

The RESTYLANE publications booklet



6th edition

Restylane
NATURAL BEAUTY MADE IN SWEDEN

Introduction

The field of soft tissue augmentation has a long and colourful history. Over the years we have seen the number of new products increase rapidly. The search of an ideal filling substance might be a continuous struggle for you as a professional. For us in the industry it is a continuous battle!

We hear many physicians asking for dermal fillers that are safe, durable and easy to inject. An ideal filler should also be biocompatible, non-antigenic, non-pyrogenic, non-inflammatory, non-toxic, non-animal, stable after injection, non-migratory long-lasting - but resorbable, natural looking and not too expensive. Very few fillers, if any, meet all of these criteria. This means that the selection process is somewhat difficult and a compromise often becomes necessary.


In this booklet we have compiled references to, or abstracts of, scientific publications on RESTYLANE. We have also included references to a few reviews and overviews of dermal fillers intended for soft tissue augmentation.


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NASHA™ - The monograph

Ågerup B, Wik O

Q-Med, 2007

Introduction

“NASHA™ is a unique gel based on the technology for production of stabilized non-animal hyaluronic acid, patented and developed by Q-Med AB, Uppsala, Sweden.

NASHA™ is used in products for facial tissue augmentation (Restylane®) and for body tissue augmentation (Macrolane®), for treatment of osteoarthritis in the knee (Durolane®) and for the treatment of vesicourethral reflux in children (Deflux®), for the treatment of stress urinary incontinence in women (Zuidex®) and for the treatment of fecal incontinence (Solesta®).

The manufacturing of NASHA™ is based on hyaluronic acid (HA). Hyaluronic acid (HA) is one of nature's most versatile and fascinating macromolecules. Since this polysaccharide was first isolated from bovine vitreous in the mid-1930s, it has been found in all tissues in all vertebrates. Thus, hyaluronic acid is a universal component of the extracellular space, where the molecule has multiple properties to constitute a matrix that supports the normal function of cells and tissues.”

Copyright ©2007 Q-Med AB, Uppsala, Sweden.

The first clinical study using a new biodegradable implant for the treatment of lips, wrinkles and folds

Olenius M.¹

Aesth Plast Surg 1998; 22: 97–101

Abstract

A new tissue augmentation product, made from hyaluronic acid, was clinically evaluated at three clinics in accordance with the new directive, EN 540, for medical implants. One hundred patients were fully assessed following treatments in 285 locations. The treatment was completed when the skin was levelled following one to two injections. At 6 months follow-up of all patients and at 12 months follow-up of a randomized group of the patients all showed that close to 60 % of the effect was still there. No serious or permanent adverse events were noted.

Conclusion

Stabilized hyaluronic acid fulfilled the expectations of giving a safe and efficient tissue augmentation.

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**Injectable hyaluronic acid gel for soft tissue augmentation.
A clinical and histological study**

Duranti F¹, Salti G¹, Bovani B¹, Calandra M², Rosati M²
Dermatol Surg 1998; 24(12)1317–25

Background

Several biomaterials are available for the purpose of soft tissue augmentation, but none of them has all the properties of the ideal filler material. The recent development of hyaluronic acid gels for dermal implantation give the physician new possibilities of effective treatment in this field.

Conclusion

Stabilized, non-animal, hyaluronic acid gel is well tolerated and effective in augmentation therapy of soft tissues of the face. This material presents several advantages in comparison to previously used injectable biomaterials and expands the arsenal of therapeutic tools in the field of soft-tissue augmentation.

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A Randomized, Double-Blind, Multicenter Comparison of the Efficacy and Tolerability of Restylane Versus Zyplast for the Correction of Nasolabial Folds

*Narins RS¹, Brandt F², Leyden J³, Lorenc PZ⁴, Rubin M⁵, and Smith S⁶,
Dermatol Surgery 2003; 29:588-95*

Background. Bovine collagen is extensively used for facial soft tissue augmentation but provides only temporary correction and can cause hypersensitivity reactions. Hyaluronic acid derivatives potentially offer improved longevity of correction and a reduced risk of immunogenicity and hypersensitivity.

Objective. To compare the efficacy and safety of nonanimal stabilized hyaluronic acid gel (Restylane; Q-Med, Uppsala, Sweden) with that of bovine collagen (Zyplast) for treatment of nasolabial folds.

Methods. One hundred thirty-eight patients with prominent nasolabial folds were randomized to treatment with hyaluronic acid gel and bovine collagen on contralateral sides of the face. Treatments were repeated at 2-week intervals, as required, to achieve “optimal cosmetic result” (baseline). Outcomes were evaluated by a blinded investigator at 2, 4, and 6 months after baseline.

Results. Less injection volume was required for “optimal cosmetic result” with hyaluronic acid gel than with bovine collagen, and patients and investigators judged hyaluronic acid gel to be more effective in maintaining cosmetic correction. The investigator-based Wrinkle Severity Rating Scale and Global Aesthetic Improvement Scale assessments at 6 months after baseline indicated that hyaluronic acid gel was superior in 56.9% and 62.0% of patients, respectively, whereas bovine collagen was superior in 9.5% and 8.0% of patients, respectively. The frequency, intensity, and duration of local injection-site reactions were similar for the two products.

Conclusion. Nonanimal stabilized hyaluronic acid provides a more durable aesthetic improvement than bovine collagen and is well tolerated.

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A Randomized, Evaluator-Blind, Multicenter Comparison of the Efficacy and Tolerability of Perlane Versus Zyplast in the Correction of Nasolabial Folds

Lindqvist C¹, Tveten S², Eriksen Bondevik B³, Fagrell D¹
Plast Reconstr Surg 2005;115(1)282-289

Bovine collagen is widely used as a dermal filler for facial soft-tissue augmentation, but it provides only temporary cosmetic improvement. Nonanimal stabilized hyaluronic acid has reduced potential for immunogenicity and hypersensitivity and may provide a more durable aesthetic result. Sixty-eight patients with prominent nasolabial folds were randomized to intradermal treatment with nonanimal stabilized hyaluronic acid gel (Perlane) and bovine collagen (Zyplast) on contralateral sides of the face. On achievement of "optimal cosmetic result" (baseline), patients were followed up for 6 months; bilateral retreatment with Perlane was offered at 6 or 9 months after baseline. Responses were evaluated at 2, 4, 6, 9, and 12 months after baseline. Investigator-based and patient-based ratings indicated that Perlane was more effective than Zyplast in maintaining cosmetic correction. According to investigator based Wrinkle Severity Rating Scale assessments at 6 and 9 months after baseline, Perlane was superior in 50.0 percent and 48.8 percent of patients, respectively, whereas Zyplast was superior in 10.3 percent and 14.0 percent of patients, respectively ($p < 0.0004$). Investigator based Global Aesthetic Improvement Scale assessment at 9 months after baseline indicated that Perlane was superior in 48.8 percent of patients, whereas Zyplast was superior in 14.0 percent of patients ($p=0.0025$). "Optimal cosmetic result" was achieved with a smaller volume of Perlane than Zyplast (mean, 1.2 ml versus 2.1 ml). Local injection-site reactions (redness, swelling, pruritus, and induration) were less frequent with Perlane than with Zyplast. Delayed-onset reactions were rare and did not reoccur after Perlane retreatment. Perlane has acceptable long-term safety and offers a longer-lasting aesthetic improvement than Zyplast.

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Randomized, Double-Blind Comparison of the Efficacy of Two Hyaluronic Acid Derivatives, RESTYLANE Perlane and Hylaform[®], in the Treatment of Nasolabial Folds
*Carruthers A¹, Carey W², De Lorenzi C³, Remington K⁴, Schachter D⁵, Sapra S⁶,
Dermatol Surg 2005; 31(11)Part2:1591-1598*

Background. To compare the efficacy and safety of a non-animal stabilized hyaluronic acid gel (RESTYLANE Perlane, Q-Med, Uppsala, Sweden) with that of a hylan B gel (Hylaform[®], Genzyme Corp., Cambridge, MA, USA), a cross-linked hyaluronic acid from chicken combs, for treatment of nasolabial folds.

Methods. One hundred fifty patients with moderate or severe nasolabial folds were randomized to contralateral treatment with RESTYLANE Perlane and Hylaform. Efficacy was assessed using semiobjective outcome instruments at 3, 4.5, and 6 months after achievement of an "optimal cosmetic result." Patients subsequently underwent open-label bilateral retreatment with RESTYLANE Perlane (if required) and were followed up for a further 6 months.

Results. The two products were equally effective in producing an optimal cosmetic result, although fewer treatment sessions were required with RESTYLANE Perlane. At 6 months post-treatment, a higher proportion of patients showed a ≥ 1 -grade improvement in Wrinkle Severity Rating Scale (WSRS) score with RESTYLANE Perlane (75%) than with Hylaform (38%). Restylane Perlane was considered superior in 64% of patients, whereas Hylaform was superior in 8% of patients. Treatment-related adverse events tended to be more frequent with RESTYLANE Perlane. Local injection-site reactions were generally transient and mild or moderate in intensity and were no more frequent after RESTYLANE Perlane retreatment.

Conclusions. RESTYLANE Perlane provides a more durable esthetic improvement than Hylaform and offers acceptable tolerability.

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Multicenter Study of the Efficacy and Safety of Subcutaneous Nonanimal-Stabilized Hyaluronic Acid in Aesthetic Facial Contouring: Interim Report

Claudio De Lorenzi¹, Michael Weinberg², Nowell Solish³, Arthur Swift⁴
Dermatol Surg 2006; 32(1):208-21

Background

Nonanimal-stabilized hyaluronic acid (NASHA) gel may offer longer-lasting cosmetic correction and lower antigenic risk than other soft tissue augmentation agents.

Objective

To assess the efficacy and safety of the NASHA gel Restylane SubQ (Q-Med AB, Uppsala, Sweden) in aesthetic facial contouring.

Methods

Fifty-seven adult patients seeking cheek and/or chin augmentation received subcutaneous and/or supraperiosteal injections of Restylane SubQ (20 mg/mL) at 114 treatment sites; 13 of these patients received “touch-up” injections at 20 sites. Efficacy was assessed subjectively using a 5-grade Global Aesthetic Improvement Scale at 1, 3, 6, 9, and 12 months after the initial treatment.

Results

At 3 months postbaseline, patients and investigators independently considered the treatment sites to be improved in 96.4% and 100% of cases, respectively. Patient- and investigator-assessed response rates (proportion of patients showing moderate or better improvement) were 84% and 95%, respectively. The majority of reported adverse events were treatment related (local injection-site reactions, implantation complications, skin tightness, and skin induration), but these were generally of mild intensity and short-lived.

Conclusion

Restylane SubQ is well tolerated and maintains aesthetic correction of the cheeks and chin for at least 3 months after subcutaneous and/or supraperiosteal treatment.

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Restylane Lip Implantation: European Experience

Bousquet MT¹, and Ågerup B²

Operative Techniques in Oculoplastic, Orbital, and Reconstructive Surgery 1999; 2(4)172-76

A prospective study has been performed that covered 192 patients treated with a new implant for the purpose of cosmetic correction of the lips. The new implant, Restylane (Q-Med AB, Uppsala, Sweden), is based on nonanimal stabilized hyaluronic acid (NASHA). Each patient was offered an initial treatment and 1 to 2 touch-ups, if necessary, to achieve optimal results. The mean duration for the 192 patients was 8,8 months. In all, between 0.7 and 1.1 mL was used. About 72% of the patients decided to continue to have their lips treated with Restylane and asked for a second treatment session (retreatment). The mean duration for these 138 patients was 6.4 months. Swelling was noted in 86% of the patients during the first 24 hours and was noticeable at 5 days in 14% of the patients and for 10 days in 1% of the patients. Redness was noted during the first 24 hours in 52% of the patients and in 36% of the patients the following day. On the third day 12% of the patients noted some redness. Thereafter, all patients were well except for 1 delayed effect after 4 weeks. No one experienced a permanent negative reaction. The injection of Restylane into the lips can be compared with injection into a muscle. Using the muscle implantation test in rabbits, a very good tolerance was noted with minor reactions to Restylane. The minor reactions noted for Restylane were similar to the reactions from the negative control implant.

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¹ Paris, France

² Q-Med, Uppsala, Sweden

Erian's original technique of lip enhancement

Erian A¹, Ionescu NE²

Int J of Cosmetic Surgery and Aesthetic Dermatology 2000; 2(1): 17-19

Abstract

The lips are superficially located, subject to trauma, and must conform to multiple geometric shapes. Various injectable fillers and inserted materials have been used to fill out the lips. The authors hypothesize that lip augmentation with Restylane would give better results than with other fillers presently in use. Restylane is well tolerated and can be used for lip augmentation lasting longer than fat or collagen.

Conclusion

The use of Restylane in lip augmentation results in full shapely lips, although it lasts only 9 - 12 months. The material is safe and without complications if properly injected.

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Restylane and Perlane: A six year clinical experience

Bosniak S¹, Cantisano-Zilkha M¹

Operative Techniques in Oculoplastic, Orbital and Reconstructive Surgery 2003; 4(2):89-93

Hyaluronic acid is a naturally occurring substance in the human body. It is in every organ of the body. As ophthalmic surgeons know, it has been well tolerated inside the human eye for the last 30 years. When we used it to reconstruct monkey eyelids that had been deformed by trauma, it maintained volume for more than 2 years. Because it is not a foreign protein, and because it is derived from a non-animal source, the potential for inflammatory reaction and allergy is remote. This article will review our 6-year experience utilizing Restylane and Perlane in 2241 patients.

Restylane and Perlane have been effective agents used to fill nasolabial folds, marionette lines, glabellar furrows, depressed scars, upper lip lines and to augment lips. We have observed only mild, transient erythema and edema at the injection sites lasting one to two days. Rarely punctate echymoses followed the injections and lasted one to five days. Patients have noted the results to be satisfying and long lasting. These products compliment Botox and non-ablative laser therapies.

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¹ *Center for Clinical Studies at Oftalmoclinica Botofogo, Rio De Janeiro, Brazil; the New York Eye and Ear Infirmary; and the Manhattan Eye, Ear, Nose and Throat Hospital, New York, NY.*

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 (Restylane) 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

Carruthers J¹, Carruthers A²

Dermatol Surgery 2003; 29: 802-9

Background. Over the past 15 years, BTX-A has become the standard treatment for dynamic glabellar furrowing. Some individuals have resting glabellar rhytides that are sufficiently deep that they respond poorly to BTX-A alone.

Objective. To compare the efficacy of BTX-A combined with intradermal nonanimal stabilized hyaluronic acid (NASHA) with the efficacy of NASHA alone in females with moderate to severe glabellar rhytides.

Methods. This was a prospective randomized study of 38 subjects with moderate to severe glabellar rhytides. Half of the subjects were treated with BTX-A and NASHA and the other half with NASHA alone. Their response was assessed clinically and photographically.

Results. By comparison with the NASHA-alone group, the BTX-A plus NASHA group showed a better response both at rest and on maximum frown, and this response was maintained for longer. The median time for return to preinjection furrow status occurred at 18 weeks in the NASHA-alone group compared with 32 weeks for the BTX-A plus NASHA group.

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Soft Tissue Augmentation Using Restylane

Biesman, B¹

Facial Plastic Surgery 2004; 20(2):171-77

Abstract

Soft tissue augmentation plays an important role in facial rejuvenation. To accomplish this goal, numerous materials have been used. Hyaluronic acids represent the latest family of products to become available in the United States. This article provides an introduction to the proper use of Restylane, the first hyaluronic acid product to be approved by the United States Food and Drug Administration for soft tissue augmentation.

Invited Discussion

Olson, J²

Facial Plastic Surgery 2004; 20(2): 178-9

“Dr. Biesman has written an overview of the nonanimal stabilized hyaluronic acid (NASHA) fillers. Restylane is approved by the Food and Drug Administration as a dermal filler for the correction of soft tissue contour deficiencies. Streptococcal bacterial fermentation is used to produce the Restylane. Marketed in the United States and Canada by Medicis, Restylane is a medium viscosity glycosaminoglycan, and very versatile as a mid to deep dermal filler. An expanded spectrum of NASHA fillers is awaited to be able to fill more superficial dermal lines as well as to use more deeply as a facial contouring substance.

In addition to the treatment of facial wrinkles, I find that Restylane is useful for filling the lips and for deeper facial contouring periorbitally and periorally.”

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¹ Dept. of Otolaryngology, Dept. of Ophthalmology and Visual Sciences, Vanderbilt University Medical Center, Nashville, Dept. of Ophthalmology and Visual Sciences, Univ. of Tennessee Health Sciences Center, Memphis, Tennessee, US

² Dept. of Ophthalmology, Yale University School of Medicine, New Haven, CT, US

Nonanimal Stabilized Hyaluronic Acid for Lip Augmentation and Facial Rhytid Ablation

Bosniak S¹, Cantisano-Zilkha M², Glavas IP¹

Arch Facial Plast Surg 2004; 6:379-83

Objective

To evaluate the effectiveness of nonanimal stabilized hyaluronic acid as an injectable filler agent.

Design

Nonrandomized, retrospective, interventional case series.

Results

A total of 1446 consecutive patients (1029 women and 417 men) underwent intradermal injection of commercially available nonanimal stabilized hyaluronic acid (2242) treatments) for the enhancement of the lip volume and contour and the reduction of visible facial rhytids. Almost 61 % of all patients remained satisfied with their results after 9 months. The effect was longest in the glabellar and nasolabial folds areas. Minimal transient sequelae were noted.

Conclusion

Nonanimal stabilized hyaluronic acid is an effective and safe facial soft tissue expander. Its duration varies with each facial area treated.

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¹ *Manhattan Eye, Ear and Throat Hospital, New York, NY*

² *Center for Clinical Studies, Oftalmoclinica Botafogo, Edificio Colegio Brasileir De Cirurgioes, Rio de Janeiro, Brazil*

Use of Hyaluronic Acid for Soft Tissue Augmentation of HIV-Associated Facial Lipodystrophy

Gooderham M¹, Solish N¹

Dermatol Surg 2005;31(1): 104–108

Background. Lipodystrophy syndrome is a devastating complication of antiretroviral therapy in individuals with human Immunodeficiency virus (HIV). The appearance of the associated facial lipoatrophy can be demoralizing and stigmatizing for the affected individuals to a point at which it may compromise their compliance with antiretroviral medication.

Objective. We describe the use of hyaluronic acid as an intradermal filler for correction of this disfiguring problem.

Methods. We treated five patients with grade 2 to 3 facial lipoatrophy. Each patient received approximately 5 to 6 cc in total of hyaluronic acid in the malar area via intradermal injection.

Results. There were no adverse events. We found that this technique provided a good cosmetic result with high patient satisfaction. At 6-month follow-up, sustained longevity was observed.

Conclusions. We propose the use of hyaluronic acid for HIV-associated facial lipoatrophy as an efficacious and safe, but temporary, option for this problem until a more cost-effective option is available.

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¹ Department of Dermatology, Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario

Clinical Use of RESTYLANE®

*Dover JS¹, Carruthers A², Carruthers J³, Alam M⁴
Skin Therapy Letter 2005; 10(1):5-7*

Abstract

There is no ideal filler, nor will there be a single product that can satisfy all requirements. However, RESTYLANE®, a non-animal, stabilized hyaluronic acid (NASHA, Medicis), is a very versatile augmenting agent. It has been in clinical use for 8 years and experience has shown it to be close to the ideal filler in many respects. This review will outline the background to the use of RESTYLANE®, and will focus on the clinical use of this material.

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Treatment of Tear Trough Deformity and Lower Lid Bowing with Injectable Hyaluronic Acid

Kane MAC¹

Aesth Plast Surg 2005; 29:363-367

Abstract

Tear trough deformity of the lower eyelid is one of the most difficult depressions to correct surgically. The thin skin of the trough, the overhanging abundant lower lid fat, the underlying cheek mound, and the tethering effect of the orbitomalar ligament create a surgical challenge. Until now, noninvasive methods used to treat this depression have been problematic, yielding a poor benefit-to-risk ratio in most hands. Even surgery does not completely manage this depression. The most common surgical techniques for lower eyelid rejuvenation do not even address it. Since December of 2003, 24 patients have had their tear troughs treated with injectable hyaluronic acid. For 23 patients, Restylane® was injected superficially to elevate the surface from the orbitomalar ligament and add volume to the trough. Only two patients were dissatisfied with their results.

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¹ *Manhattan Eye, Ear and Throat Hospital, New York, NY, USA*

Safety and Efficacy of Nonanimal Stabilized Hyaluronic Acid for Improvement of Mouth Corners

*Carruthers J¹, Klein AW², Carruthers A³, Glogau RG⁴, Canfield D⁵
Dermatol Surg 2005;31(3):276–280*

Background. Esthetic concern with downturned mouth corners (“mouth frown”) is increasing in the aging baby-boomer generation. A new technique to offer structural support using the recently approved filler nonanimal stabilized hyaluronic acid (NASHA; Restylane, Q-med Inc., Uppsala, Sweden) is described.

Method. Fifteen women with prominent downturned mouth corners met the inclusion criteria for the study. All were photographed before and at 1 week, 3 months, 4.5 months, and 6 months after treatment using a standardized clinical photographic system. NASHA was injected using a standardized technique with nerve block anesthesia to ensure patient comfort.

Results. All 15 women noted swelling, redness, and some local discomfort for several days after the injection. All noted an improvement in the downward angulation of their mouth corners at the first post-treatment visit, with at least partial improvement maintained through the 6-month post-treatment follow-up visit.

Conclusions. NASHA injection to support the age-related downturn of lateral lip corners was effective, safe, and well tolerated in a small prospective study of middle-aged female subjects. Esthetic satisfaction was greatest in the first 3 months post-treatment, but 40% of subjects still noted improvement at the 6-month follow-up visit.

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Clinical Comparison between Two Hyaluronic Acid–Derived Fillers in the Treatment of Nasolabial Folds: Hylaform versus Restylane

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Dermatol Surg 2005;31(11):Part 2:1587-1590

Background. Hyaluronic acid–derived injectible fillers are ideal to reduce the appearance of nasolabial folding because their effect is relatively long-lasting, the material is malleable and easy to use, and there is a very low incidence of allergic reaction.

Objective. To compare the tolerability and efficacy of two commercially available hyaluronic acid–based fillers, Hylaform (INAMED Aesthetics, Inc., Santa Barbara, CA, USA) and Restylane (Medicis Pharmaceutical Corporation, Scottsdale, AZ, USA), in the treatment of nasolabial folds.

Methods. Eight healthy adult female subjects underwent filler injection therapy for tissue augmentation of their nasolabial folds. Each subject was randomized to receive Restylane 0.7 mL to either the right or the left nasolabial fold and Hylaform 1.0 mL to the contralateral side. High-quality digital photography was performed both at baseline and at 12 weeks post-treatment. These photographs were assessed by four blinded, independent dermatologist reviewers for improvement. Subjects completed questionnaires to document tolerability and satisfaction.

Results. All subjects found the procedure to be tolerable and completely pain free after the use of oral infraorbital regional anesthesia blocks. The average subject satisfaction score was 3.00 of 5 for Hylaform and 3.78 of 5 for Restylane. The blinded, independent reviewer panel attributed an average improvement score of 2.86 of 5 for Hylaform and 3.78 of 5 for Restylane.

Conclusion. Both Hylaform and Restylane are effective fillers for tissue augmentation of the nasolabial folds. Restylane demonstrated higher efficacy and subject satisfaction than Hylaform. With regional nerve blocks prior to injection, both agents are completely painless.

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Soft-Tissue Reconstruction of the Brow with Restylane

Kornstein AW¹

Plastic and Reconstructive Surgery 2005; 116(7):2017-2019

“Facial aging is primarily an atrophy of the hard and soft tissues of the face leading to a loss of three-dimensional structure and antigravity support of the overlying skin - in this case, the brow/upper-lid interface. Because of this, an integral component of my approach to periorbital rejuvenation is volume restoration.”

“Patients enjoy the synergy of the lifting, tightening, and recontouring, yet more and more patients are seeking “limited downtime” procedures to supplant or delay more costly or time-intensive ones. Restylane (Medicis Aesthetics, Inc., Scottsdale, Ariz.) has provided this option. If surgery is not an option, or the time constraints exist, I have found that the combination of Restylane and Botox can be used effectively to temporarily reconstitute brow shape and form, while enhancing upper-lid aesthetics.”

Procedure

“Restylane brow restoration can be accomplished easily under local anesthesia using a supraorbital nerve block. This should be done after marking the brow and with a small volume to minimize distortion of the area.”

“As a right-handed surgeon, I typically start my injections on the right brow from the central aspect of the brow and work laterally. Conversely, I start the left brow from the central position and finish at the most lateral aspect of the lateral aspect of the brow.”

“In general, approximately 0.4 cc are used for each lateral brow. The entire brow requires 0.6 to 0.8 cc each (Figs. 1 through 3). The patient is instructed to ice postoperatively and there have been no complications reported with the first 24 patients. In general, edema is minimal (12 to 48 hours) and bruising is rare. Longevity has been excellent, from 6 months up to 1 year.”

Conclusion

This procedure has been a wonderful adjunct to upper-lid blepharoplasty and to reduce recurrence of brow ptosis following brow lifts, in addition to its use as a primary nonsurgical procedure. The rate of acceptance has been high.

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Injectable Hyaluronic Acid Implant for Malar and Mental Enhancement

Lowe NJ¹, Grover R²

Dermatol Surg 2006; 32:881-5

Background

The use of a thicker injectable implant version of one of the hyaluronic acid dermal fillers (Restylane SubQ, Q-Med, Uppsala, Sweden) is described.

Objective

A group of treated patients has been studied for more than 1 year. Restylane SubQ was injected to the submuscular plane of the upper cheeks and chin to observe efficacy of augmentation and side effect profile, and further observations were made of the duration of benefit.

Methods

Patient details - 72 patients were treated, 68 for upper cheek augmentation, 2 for chin augmentation, and 2 for both areas. Four patients received second injections 8 weeks after the first to increase augmentation.

Results

Patients all showed a persistence of benefit during the posttreatment observation period of up to 64 weeks. Four patients had minor side effects that resolved with local treatment and time. Four patients had second injections to complete augmentation without complications.

Conclusions

Restylane SubQ is a useful injectable agent to augment and lift upper cheeks and recontour chins. Further efficacy studies seem justified.

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Deep-fill hyaluronic acid for the temporary treatment of the naso-jugal groove: a report of 303 consecutive treatments

Steinsapir KD¹, Steinsapir SM¹

Ophthalm Plast Reconstr Surg. 2006; 22(5):344-8

Purpose

To report a 2-year experience of treating the naso-jugal groove with injectable hyaluronic acid gel, using a deep-fill method.

Methods

This was a consecutive, retrospective, nonrandomized case series of patients presenting with concerns involving dark circles, lower eyelid hollows, or other contour irregularities that make up the naso-jugal groove. One author performed all treatments, consisting of transcutaneous injection of hyaluronic acid gel filler, to address the naso-jugal groove. The filler was placed deep on the anterior lip of the orbital rim and molded to the desired shape.

Results

Between December 2003 and December 2005, 164 patients (34 male and 130 female) received hyaluronic acid gel filler in the face. Ninety-eight patients were treated just once and 66 had multiple treatment sessions. The mean dose of filler per session was 1.53 +/- 0.8 ml, with 0.84 +/- 0.38 ml divided between the two lower eyelids. The most common complication was localized swelling, followed by bruising, asymmetry, cellulitis (2 cases), and migraine (1 case). There were no cases of visual loss.

Conclusions

Hyaluronic acid gel fillers have had an enormous impact on the practice of cosmetic surgery, and this series demonstrates the usefulness of these fillers for treatment of the lower eyelid and midface. The authors recommend the deep-fill method described as a reliable means of addressing the hollow created by the naso-jugal groove.

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Nasal reconstruction using 20 mg/ml cross-linked hyaluronic acid

Beer KR¹

J Drugs Dermatol. 2005(5):465-6

According to American Society for Aesthetic Plastic Surgery (ASAPS), 200,924 people had rhinoplasties in 2005. Patients typically have surgical rhinoplasty to correct unsightly noses resulting from trauma, surgery, or heredity. Several alternatives presently exist for patients considering surgical rhinoplasty. These include injections of botulinum toxins to correct the shape of the nasal tip and the use of various fillers to correct contour and profile defects. This article presents a simple and effective alternative using hyaluronic acid for some patients requiring nasal recontouring. The procedure offers patients the opportunity to avoid the risks and expense associated with surgical correction.

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Filling the periorbital hollows with hyaluronic acid gel: initial experience with 244 injections

Goldberg RA¹, Fiaschetti D¹

Ophthalm Plast Reconstr Surg. 2006; 22(5):335-41

Purpose

To review our initial experience using hyaluronic acid gel (Restylane) as a filler to treat the periorbital hollows.

Methods

This is a retrospective, anecdotal case review of 244 cosmetic hyaluronic acid gel injections in 155 patients. An average volume of 0.9 ml per injection session was used in an individualized pattern that variably included the orbital rim hollow, zygomatic hollow, septal confluence hollow, and eyebrow and cheek fat pad. To achieve smooth contours, a layered, feathered threading technique was used, placing the filler deep to the orbicularis. Hyaluronidase injections were used in 11% of patients at follow-up visits to “dissolve” some of the filler to reduce contour irregularities.

Results

One hundred eight of 121 (89%) patients with follow-up visits were satisfied with the cosmetic improvement after hyaluronic acid gel injections. For maintenance, the interval to second injection averaged 6.5 months. Side effects included lumps or contour irregularities (11%), bruising (10%), color change (7%), and fluid (15%). Twelve patients were unsatisfied and were not interested in additional injections: 5 with malar fluid, 3 with lumpy irregularity, and 3 with color change.

Conclusions

Complex 3-dimensional contours and thin skin over bone render periorbital filling difficult. However, with individualized planning and with care taken to create smooth, feathered contours, it is possible to achieve acceptable improvement. We found that most patients considered themselves improved cosmetically, despite occasional side effects including contour irregularity or lumps, bruising, color change, and fluid accumulation. Patients with very thin skin, preexisting color problems, or preexisting eyelid fluid may not be good candidates for periorbital filling with hyaluronic acid gel. The effect of the filler is temporary, of course, and we counsel patients to anticipate maintenance injections at 6- to 12-month intervals.

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Hyaluronic acid gel (Restylane) filler for facial rhytids: lessons learned from American Society of Ophthalmic Plastic and Reconstructive Surgery member treatment of 286 patients

McCracken MS¹, Khan JA², Wulc AE³, et al

Ophthalm Plast Reconstr Surg. 2006; 22(3):188-91

Purpose

To review injection techniques and patient satisfaction with injection of Restylane in various facial areas by American Society of Ophthalmic Plastic and Reconstructive Surgery members.

Methods

Data from 286 patients treated with Restylane in nine American Society of Ophthalmic Plastic and Reconstructive Surgery practices were abstracted to a spreadsheet for analysis.

Results

Nine practices performed Restylane injections for 8.8 months on average (range, 2 to 28 months). Average practice volume per patient was 1.2 ml (range, 0.7 to 2.1 ml). Nine of nine practices injected the nasolabial and melolabial folds, 9 of 9 practices injected the lips, and 6 of 9 injected the glabella. Only 2 of 9 practices injected other fillers concurrently. Botox was injected concurrently by 8 of 9 practices. On a scale of 1 to 10, physicians rated average patient discomfort during Restylane injection 4.6 with topical anesthesia and 2.1 with injectable lidocaine, with or without topical anesthesia. The end point for injection was determined by visual cues, volume of injection, extrusion of the product, and palpation. "Problematic" complications, including bruising, swelling, bumpiness, and redness each had an incidence of 5% or less. Patient satisfaction on a scale of 1 to 10 had an average rating of 8.1, compared with that of Botox injection (8.9), upper blepharoplasty (8.9), and collagen injection (6.6). The source of Restylane patients was estimated to be existing Botox patients (45%); existing non-Botox patients (18%); word of mouth (14%); and new patients for other services (13%).

Conclusions

Injection techniques, volume, end points, and anesthesia vary for different facial areas and between practices. Patients experience mild to moderate injection discomfort that is lessened with injectable lidocaine. Self-limited problems occur in about 5% of patients. Physician-determined patient satisfaction is perceived to be higher than that of collagen injection but slightly lower than that of botulinum toxin injection. The major source of Restylane patients was from existing practice patients, especially botulinum toxin patients.

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The Use of Restylane in Cosmetic Facial Surgery

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J Oral Maxillofac Surg 2006; 64:317-25

The injection of filler substances is one of the most common procedures in cosmetic surgery. In 2003, the number of nonsurgical procedures increased 22 % from 2002. The last 5 years have brought about an extreme interest in minimal invasive rejuvenation techniques. The ease and popularity of Botox (Allergan Inc, Irvine, CA) has popularized and expanded the use of rejuvenative injections. This, coupled with the introduction of multiple new products, has increased the number of treatment options for cosmetic patients. Multiple substances are available to inject into facial wrinkles, folds, lips, traumatic defects, and depressed scars, and to augment facial form.

Over the last century some substances, such as paraffin and silicone, have been used with associated problems. For over 2 decades the gold standard for injectable facial fillers in the United States has been bovine-derived collagen (Zyplast; Inamed Inc, Santa Barbara, CA). This product was available in several viscosities (particle sizes) to use in different indications from fine lines and wrinkles to lip plumping.

Various advantages and disadvantages exist with all filler substances. One of the biggest disadvantages has been the need for allergy testing with the non-human preparations. In addition to the possible allergic reaction, cosmetic patients are very impulsive consumers and having to wait a month for an allergy test before treatment is a huge drawback. Many of the newer products are non-animal and do not require allergy testing.

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In Vivo Stimulation of De Novo Collagen Production Caused by Cross-linked Hyaluronic Acid Dermal Filler Injections in Photodamaged Human Skin

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Arch Dermatol. 2007;143:155-163

Objective: To determine whether endogenous synthesis of new extracellular matrix may contribute to the degree and duration of clinical benefits derived from crosslinked hyaluronic acid dermal filler injections.

Design: In vivo biochemical analyses after filler injections.

Setting: Academic referral center.

Participants: Eleven healthy volunteers (mean age, 74 years) with photodamaged forearm skin.

Interventions: Filler and vehicle (isotonic sodium chloride) injected into forearm skin and skin biopsy specimens taken 4 and 13 weeks later.

Main Outcome Measures: De novo synthesis of collagen, the major structural protein of dermal extracellular matrix, was assessed using immunohistochemical analysis, quantitative polymerase chain reaction, and electron microscopy.

Results: Compared with controls, immunostaining in skin receiving cross-linked hyaluronic acid injections revealed increased collagen deposition around the filler. Staining for prolyl-4-hydroxylase and the C-terminal and Nterminal epitopes of type I procollagen was enhanced at 4 and 13 weeks after treatment (P .05). Gene expression for types I and III procollagen as well as several profibrotic growth factors was also up-regulated at 4 and 13 weeks compared with controls (P .05). Fibroblasts in filler-injected skin demonstrated a mechanically stretched appearance and a biosynthetic phenotype. In vitro, fibroblasts did not bind the filler, suggesting that cross-linked hyaluronic acid is not directly stimulatory.

Conclusions: Injection of cross-linked hyaluronic acid stimulates collagen synthesis, partially restoring dermal matrix components that are lost in photodamaged skin. We hypothesize that this stimulatory effect may be induced by mechanical stretching of the dermis, which in turn leads to stretching and activation of dermal fibroblasts. These findings imply that cross-linked hyaluronic acid may be useful for stimulating collagen production therapeutically, particularly in the setting of atrophic skin conditions.

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Study of the effects of stabilized non-animal hyaluronic acid on the biophysical properties of the skin

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Division of Cosmetic Sciences, University of Hamburg, Hamburg, Germany

Poster presented at American Academy of Dermatology, Washington D.C., USA, Feb 2007

Introduction: Hyaluronic acid (HA) is important for the structural properties of skin and also as a regulator of cell behaviour and metabolism. Intradermal injection of HA is commonly used for facial augmentation in patients with signs of aging skin, but its effects on skin physiology needs to be further evaluated.

Objective: To evaluate the effects of NASHA injections on the physiology of aged skin using non-invasive biophysical techniques.

Methods: Participants were healthy women (n=20) aged 40–60 years with visible signs of skin aging (eg reduced elasticity, reduced turgor, actinic elastosis, small and large wrinkles). Study duration was 6 months, and each subject received 3 treatments (week 0, after 4 weeks and after 8 weeks) and 5 examinations (weeks 0, 4, 8, 12 and 24). Both sides of the face were treated in an identical manner, and no changes to skin care regimens were allowed 12 weeks before or during the study. Biophysical properties assessed were skin thickness and density measured by 20 MHz, elasticity, surface roughness, stratum corneum hydration, transepidermal water loss and surface pH. Potential adverse events related to study treatment were monitored to assess tolerability.

Results: The mean age of participants was 53.9 years. Skin surface roughness improved significantly ($p \leq 0.001$) between baseline and week 24. Elasticity also improved significantly from baseline to 24 weeks ($p \leq 0.05$), with the greatest improvement between weeks 12 and 24. No significant difference in skin thickness was observed on either side of the face. Skin density decreased during the first 8 weeks of the study, before returning to baseline levels by week 24. Transepidermal water loss and skin surface pH remained within the physiological range throughout the study period. No remarkable changes were observed in stratum corneum hydration. Treatment was well tolerated. Four patients developed mild hematoma after injection, 2 experienced erythema and 1 developed a nodule; all events were transient and resolved spontaneously.

Conclusions: This study shows for the first time significant improvements in skin physiology (surface roughness and elasticity) following intradermal injection of NASHA. These objectively determined biophysical findings may explain the clinical improvement in skin that is commonly observed after HA treatment.

Hyaluronic acid skin fillers: Adverse reactions and skin testing

Lowe, NJ^{1,2,3}, Maxwell C.A¹, Lowe, P¹, Duick, MG² Shah, K^{1,4}

J Am Acad Dermatol 2001;45:930-3

Background

Hyaluronic acid (HA) fillers have been proposed as alternatives to other temporary skin fillers, such as bovine collagen, for treating facial skin lines and for providing lip augmentation. Several types of commercial HA fillers are now available in many countries. They include Restylane, which is produced by microbiologic engineering techniques, and Hylaform, which is HA extract derived from rooster combs. They have been approved for use in several countries, but not currently in the United States. There are no recommendations to perform pretreatment skin testing by the manufacturers.

Conclusion

There was a slight incidence of delayed inflammatory skin reactions to two HA fillers. Both of these reactions occurred after the first and repeat injections. Challenge skin testing was positive in 4 of 5 tested patients.

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Safety data of injectable nonanimal stabilized hyaluronic acid gel for soft tissue augmentation

*Friedman PM^{1,2}, Mafong EA¹, Kauvar ANB¹, Geronemus RG¹
Dermatol Surg 2002; 28(6): 491–4*

Background

Nonanimal hyaluronic acid gel was recently developed for soft tissue augmentation and volume expansion and has been shown to offer several advantages in comparison to other augmentation materials. There are rare reports of adverse events believed to be secondary to trace amounts of proteins in the hyaluronic acid raw material.

Conclusion

According to the reported worldwide adverse events data, hypersensitivity to nonanimal hyaluronic acid gel is the major adverse event and is most likely secondary to impurities of bacterial fermentation. According to data from 2000, the incidence of hypersensitivity appears to be declining after the introduction of a more purified hyaluronic acid raw material.

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Evaluation of the safety of non-animal stabilized hyaluronic acid (NASHA – Q-Med, Sweden) in European countries: a retrospective study from 1997 to 2001

André P¹

JEADV 2004; 18: 422-25

Background. In Europe, several filler devices are currently on the market for use in aesthetic dermatology and some of them cause severe, permanent, adverse reactions. Since 1996 a non-animal stabilized hyaluronic acid (NASHA) from Q-Med, Sweden, has been introduced and is becoming a leading product in aesthetic dermatology. Hyaluronic acid has no species specificity and skin testing is not recommended before treatment.

Objective. Our purpose was to evaluate the incidence of adverse reactions from 1997 to 2001 and the safety of NASHA after injections into the skin for aesthetic reasons.

Method. Surveys were sent to physicians in European countries that agreed to participate. This is a retrospective study. A total of 12 344 syringes were sold by Q-Med to these physicians and we evaluated the total number of patients treated to 35 % of this number (4320). We separated immediately hypersensitivity reactions from delayed reactions and analysed infectious and other types of reactions.

Results. From 1997 until 2001, 34 cases of hypersensitivity were reported: 16 cases of immediate hypersensitivity and 18 cases of delayed. The global risk of sensitivity is 0.8 %. Since 2000, the amount of protein in the raw product has decreased and the incidence of hypersensitivity reactions is around 0.6 %. As 50 % of these reactions are immediate and resolved within less than 3 weeks, the risk of strong but transient, delayed reaction is around 0.3 %. Four cases of abscess were reported. They were all sterile. No bacterial infection was found. Herpetic recurrence is possible after lip augmentation according to the technique of injection. No systemic reactions were reported.

Conclusion. NASHA is a very useful and safe filler product. Skin testing does not seem to be necessary.

¹ Paris, France

Management of complications after implantation of fillers

De Boulle K¹

J of Cosmetic Dermatol 2004; 3:2-15

Summary

Soft tissue augmentation is widely practised by a variety of different practitioners. A new classification of filler substances and procedures, taking into account long-term safety and reversibility of side effects, is proposed:

- i** *non-permanent and biodegradable,*
- ii** *semi-permanent and biodegradable,*
- iii** *permanent and reversible,*
- iv** *permanent and non-reversible.*

Complications and adverse effects occur with all fillers and all filler procedures. Insufficient experience is an important contributory factor. Underreporting is probably common. Commonest are haematomas, ecchymoses, infections, papulopustular or acneiform lesions, non-hypersensitivity related swelling and oedema, erythema, changes in pigmentation, palpability of the implant and necrosis of overlying tissue. Specific therapeutic approaches for these complications and practical recommendations to minimize or avoid them are discussed. Hypersensitivity reactions and granuloma formation are the most distressing adverse effects. They can occur with most fillers. Mostly these hypersensitivity reactions are local granulomas but, rarely, generalized reactions also occur. Case reports of systemic reactions after injection of hyaluronic acid are documented. Treatments include steroids, minocycline and immunomodulatory agents, such as cyclosporin, tacrolimus and ascomycin. In selected cases, surgical procedures are necessary to eliminate granulomatous reactions. Implant migration and facial lipoatrophy are encountered with certain compounds. Extreme caution is therefore advocated before using permanent and nonreversible products for soft tissue augmentation. Those who use fillers need to be familiar with the complications of fillers and with the treatment of those complications.

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Use of Hyaluronidase in the Treatment of Granulomatous Hyaluronic Acid Reactions or Unwanted Hyaluronic Acid Misplacement

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Dermatol Surg 2005;31:893–897.

Background

In the past, reactions or misplacement of soft tissue fillers has been fraught with anxiety because time has been the main thrust for improvement in spite of ancillary treatments. Hyaluronidase is an enzyme that dissolves hyaluronic acid in the skin and also assists in the management of granulomatous foreign-body reactions to hyaluronic acid. These reactions may be caused by allergy to the material or immunologic response to the protein contaminants in the hyaluronic acid preparations. Dissolution of material in erroneous placement of material and in allergic reactions can be a time saver and a deterrent to patient dissatisfaction.

Objective

To evaluate the use of hyaluronidase in the treatment of both allergic reactions and the erroneous misplacement of hyaluronic acid in the skin.

Methods

A case of persistent granulomatous reaction to injectable hyaluronic acid and a case of hyaluronic acid erroneous misplacement with their successful subsequent treatments using intracutaneous hyaluronidase are reported, along with illustrative examples of hyaluronidase use.

Results

The use of hyaluronidase reduced the patient discomfort within 24 to 48 hours, deterring any patient anxiety or patient dissatisfaction.

Conclusions

Hyaluronidase has a place in the treatment of allergic reactions to hyaluronidase and in the erroneous misplacement of the material.

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Adverse Reactions to Dermal Fillers: Review

Lowe NJ¹, Maxwell CA², Patnaik R³, Md†

Dermatol Surg 2005; 31(11:Part2)1616-1625

Background

For many patients, injectable filling agents offer the promise of facial rejuvenation while offering reduced risks compared with more invasive surgery. With the increase in products available and the rise in the number of patients seeking this type of intervention, it is crucial that both the physician and the patient are fully cognizant of the risks involved with each product.

Objective

To review the incidences and types of reaction to various commonly used injectable products.

Methods

A literature review and personal experiences (gained largely in Europe over the past 8 years) of dermal fillers from 1996 to the present, including illustrative case reviews.

Results

Reactions can be attributed to the procedure itself, the procedural technique, and the agent injected. Some of these reactions are preventable, whereas others are inevitable; most are mild and transient. Improving product formulations, altering the concentration of product injected, or changing the injection technique can dramatically reduce the incidence of adverse reactions. Since its reformulation in mid-1999, the biologically engineered hyaluronic acid filler Restylane (Medicis Pharmaceuticals, Scottsdale, AZ, USA) elicits less than one allergic reaction in 1,600 treatments. Skin reactions with poly-L-lactic acid (New-Fill/Sculptra, Dermik Laboratories, Berwyn, PA, USA) are considerably less likely if a greater dilution and deeper injection technique are employed.

Conclusion

Different injectable products have highly divergent properties, associated risks, and injection requirements. The dermatologist should be suitably experienced to select and use these products correctly.

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Clinical conference: management of rare events following dermal fillers-focal necrosis and angry red bumps.

Narins RS¹, Jewell M², Rubin M³, Cohen J⁴, Strobos J⁵

Dermatol Surg 2006;32:426-34

Typical complications related to hyaluronic facial fillers used in the treatment of wrinkles are well described and readily manageable without sequelae. These events include transient local inflammatory reactions in which edema, erythema, tenderness or pain predominate and which typically resolve spontaneously within a few days but whose resolution may be facilitated by the use of topical steroids or low doses of oral anti-inflammatory agents or oral steroids. As these reactions can occasionally be severe, some physicians pretreat patients known to have such reactions with low doses of oral prednisone continued through a few days after intradermal injection. Historically, collagen-based products are known to induce more severe and long-lasting local allergic reactions. In contrast, with the hyaluronic acid products, including Hylaform[®] and Restylane[®], local bruising is more common as collagen products stimulate platelet activation. Infections may result from any injection procedure involving placement of an implant. Dermal fillers are also thought to be a trigger for recurrent herpetic lesions and, similarly, may be followed by acneiform eruptions, headache, viral exanthems, or other common conditions. Overly superficial injection may result in product visibility, either as bluish or yellowish lines depending on the product, that can also be managed by local massage or physical removal with a needle. More complex side effects have been rare. A clinical conference was organized to permit review of the likely etiology and management of two such rare events: focal necrosis and delayed onset angry red bumps. These two unusual events are both described on approved labeling, but health care reports to the manufacturer have requested assistance in either limiting incidence or in postevent management. All spontaneously reported cases for these events for 2004 in the United States were compiled and submitted to an expert panel. This report represents a summary of the discussants' comments.

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The History of Substances for Soft Tissue Augmentation

Klein AW¹, Elson ML²

Dermatol Surg 2000;26:1096-1105

“SOFT TISSUE AUGMENTATION has seen a renaissance of interest as an increasing number of patients seek aesthetic improvement without major downtime. Why this renewal of interest in filling agents? One huge reason is the availability of Botox (Allergan, Inc., Irvine, CA) which works superbly in the upper face. This accomplishment of rejuvenating the upper face using Botox has created a need for agents that work equally well in the lower face. A second reason is that the introduction of many new implantable materials and techniques has contributed to the advancement of the field of cosmetic surgery over the past 15 years. Another reason for this re-interest is the concept of the three-dimensional face. The youthful face has a much fuller look, not a pulled, flat, two-dimensional look. This has become one of the central tenets of the field of soft tissue augmentation.

Filling can augment and even, at times, replace pulling. In addition subtle lip enhancement is something that is here to stay. In fact, it is the number one indication for injectable fillers.”

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Comparison of Resorbable Soft Tissue Fillers

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Aesthetic Surg J 2004; 24(1) 33-46

Soft tissue fillers for wrinkle treatment and facial reshaping offer numerous advantages for both doctors and patients. They are extremely well tolerated and efficacious and can produce long-lasting improvement with regular use. In this article a detailed, thorough review of the resorbable injectable filler implants available on the international market is offered and the most suitable for various treatment areas are identified. The chemical nature, formulation, indications, recommendations for technique, and possible side effects of each family of fillers are described.

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Reliable Soft Tissue Augmentation A Clinical Comparison of Injectable Soft-Tissue Fillers for Facial-Volume Augmentation

Kahnchwala SK., Holloway L, Bucky LP

Ann Plast Surg 2005; 55:30-35

Abstract

While injectable fillers for facial-volume augmentation have been extensively marketed, there are few published reports comparing the clinical efficacy and cost-effectiveness of multiple injectable agents for soft-tissue augmentation in the face. We present our experience in 976 patients with the use of 4 common injectable agents: autologous fat, Hylaform, Restylane, and Radiesse. We analyzed the injection characteristics of each filler, including injection volume, complication rate, revision rate, and longevity, across 3 commonly treated anatomic regions: the nasolabial fold, glabella, and lips. We subsequently performed a detailed cost-effectiveness analysis of each filler in each anatomic region. Our results demonstrate that autologous fat transplantation is ideally suited for the treatment of the nasolabial and glabella, particularly in combination with other procedures. Fat grafting to the lips is limited to use as an adjunct to other facial surgery due to the prolonged recovery time required. We prefer Radiesse for the isolated treatment of the nasolabial folds and glabella. However, Radiesse is not recommended in the lips due to the increased incidence of complications. Last, the hyaluronic fillers Restylane and Hylaform have an excellent safety profile and are our first choice for isolated lip augmentation procedures.

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Injectable Skin Fillers

Narins RS¹, Bowman PH²

Clin Plastic Surg 2005; 32:151-162

“Recent advances in soft tissue augmentation have expanded our options in the search for an ideal filling agent, and several new fillers have recently been approved by the US Food and Drug Administration (FDA). Fillers can be used aesthetically to reduce the effects of aging and to de-emphasize previous scars. With aging, there is shifting and loss of connective and subcutaneous tissue, most notably in the face, neck, and hands. Subcutaneous augmentation in appropriate areas with injectable fillers replaces this lost tissue, producing a rejuvenating effect. Fillers can work synergistically with surgical procedures (eg. facelifts) to improve results. Patients who do not want to undergo a surgical procedure can often obtain excellent results noninvasively using fillers combined with other modalities (eg. laser resurfacing, peels, botulinum toxin).

Facial fillers are most useful in the lower third of the face. The gravitational effects of aging mean that tissue shifts inferiorly, resulting in accentuated nasolabial and melolabial folds. Moreover, botulinum toxin is unmatched in its ability to rejuvenate the upper third of the face. Scars from acne, surgery, or trauma that result predominantly from loss or contraction of tissue can also be improved greatly with fillers. Each type of filler has different strengths and weaknesses (Table 1). Physicians who are familiar with many fillers thus are best equipped to maximize the benefits of this class of agents and to serve their patients.”

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Dermal fillers

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J of Cosmetic Dermatol 2005; 3:249–250

Summary

The new bioengineered human collagen products and the various hyaluronic acid (HA) fillers are all safe and effective agents for soft tissue augmentation. There is no one best filler for all purposes and optimal results are achieved by using these products in various combinations. In my opinion, HA-containing products provide volume while collagen products are better suited to provide structural support. Less downtime is associated with the collagen products, due to the platelet-aggregating effects of collagen and the eosinophilstabilizing effects of lidocaine. Using collagen in combination with HA, during the same office visit, may help reduce some of the bruising and swelling seen with HA alone.

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Consensus recommendations for soft-tissue augmentation with nonanimal stabilized hyaluronic acid (Restylane)

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Plast Reconstr Surg. 2006;117(3 Suppl):3S-34S; discussion 35S-43S*

The American Society for Aesthetic Plastic Surgery recently reported that there were nearly 12 million cosmetic procedures (2.1 million surgical and 9.7 million nonsurgical) performed in the United States in 2004. Almost 900,000 of the nonsurgical procedures were soft-tissue augmentation procedures using hyaluronic acid fillers. Restylane (Medicis Aesthetics, Inc., Scottsdale, Ariz.), nonanimal stabilized hyaluronic acid, was approved for use in the United States in December of 2003. Although the use of all fillers increased from 2003 to 2004, use of hyaluronic acid fillers increased nearly 700 percent. The dramatic increase in all cosmetic procedures reflects the growing trend, especially with increasing job competition, to maintain a youthful lifestyle and appearance. Basic recommendations for aesthetic use of Restylane were established based on short- and long-term efficacy and safety studies (Medicis Aesthetics, package insert). With the widespread and growing use of Restylane, a cross-sectional panel of experts with extensive clinical experience, including cosmetic dermatologists and surgical specialists (cosmetic, plastic, and ocular), convened to develop consensus guidelines for the use of Restylane. This supplement reviews the aesthetic affects of aging on the face, the role of fillers in facial soft-tissue volume replacement, and general principles for the use of Restylane, including patient comfort and assessment techniques. Specific recommendations for Restylane use in each potential target area, including type of anesthesia, injection techniques, volume for injection, use in combination with other procedures, and expected longevity of corrections, are provided. Techniques for optimizing patient outcomes and satisfaction and for minimizing and managing expected problems and potential complications are described.

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Available as Reprint from your local RESTYLANE representative.

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Soft tissue augmentation 2006: filler fantasy

Klein AW¹

Dermatol Ther. 2006; 19(3):129-33

Abstract

As an increasing number of patients seek esthetic improvement through minimally invasive procedures, interest in soft tissue augmentation and filling agents is at an all-time high. One reason for this interest is the availability of botulinum toxin type A, which works superbly in the upper face. The rejuvenation of the upper face has created much interest in injectable filling agents and implant techniques that work equally well in the restoration of the lower face. One of the central tenets of soft tissue augmentation is the concept of the three-dimensional face. The youthful face has a soft, full appearance, as opposed to the flat, pulled, two-dimensional look often achieved by more traditional surgical approaches. Injectable filling agents can augment and even at times, replace pulling. Additionally, with the lip as the focal center of the lower face, subtle lip enhancement is here to stay, and is in fact, the number one indication for injectable fillers. Moreover, minimally invasive soft tissue augmentation offers cosmetic enhancement without the cost and recovery time associated with more invasive procedures. As more and more physicians take interest in minimally invasive surgery, courses in cosmetic surgery techniques are becoming increasingly popular at the medical meetings of many specialties. Today, physicians have a much larger armamentarium of techniques and materials with which to improve facial contours, ameliorate wrinkles, and provide esthetic rejuvenation to the face. For a substance or device to be amenable for soft tissue augmentation in the medical community, it must meet certain criteria. It must have both a high "use" potential, producing cosmetically pleasing results with a minimum undesirable reactions, and have a low abuse potential in that widespread or incorrect or indiscriminate use would not result in significant morbidity. It must be nonteratogenic, noncarcinogenic, and nonmigratory. In addition, the agent must provide predictable, persistent correction through reproducible implantation techniques. Finally, the substance, agent or device must be approved by the U.S. Food and Drug Administration, which assures purity, safety, and accessibility, as well as much-needed information regarding use. Having a thorough understanding of the filling agents available, their indications and contraindications, as well as having thorough knowledge of implant technique are vital in providing the patient with an esthetically pleasing result.

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Cross-Linked Hyaluronic Acid Fillers

Coleman S and the Plastic Surgery Educational Foundation DATA Committee¹

Plast Reconstr Surg 2006; 117(2):661-5

After more than 9 years of use in Europe, three injectable hyaluronic acid gel filler products have been approved for use in the United States by the U.S. Food and Drug Administration over the last year and a half: Restylane (Q-Med AB, Uppsala, Sweden), on December 12 2003; Hylaform, on April 23, 2004; and Hylaform Plus, on October 13, 2004 (Genzyme Biosurgery, Ridgefield NJ). They reportedly have many characteristics of an ideal soft-tissue filler: efficacy, biocompatibility, and safety. Those qualities are the subject of this article.

At least one of these fillers will be incorporated into most aesthetic surgery practices. To provide a proper informed consent to our patients, it is important for us to understand the different formulations approved by the Food and Drug Administration, their suggested uses, their supposed longevity, and the potential complications.

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Letter to the Editor

The American filler experience – a response to Dr Baumann

Klein AW¹

“I read with interest Leslie Baumann’s review of the American Filler experience in the Journal of Cosmetic Dermatology. At the American Academy of Dermatology annual meeting in 2004, Dr Baumann suggested mixing Hylaform and Cosmoderm in the same syringe when augmenting the lip. At that meeting, I presented the concept of pretreating the lip with any collagen product prior to the injection of the hyaluronic acid. Has she now abandoned her mixing technique in favor of my recommended technique? While I use Cosmoderm and Cosmoplast, I, as many experienced Injectors do, feel that Zyderm and Zyplast have much greater longevity. The improved flow characteristics of the bioengineered products may be caused by a decreased concentration of collagen in these products. Restylane and its “stiffer consistency” and application in scars are all that is mentioned of this very popular and effective agent. Restylane currently represents almost 80% of the filler market in the United States. In a clinical trial of 138 patients, in the United States, Restylane was found superior to Zyplast in 56.9%, equal to Zyplast in 33.6% and Zyplast superior to Restylane in 9.5%. Moreover, after I re-evaluated these results, investigators who had used the serial puncture injection technique with this product had the greater longevity of correction. Studies were then performed in Vancouver regarding the use of Restylane for lip augmentation and restoration of the lower third of the face. These studies further supported the excellent longevity of Restylane as well as serial puncture technique as the best manner in which to inject this product.”

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Hyaluronic acid beats collagen in soft tissue fillers

Dermatology Times of Canada

July 2001

“Hyaluronic acid-based fillers are showing a distinct advantage compared with collagen-based fillers, said Steven Bernstein, MD, assistant professor and director of dermatologic surgery, University of Montreal.

‘The gold standard previously was collagen which was bovine-based, so it carried an increased risk of antigenicity and immunogenicity’, Dr. Bernstein said, speaking at the annual Atlantic Dermatological Conference here.

Hyaluronic acid, however, is a non-animal-based, synthetic poly-saccharide, and it appears to last longer than collagen.

An efficacy study by Q-Med AB, Sweden, manufacturer of the hyaluronic acid products Restylane® and Perlane®, reported that 55 per cent of patients and 66 per cent of physicians felt that the effects were still apparent one year after treatment.

‘Patients need to come back much less frequently. I normally suggest a re-touch at between nine and 12 months - and it’s about half that time with collagen’, Dr. Bernstein said.”

Perlane called the best European artificial filler

Timothy F. Kirn, Sacramento Bureau

Skin & Allergy News, 2002: 33(7)

“Of the artificial fillers perhaps destined for the United States soon, the best may be Perlane because it lasts the longest. Dr. Nicholas Lowe said at a meeting on cosmetic dermatology sponsored by the Skin Disease Education Foundation.

Perlane, which is hyaluronic acid (Q-Med, Uppsala, Sweden) remains where it is injected long enough to produce adequate augmentation in the lips for 12 months and in the nasolabial folds for 18 months, said Dr. Lowe, who practices both in Los Angeles and in London, where Perlane is available.

It lasts considerably longer than Zyplast (bovine collagen). I think it is a very good product. The only thing that is a little bit different from Zyplast is that for the first few days after the injection, you get more swelling, particularly in the lips. It is not drastic, but the patients do have to be aware of that Dr. Lowe says.

Of all the different types of filler products that are available in Europe, Dr. Lowe said he prefers Perlane, or Restylane, which is the more viscous hyaluronic acid product from the same company.”

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Advantages of the presence of living dermal fibroblasts within RESTYLANE for soft tissue augmentation

Eul-Sik Yoon¹, Seung-Kyu Han¹, Woo-Kyung Kim¹

Annals of Plastic Surgery 2003; 51(6):587-592

For the elimination of facial wrinkles and skin contour defects, injectable filler substances composed of commercially prepared nonanimal stabilized hyaluronic acid (Restylane) are now widely used. Although this method of suspension has been shown to be relatively safe and convenient, varying degrees of resorption have required repeated percutaneous injections. This study was undertaken to evaluate the feasibility of Restylane, which is a modified hyaluronic acid, combined with cultured human dermal fibroblasts, to enhance the longevity of injected implants. The histologic changes of the injected implants were also evaluated. For the test group, fibroblasts from the dermis of healthy adults were isolated and cultivated. The cultured fibroblasts were measured with a hemocytometer. Five $\times 10^5$ fibroblasts suspended in 200 μ l of Dulbecco phosphate-buffered saline (DPBS) were then dispersed in 200 μ l of Restylane to form a 400- μ l human fibroblast-Restylane mix. For the control group, 200 μ l of DPBS without fibroblasts were mixed with 200 μ l of Restylane. These implants were subcutaneously injected into the back of an athymic nude mouse at 6 sites, the 3 left sites composing the control group and the 3 right sites composing the test group. Twelve nude mice were injected for a total of 36 injections per group. The nodular swellings that resulted from the injections were excised to include skin beyond the swelling points down to the panniculus carnosus layer using 5-mm punches and the weights were measured at 1, 2, 4, 8, 12 and 16 weeks after the injections. Histologic comparisons were also performed to confirm the presence of human collagen in the fibroblast-mixed Restylane group using immunohistochemical study with antihuman collagen type I polyclonal antibody. The mean weight of the control group nodules decreased throughout the examination period. The mean weight at the 16th week was 60 % of the weight at the first week. On the other hand, the mean weight of the test-group nodules decreased only over the first 2 weeks. Beyond 2 weeks, there was no further significant weight change. The mean weight at the 16th week was 91 % of the weight measured at the first week. Histologic examinations of the control group exhibited negative immunohistochemical staining for human collagen at each examination period. The test group exhibited positive staining after 2 weeks, indicating the presence of human collagen. These results indicate that Restylane mixed with cultured human dermal fibroblasts may be successfully injected as living grafts for long-term retention of implants.

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Restylane Persistent for 23 Months Found during Mohs Micrographic Surgery: A Source of Confusion with Hyaluronic Acid Surrounding Basal Cell Carcinoma

Bennett R¹, Taher, M²

Dermatol Surg 2005;31:1366–1369

Background. Restylane (Q-Med, Uppsala, Sweden), a hyaluronic acid (HA) that is microbiologically produced and then cross-linked, is becoming popular as a dermal filler for improvement of facial lines and wrinkles. However, it is currently believed that the clinical and histologic persistence of this filler is from 6 to 9 months. We recently encountered Restylane in tissue where it had been implanted 23 months prior to removal of a basal cell carcinoma (BCC) on the lip, and its presence caused some confusion with HA that surrounds BCC nests.

Objective. To show and to contrast the histologic dermal appearance of Restylane and its metachromatic staining characteristics With toluidine blue from those of HA that surrounds BCC nests.

Method. Toluidine blue staining at pH 7.07 was performed on excised tissue containing Restylane and BCC on the upper lip.

Results. Restylane appeared as reddish-purple amorphous masses, whereas the HA that frames BCC nests appeared redder and more well defined.

Conclusion. The amorphous metachromatic reddish-purple color staining of Restylane with toluidine blue is due to its HA content. This staining pattern should be differentiated from the well-defined red color of HA that normally borders BCC nests. Restylane may persist in the dermis as long as 23 months after implantation.

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Injection necrosis of the glabella: protocol for prevention and treatment after use of dermal fillers

Glaich SA¹, Cohen JL², Goldberg LH³
Dermatol Surg 2006; 32(2):285-290

Background

Injection of filler materials into the dermis is well tolerated, with few mild and transient side effects. Injection necrosis is a rare but clinically important potential complication caused by interruption of the vascular supply to the area by compression, injury, and/or obstruction of the vessel(s). The glabella is a particular danger zone for injection necrosis regardless of the type of filler used.

Objective

We recommend a protocol that may be used to help prevent and treat injection necrosis of the glabella after injection with dermal fillers.

Conclusion

Injection necrosis in the glabellar region may be prevented by knowledge of the local anatomy and an understanding of its pathophysiology and treated by a suggested protocol.

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Facial Sculpting and Tissue Augmentation

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Dermatol Surg 2005; 31(11 Part 2)1604-1612

Background

Until recently, deep facial sculpting was exclusively the domain of surgical interventions. Recent advances in the available array of dermal and subdermal fillers combined with an esthetic appreciation by both surgeons and nonsurgeons alike of the positive effect of filling the volume-depleted face have led to an expansion in the indications for the use of soft tissue augmenting agents.

Method

Subdermal support of the lateral two-thirds of the brow, the nasojugal fold, the malar and buccal fat pads, the lateral lip commissures, and the perioral region, including the prejowl sulcus, all restore youthful facial contour and harmony. An important advance in technique is the subdermal rather than the intradermal injection plane.

Results

“Instant” facial sculpting giving a brow-lift, cheek-lift, lip expansion, and perioral augmentation is possible using modern soft tissue augmenting agents. The softer, more relaxed appearance contrasts to the somewhat “pulled” appearance of subjects who have had surgical overcorrections. Treatments can be combined with botulinum toxin and other procedures if required.

Conclusion

Newer advances in the use of fillers include the use of fillers injected in the subdermal plane for “lunchtime” facial sculpting. Using the modern esthetic filler compounds, which are biodegradable but longer lasting, subjects can have a “rehearsal” treatment or make it ongoing. Some individuals, such as those with human immunodeficiency virus (HIV)-related lipoatrophy or those who desire to obtain a longer-lasting effect, may elect to use a nonbiodegradable filling agent.

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Biocompatibility of two novel dermal fillers: histological evaluation of implants of a hyaluronic acid filler and a polyacrylamide filler

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Plast Reconstr Surg 2006; 117(6):1789-96

Background

Several biomaterials are currently available for soft-tissue augmentation. Biocompatibility is an indispensable condition for any such product. Appropriate histologic evaluation is a prerequisite for understanding the responses of tissues to implant materials. Recently, hyaluronic acid and polyacrylamide gel products have been introduced as dermal fillers. Both types of product are widely considered to be biocompatible.

Methods

The present study compared tissue responses in a rat in vivo model (n = 80) to a hyaluronic acid filler (Restylane Perlane; Q-Med AB, Uppsala, Sweden) and a polyacrylamide gel filler (Aquamid; Contura SA, Montreux, Switzerland). Four groups were evaluated: group 1 (n = 20) received the Restylane Perlane implant, group 2 received the Aquamid implant (n = 20), group 3 comprised a placebo group (n = 20), group 4 was the control group (n = 20). Responses and biocompatibility were assessed by histopathologic and histomorphometric evaluations between 1 week and 8 months after implantation.

Results

The two products induced very different tissue responses. The polyacrylamide gel filler was highly bioactive, undergoing cell infiltration and integration into tissues. The hyaluronic acid filler underwent minimal cell infiltration, and the product remained surrounded by a uniformly thin capsule.

Conclusions

This study reveals that two soft-tissue fillers considered to be biocompatible induce very different tissue reactions. This indicates that their behavior in clinical practice is likely to be different.

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