

AQ: A

Patient-Preferred Sites of Restylane Injection in Periocular and Facial Soft-Tissue Augmentation

AQ: B

Carrie L. Morris, M.D., and Julie A. Woodward, M.D.

AQ: C

Duke University Eye Center, Durham, North Carolina, U.S.A.

Purpose: To determine patient-preferred injection sites and frequency for facial volume augmentation with nonanimal stabilized hyaluronic acid (Restylane).

Methods: The authors retrospectively reviewed the records of 145 consecutive patients who received 0.4 ml or 1.0 ml subcutaneous facial injections of Restylane. Location, amount, supplemental anesthetic, injection frequency, follow-up time, and use of botulinum toxin type A or other facial aesthetic interventions were reviewed. If recorded, patient satisfaction, revision rate, and any adverse reactions were also noted and analyzed.

Results: Median age at time of initial injection was 54 years; median follow-up was 8 months (mean 10.4 months, range 1–37 months). A total of 309 patient injections were performed (mean, 2.14 injections/patient), with 26% of patients receiving adjunctive anesthesia. Injection site frequencies among the 145 patients were nasolabial folds (72%), melolabial folds (70%), lips (51%), infraorbital rims (24%), perioral rhytids (24%), glabella (23%), malar hollows (10%), chin (8%), and other (8%). Among the 75 patients who received repeat injections, injection intervals were ≥ 4 months in 56 (76%) and ≥ 6 months in 28 (38%). Forty-four percent of patients received Botox and Restylane injections during the same office visits. Six complications included edema (2); vasovagal reaction during injection (1); ecchymosis (2); and herpes simplex virus dermatitis (1). Three revisions were performed. One patient was dissatisfied with the procedure.

Conclusions: Patients elect to undergo Restylane injections to improve the appearance of rhytids and augment volume along infraorbital rims, malar hollows, lips, and depressed scars. Complications are minimal and easily treated. Restylane is a valuable and safe tool for all areas of facial rejuvenation, creating a balanced, youthful, and natural appearance.

The options for soft-tissue augmentation of the face have increased and now include various soft-tissue fillers. Nonhuman, stabilized, hyaluronic acid, a transparent-gel, soft-tissue filler, is commercially available as Restylane (Medicis Aesthetics, Inc., Scottsdale, AZ, U.S.A.). It has been used clinically in Europe since 1996 and in Canada since 1998, and it gained U.S. Food and Drug Administration approval for dermal implantation to correct wrinkles and folds in December 2003. Numerous studies have shown Restylane to be both effective and safe for mid to deep dermal injection in the treatment of facial wrinkles, lines, folds, and contour defects.¹ Common injection sites include the glabella, lips, perioral rhytids, malar hollows, nasolabial folds, melolabial folds, and infraorbital rims. Because Restylane is predominantly used in elective procedures, an excellent safety profile is mandatory. Since its

reformulation and further purification in 1999, several studies have reported a decreased incidence (0.05%) of injection site reaction.^{2,3}

Soft-tissue augmentation with fillers such as Restylane can also be used for reconstruction, as in the correction of facial soft-tissue atrophy related to HIV AIDS, or for depressed scars due to surgical or accidental trauma.

Patient satisfaction and preference are key parameters in the success of cosmetic procedures. To our knowledge, no studies have evaluated patients' preferred areas for injection of Restylane. Although a few studies have reported the use of Restylane to correct tear-trough deformity, none have discussed augmentation of orbital rim hollows in conjunction with other areas of the face.⁴⁻⁷ The adjunctive use of Botox and other cosmetic procedures, and the frequency of repeat injections are also useful information in formulating a global treatment plan.

METHODS

We retrospectively reviewed the records of 145 consecutive patients who underwent intradermal and subcutaneous injection of the face with Restylane (0.4 ml or 1 ml) for volume augmentation and/or to improve rhytid appearance. Patients were treated at Duke University Eye Center between February

Accepted for publication June 18, 2007.

Presented at the ASOPRS Fall Symposium, Las Vegas, NV, November 16, 2006.

The authors have no proprietary or financial interests related to this study.

Address correspondence and reprint requests to Carrie Lynn Morris, Duke University Eye Center, DUMC Box 3802, Durham, NC 27717. E-mail: woodw005@mc.duke.edu

DOI: 10.1097/IOP.0b013e318166dd2a

2005 and March 2006. IRB approval was obtained and the study protocol was in compliance with HIPAA regulations.

Patient age; sex; race; ethnicity; ocular, surgical, and medical history; Fitzpatrick skin type; and tobacco and sun exposure were recorded. Other pertinent abstracted data included concurrent and previous use of botulinum toxin, the use of anesthesia (EMLA cream, mental and/or infraorbital nerve blocks), previous Restylane injections, and other cosmetic procedures (e.g., facelift, blepharoplasty, brow lift, CO₂ laser resurfacing, microdermabrasion, collagen injection, auto fat transplants, chemical peels, alloderm grafts, and lasering of telangiectasia). The sites of injection, amount of injection per visit, injection intervals, number of injections per location, complications, adverse effects, failure, revision, patient satisfaction, and follow-up time were also noted. Collected data underwent statistical analysis.

The method of injection was tailored to the patient's needs, area of the face, type of defect, and surgeon preference. The linear threading technique uses a bevel-down, 30-gauge needle in a reverse fashion. The surgeon advances the needle to the proximal portion. Restylane is implanted intradermally and subcutaneously to fill deep folds and hollows, including nasolabial and melolabial folds, perioral areas, chin, infraorbital hollows, and lips. In cases of extremely deep folds and infraorbital hollows, the product is placed subcutaneously or deep to orbicularis oculi muscle to minimize visibility and properly fill the defect.

Sharp, superficial creases are corrected with the serial puncture technique, which involves multiple punctures using a bevel-down, 30-gauge needle, injecting small aliquots (0.02 ml), titrated to effect.

RESULTS

From February 2005 to March 2006, 309 Restylane injections were performed on 145 patients (mean, 2.14 injections/patient). Gender distribution was 139 female and 6 male, and median age was 53 years (mean, 54 years). There was a median follow-up time of 8 months (mean, 10.4 months; range, 1–37 months) for all returning patients. Median follow-up time was

11 months (mean, 12 months; range, 1–37 months) for the 75 patients (52%) who underwent reinjection. Thirty-seven of 140 patients (26%) received adjunctive anesthesia. Injection locations were as follows: nasolabial folds [72% (104/145)], melolabial folds [70% (102/145)], lips [51% (74/145)], infraorbital rims [24% (35/145)], perioral rhytids [24% (35/145)], glabella [23% (34/145)], malar hollows [10% (14/145)], chin [8% (12/145)], and other [8% (12/145)]. Figures 1 and 2 depict the degree of soft-tissue augmentation in representative patients. A mean of 0.85 ml per patient was injected per session. Eighty-three percent of patients were treated with the 1.0-ml vial per session whereas 17% of patients requested the 0.4-ml vial per treatment session. There was no statistically significant difference between the 2 groups in terms of injection interval greater than 6 months (26/64, 1.0-ml syringe; 2/8, 0.4-ml syringe; $p = 0.69$).

Among the 75 patients (52%) who received repeat injections, 56 patients (76%) had an injection interval ≥ 4 months and 28 patients (38%) had an injection interval ≥ 6 months. The Table lists the injection interval for each implantation site. Nasolabial and melolabial folds were the most common areas to have an injection interval greater than 6 months [($n = 26, 24$), respectively]. The number of repeat injections ranged from 1 to 7. Sixty percent (45/75) of patients undergoing reinjection received 2 or more injections. Only 20/45 patients who underwent 2 or more *reinjections* had a subsequent increase in injection interval.

Forty-four percent (64/144) of patients received Botox and Restylane injections during the same office visit. There was no statistical difference in injection interval between patients receiving concurrent Botox and those receiving only Restylane ($p = 0.356$). Aside from concurrent Botox injections, patients commonly underwent other minimally invasive procedures: previous Botox injection (%), laser resurfacing (31%), microdermabrasion (15%), and collagen injections (15%). The most common cosmetic surgical procedures that our patient population underwent were blepharoplasty [40% (58/144)], facelift [12% (17/144)], browlift [8.5% (11/129)], breast augmentation [9% (13/144)], and autologous fat transplantation [4% (6/138)].

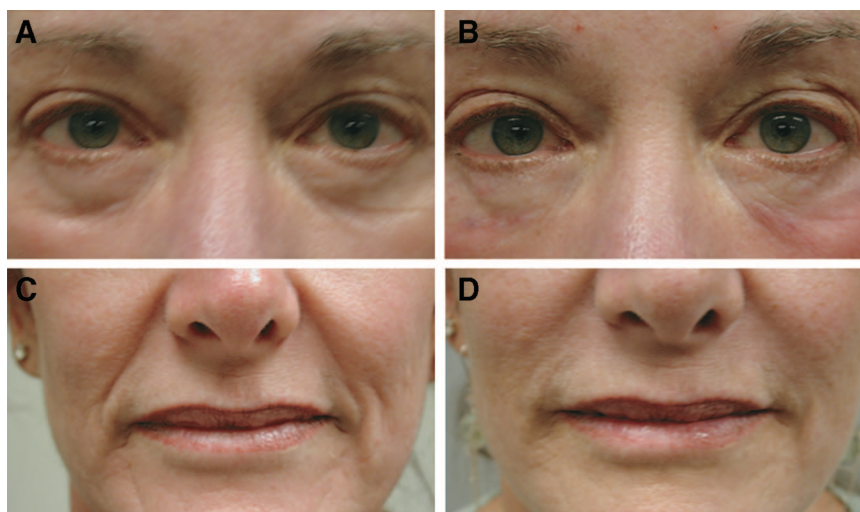


FIG. 1. A, Tear-trough deformity before injection. B, Noticeable volume augmentation is seen immediately after treatment. Nasolabial and melolabial folds and perioral rhytids preinjection (C), and 6 months after injection (D).



FIG. 2. A, Vertical glabella furrows are evident preinjection. B, One week after injection. C, Perioral scars. D, Immediately after injection. E, Eight months after injection.

One patient was dissatisfied with the results of the procedure. We attributed this to patient selection of an insufficient amount to correct the severity of the patient’s rhytids. Alternative uses for soft-tissue volume augmentation included pectus

excavatum, and scars due to acne, radiation, trauma, or Mohs reconstructive surgery. Of note, 1 patient with scleroderma had repeated injections without complications.

No reversals were necessary. No failures (inability to fill a soft-tissue defect with the filler) occurred. Three revisions were performed. Six complications occurred, including: edema (2), vasovagal reaction during injection (1), ecchymosis (2), and herpes simplex virus dermatitis (1) (Fig. 3).

F3

Distribution of injection interval durations for facial injection sites

Injection Site	Injection interval <6 months	Injection interval ≥6 months	<i>p</i>
Glabella	13	9	0.798*
Nasolabial folds	41	26	0.792
Melolabial folds	38	24	0.883
Lips	28	18	0.728
Malar hollows	8	2	0.299*
Infraorbital hollows	14	9	1.000*
Perioral rhytids	17	11	0.898
Chin	4	3	1.000*

The comparison of injection interval duration in relation to injection site is illustrated.

There was no significant difference of injection interval duration of any area of the face.

Chi-square testing was performed to obtain the *p* value, unless otherwise noted.

Values denoted with an asterisk (*) were calculated using Fisher exact test.

DISCUSSION

Over the past several years, Restylane has emerged as a useful tool for the minimally invasive, nonsurgical alteration of facial contours and rhytids. The continued refinement of injection techniques, broadening of clinical uses, and development of related products (e.g., Perlane, Lipp, Touch, FineLines, SubQ), which vary by particle size and implantation area, may further expand the options for volume augmentation and rhytid resolution.

In agreement with a survey of the practices of 9 members of the American Society of Ophthalmic Plastic and Reconstructive Surgery, the most common areas injected in our series were nasolabial folds, melolabial



FIG. 3. Herpes simplex dermatitis occurred in 1 patient after Restylane injection, and resolved with oral acyclovir treatment.

folds, and lips, respectively.⁸ Because soft-tissue augmentation is usually an elective cosmetic procedure, the areas and frequency of injection are highly dependent on patient preference, satisfaction, goals, and financial limitations. The sites chosen by patients may also indirectly reflect the efficacy of Restylane in each particular area.

Few formal studies have reported the injection of Restylane along the infraorbital rim.⁴⁻⁷ Goldberg⁴ reported the use of Restylane to fill periorbital hollows in 145 patients. Of 244 injections performed, there were 11% reversals, an 89% satisfaction rate, and a reinjection interval of 6.5 months. Steinsapir⁷ studied the use of hyaluronic acid to deeply fill the nasojugal groove in the preperiosteal tissues, using a mean dose of 0.87 ml per lower eyelid. His approach yielded a reinjection interval of 2.2 months. Kane⁵ used 0.1 ml to 0.45 ml Restylane per eyelid to correct tear-trough deformity and lower eyelid bowing in 23 patients. A good effect lasting 6 to 9 months was achieved, along with a 90% patient satisfaction rate. Another report described the use of Restylane to perform a nonsurgical eyelid lift by administering 0.35 ml to 1.4 ml along the infraorbital rim, which lasted 5 to 8 months.⁶

The intervals between injections at each site are listed in the Table. For several reasons, these data do not necessarily reflect the longevity of Restylane effect at each site. Multiple sites were injected simultaneously at each visit. Thus, although duration of effect might have varied among several sites, patients may have waited until all areas were in need of augmentation. Conversely, a particular area may not have needed immediate retreatment, but all sites may have been reinjected for patient convenience. In addition, many patients have botulinum toxin injections every 3 to 4 months and may elect to have simultaneous Restylane injections as “touch ups.” The interval of reinjection is also partially driven by cost. These confounding variables make interpretation of retrospective data difficult.

In general, our findings suggest that Restylane usually lasts 8 to 10 months. Of interest, histologic studies have shown Restylane to be present as long as 23 months after implantation.⁹ Questions remain as to whether reinjection intervals should rely on the actual dissolution of the previously implanted material or the clinical appearance. Also is there a cumulative quantity at which implantation should cease? Ideally, one would repeat injections before complete dissolution to maintain the desired level, preventing a roller-coaster effect of rhytid-present and rhytid-free intervals. However, this injection interval, which may vary according to location, presence of botulinum toxin, and other parameters, has yet to be determined. Despite reports that subsequent injections have an additive effect on the duration of action,¹⁰ our data are equivocal because the desire to reinject cannot be analyzed statistically. This is because the motivations for reinjections are affected by availability of funds for cosmetic rejuvenation and the flexibility of the patient’s schedule.

Although our study did not show a difference in injection interval of those with concurrent Botox injection and those who received only Restylane, 36% (52/145) did not return for a follow-up visit. This may be attributed to a lasting satisfactory result, dissatisfaction, or the strictly elective nature of hyaluronic acid implantation. Our retrospective study was not designed to evaluate product duration, perhaps accounting for differences between our findings and those of a prospective study, which found that concurrent Restylane and Botox injection of the glabella extended the time to relapse.¹¹ The extended duration of action may be location and amount dependent. Additional controlled prospective studies are needed to adequately establish this effect.

Depending on the patient, injection location, and amount injected, supplemental anesthesia is sometimes needed. Options include topical preparations (lidocaine, benzocaine/lidocaine/tetracaine, or tetracaine gels) and local infiltration. In our series, 26% (37/140) of patients received adjunctive anesthesia (citanest or lidocaine 1% without epinephrine) in the form of mental and/or infraorbital nerve blocks. Previous studies have reported that injectable anesthetic provides better analgesia than topical application.⁸ However, some surgeons have speculated that the anesthetics rather than hyaluronic acid fillers are responsible for erythema and hypersensitivity reactions noted in some cases.²

The excellent safety profile of Restylane in our study is consistent with its favorable status when compared with other soft-tissue fillers.¹² Unlike other soft-tissue fillers, its reversibility with hyaluronidase can help mitigate overcorrection or hypersensitivity.^{13,14} Its biodegradability and shorter duration compared with more permanent fillers are also favorable in the setting of an adverse reaction. Single cases of retinal branch artery occlusion,¹⁵ dorsal nasal artery occlusion,¹⁶ and delayed

type IV granulomatous hypersensitivity reaction after a negative skin test¹⁷ have each been reported.

In our series, only patients with a positive history of herpes simplex virus receiving perioral or chin injections were given prophylactic acyclovir. We encountered 1 episode of herpes simplex virus dermatitis. However, other practices routinely prescribe prophylactic treatment whereas others only do if history exists.¹⁰ Still other surgeons do not prescribe antivirals unless a current problem arises after injection.¹⁰

The authors' expressed purpose was to determine patient-preferred injection sites and frequency of Restylane administration. The study's primary limitation was its retrospective nature, which limited our ability to evaluate the impact of cost and motivation on injection frequency, amount, and location. Evaluating Restylane effect in specific sites would be best achieved in a controlled setting with blinded evaluators. Ultimately, however, there may be no truly objective measurements of success, and patient satisfaction may be the most meaningful endpoint.

REFERENCES

1. Carruthers J, Carruthers A. Facial sculpting and tissue augmentation. *Dermatol Surg* 2005;31:1604-12.
2. Lowe NJ, Maxwell CA, Patnaik R. Adverse reactions to dermal fillers. *Dermatol Surg* 2005;31:1616-25.
3. Friedman PM, Mafong E, Kauvar A, et al. Safety data of injectable nonanimal stabilized hyaluronic acid gel for soft tissue augmentation. *Dermatol Surg* 2002;28:491-4.
4. Goldberg RA, Fiaschetti D. Filling the periorbital hollows with hyaluronic acid gel: initial experience with 244 injections. *Ophthalm Plast Reconstr Surg* 2006;22:335-41.
5. Kane MAC. Treatment of tear trough deformity and lower eyelid bowing with injectable hyaluronic acid. *Aesthetic Plast Surg* 2005;29:363-7.
6. Airan LE, Born TM. Nonsurgical lower eyelid lift. *Plast Reconstr Surg* 2005;116:1785-92.
7. Steinsapir KD, Steinsapir SM. Deep-fill hyaluronic acid for the temporary treatment of the naso-jugal groove: a report of 303 consecutive treatments. *Ophthalm Plast Reconstr Surg* 2006;22:344-8.
8. McCracken MS, Khan JA, Wulc AE, et al. Hyaluronic acid gel (Restylane) filler for facial rhytids: lessons learned from ASOPRS member treatment of 286 patients. *Ophthalm Plast Reconstr Surg* 2006;22:188-91.
9. Lemperle G, Morhenn V, Charrier U. Human histology of various filler substances for soft tissue augmentation. *Aesthetic Plast Surg* 2003;27:354-66.
10. Matarasso SL, Carruthers JD, Jewell MK, et al. Consensus recommendations for soft-tissue augmentation with nonanimal stabilized hyaluronic acid. *Plast Reconstr Surg* 2006;117:3S-34S.
11. Carruthers J, Carruthers A. A prospective, randomized, parallel group study analyzing the effect of BTX-A (Botox) and nonanimal sourced hyaluronic acid (NASHA, Restylane) in combination compared with NASHA alone in severe glabellar rhytides in adult female subjects: treatment of severe glabellar rhytides with a hyaluronic acid derivative compared with the derivative and BTX-A. *Dermatol Surg* 2003;29:802-9.
12. Kanchwala SK, Holloway L, Bucky LP. Reliable soft tissue augmentation: a clinical comparison of injectable soft-tissue for facial-volume augmentation. *Ann Plast Surg* 2005;55:30-5.
13. Vartanian AJ, Frankel AS, Rubin MG. Injected hyaluronidase reduces Restylane-mediated cutaneous augmentation. *Arch Facial Plast Surg* 2005;7:231-7.
14. Soparkar CN, Patrinely JR. Managing inflammatory reaction to Restylane. *Ophthalm Plast Reconstr Surg* 2005;21:151-3.
15. Peter S, Mennel S. Retinal branch artery occlusion following injection of hyaluronic acid (Restylane). *Clin Experiment Ophthalmol* 2006;34:363-4.
16. Schanz S, Schippert W, Ulmer A, et al. Arterial embolization caused by injection of hyaluronic acid (Restylane). *Br J Dermatol* 2002;146:928-9.
17. Patel V, Bruck MC, Katz BE. Hypersensitivity reaction to hyaluronic acid with negative skin testing. *Plast Reconstr Surg* 2006;117:92e-94e.

AQ: E

AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES

1

A—Kindly confirm whether the short title is OK as given

B—Production Editor: Kindly confirm that there are only two authors for this article as seen in org file. Please note that the front page of the Pdf file of the same article carries an additional author name.

C—Kindly confirm whether both authors are with same affiliation

D—Kindly confirm whether place of callout is OK?

E—Please check whether the Ref. 16 is OK as edited.