is an excellent modality.[8] The lack of immediate results, need for multiple treatments, and inability to finesse smaller wrinkles, as well as lack of safety in the lips, led the author to want to find another solution for global filling. Fat is a seemingly

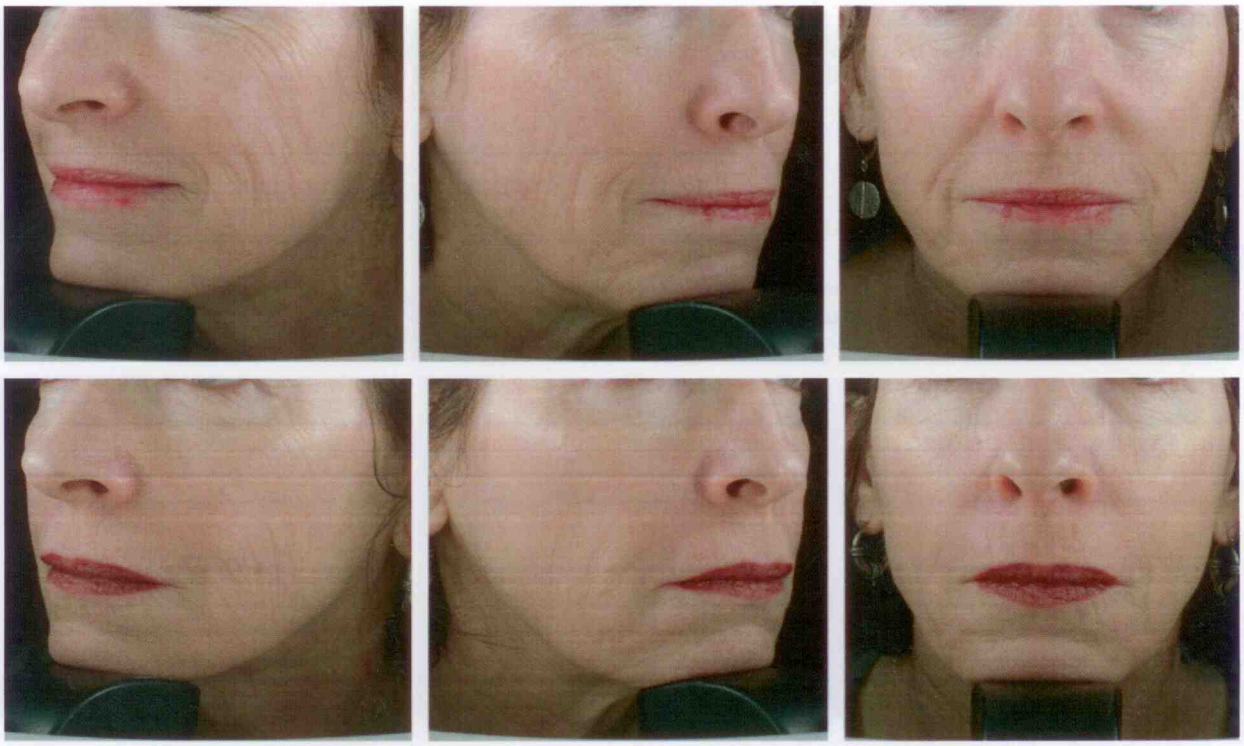

Figure 3. Before and after injection of two syringes of cross-linked hyaluronic acid 20 mg/mL of standard particle size and three syringes of same with 750- to 1,000-μm particle size.

ideal filler[9] that is highly effective for volume replacement. Autologous fat transplantation, when it is used with multiple injections in small aliquots and blended into, underneath, and above the muscles of the face, can yield dramatic rejuvenative results,[10] yet this involves fat harvesting, another invasive step that may not suit the preference of the average filler patient. One can use these fillers in combination in an individual patient; many sophisticated practitioners do this to great effect.

It is harder to perceive where volume is supposed to be (seeing the young face in the older) than to see a defect created by a "wrinkle" like the nasolabial fold. It may help to have your patients bring in old photographs of themselves to appreciate how the volume of their younger face has shifted or disappeared. It also requires more advanced techniques as well as off-label usage (the Food and Drug Administration has approved hyaluronic acid fillers for the nasolabial folds only), although because of the reversability of hyaluronic acid with hyaluronidase[11] and the immediacy of visual change, this is still easier to achieve than with other fillers.

There are a few weaknesses in this study. The data would be more powerful if the study had been performed in a larger number of patients and in multiple centers. The photographs are static, and seeing the face in motion, with its attendant dynamic wrinkles, might greatly influence our impression of age. Even with the standardized setup of the Canfield Visia CR, the subjects sometimes put their chins into the chin cups differently, resulting in a kind of compression of the lower one-third of the face (Figure 2) or smile in one and not in another (Figure 2). It would have been beneficial to use software that allowed for a "ghost" image to align the photos more accurately, allowing a more precise before-and-after comparison.

Experienced injectors have been injecting facial areas such as the tear trough, melolabial fold, maxillary

Figure 4. Before and after injection of four syringes of cross-linked hyaluronic acid 20 mg/mL of standard particle size and three syringes of same with 750- to 1,000-μm particle size.

ridge, prejowl sulcus, vermilion borders, and lip bodies for years. It is common for patients to want other areas to be filled after experiencing nasolabial fold correction. Many patients do not realize that a "lift" can be achieved with simple cheek augmentation, postponing the need for a surgical procedure that cannot replace volume but only reduce skin laxity, with its concomitant risks and permanent scars. With careful education of patients in the consultation process, enthusiasm about not only erasing their "parentheses," but also enhancing their youthfulness through volume replacement is apparent. After experiencing full-face correction, the educational circuit is complete because they have no intention of reversing course and intuitively understand the need for maintenance.

Conclusion

Multisyringe injection of hyaluronic acid filler into the aging face results in a reduction of apparent age of 6.1 to 9 years after 2 to 4 weeks. Full-face correction with hyaluronic acid is an important procedure in the armamentarium of anti-aging techniques.

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