Original Contribution

Journal of Cosmetic Dermatology, **0**, 1–6

A randomized, prospective, blinded, split-face, single-center study comparing polycaprolactone to hyaluronic acid for treatment of nasolabial folds

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Summary

Background Dermal fillers have continuingly been under development to increase safety, efficacy, and longevity. Biostimulatory dermal fillers, such as calcium hydroxylapatite fillers, have already been shown to be superior in efficacy compared to nonanimal stabilized hyaluronic acid (NASHA)-based fillers.
Aims In this randomized split-face study, we compared a novel biostimulatory polycaprolactone (PCL)-based dermal filler with a NASHA-based dermal filler, for safety, efficacy, and duration of cosmetic correction for the treatment of nasolabial folds (NLFs).
Patients/Methods Forty subjects received a PCL-based dermal filler in one of their NLFs, and a NASHA-based dermal filler on the contralateral side. Efficacy was evaluated based on the Wrinkle Severity Rating Scale and Global Aesthetic Improvement Scale.
Results After 6, 9, and 12 months post-treatment, NLFs treated with the PCL-based dermal filler showed statistically significant improvements on the Wrinkle Severity Rating Scale and greater improvements on the GAIS compared to NLFs treated with the NASHA-based dermal filler. Both products were found to be equally safe and well tolerated.
Conclusion Our results suggest that PCL-based dermal fillers offer longer-lasting performance over NASHA-based dermal fillers in NLFs treatment.

Keywords: facial filler, hyaluronic acid, nasolabial folds, polycaprolactone

Introduction

Tissue augmentation by dermal filler injection has been used for over 20 years and still continues to grow in popularity. There are several types of dermal fillers available such as fillers based on nonanimal stabilized hyaluronic acid (NASHA), calcium hydroxylapatite (CaHA), and poly-L-lactic acid (PLLA), all with their own efficacy and longevity profile.[1] Currently, the demands in the noninvasive esthetic treatments are shifting to more safer and long-lasting results with nonpermanent devices.[2]

A polycaprolactone (PCL)-based dermal filler has been introduced to the esthetic market in 2009, representing a new class of biostimulatory dermal fillers. Biostimulatory fillers such as the CaHa fillers have already been shown to be superior to NASHA-based fillers in the treatment of nasolabial folds (NLFs).[3] PCL is a bioresorbable, nontoxic medical polymer that is attractive for the

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Accepted for publication November 1, 2014

use in medical devices because of its controlled and safe bioresorption profile.[4,5] The PCL microspheres (25–50 μm) are suspended in an aqueous carboxymethylcellulose (CMC) gel carrier. Both PCL and CMC individually have an excellent and proven biocompatibility profile and have been used successfully in numerous CE-marked and FDA-approved medical devices such as oral and maxillofacial surgery, wound dressing, and controlled drug delivery systems.[6–12] In a recent study, the excellent biocompatibility profile of PCL has been extended by showing its use as a bioresorbable tracheal splint for the treatment of tracheobronchomalacia, an airway disease.[13] Furthermore, PCL microspheres are totally smooth and spherical-shaped, which has been shown to be optimal for dermal fillers.[14,15]

The PCL microspheres bioresorb into nontoxic bioresorption products and are excreted through normal metabolic pathways into CO_2 and H_2O.[4,5,16–18] With ^{3}H-labeled PCL and C^{14}-labeled PCL implantation studies, it has been shown that PCL is completely excreted from the body.[4,5]

The CMC gel carrier is gradually resorbed by macrophages over a period of several weeks. In contrast, PCL microspheres are not phagocytosed because of their size and surface characteristics. Instead, the totally smooth and spherical-shaped PCL microspheres use the body's natural response to stimulate neocollagenesis and replace the volume of the resorbed CMC carrier by deposition of newly formed collagen around the microspheres.[19] Recently, in a clinical trial for the correction of NLFs, it was found that a PCL-based dermal filler is safe and well tolerated for facial treatment.[20] Furthermore, in a pilot study, it was shown that a PCL-based dermal filler is safe, well tolerated, and effective for hand rejuvenation.[21]

This study was designed to compare the efficacy and safety of a biostimulatory PCL-based dermal filler (Ellansé-S™; AQTIS Medical, Utrecht, the Netherlands) to a NASHA-based dermal filler Perlane (Q-Med; a Galderma division, Lausanne, Switzerland) for the correction of NLFs. Perlane is a large-gel particle hyaluronic acid which has a median gel particle size of between 750 and 1000 μm and has been shown to be safe and effective in the correction of moderate to severe facial wrinkles.[1]

Materials and methods

Patient population

The study enrolled 40 patients between the ages of 31 and 60 years (mean age 46 years). All patients had moderate to severe NLFs as determined by a Wrinkle Severity Rating Scale (WSRS) score of 3 or 4 in both folds.

Study design

The study was a single-center, prospective, randomized, split-face, controlled trial. The study protocol conformed to the guidelines of the 1975 Declaration of Helsinki. The protocol and study design were approved by the College of Medicine and Health Sciences' and Tawam Hospital's institutional review board (IRB) prior to commencement.

The study inclusion criteria were as follows: Subjects were 18 years of age or older with moderate to severe NLFs as determined by the WSRS score at the pretreatment evaluation; subjects were willing to abstain from other facial cosmetic procedures through the 12-month follow-up visit which could interfere with treatment outcomes and able to comply with study follow-up procedures; and all subjects provided written informed consent for their participation in the study.

Subjects who received previous permanent implants in the nasolabial area at any time or who had any esthetic facial procedure performed in the nasolabial area within 6 months prior to enrollment that could interfere with the treatment outcome were excluded from the study. Also, patients with a history of autoimmune disorder or taking systemic corticosteroids were also excluded.

Pretreatment

Prior to treatment, all patients had a general examination including medical history and survey of current medications. Pretreatment photographs of the NLFs were taken for each patient to determine their WSRS ratings. Prior to participation in the study, all subjects received patient information and signed and dated the study consent form, which was approved for this study by the hospitals ethics committee. The original signed documents were kept with the subject's file, and copies were provided to the subjects.

Treatment

At the initial visit, each subject was randomly treated with PCL to correct one NLF and NASHA to correct the contralateral fold. In addition to the choice of filler, the facial side treated was also randomly chosen. Injections were administered into the mid-deep dermis using a 27-G needle inserted at an approximate angle of 30°

parallel to the length of fold. The initial injections were administered to obtain suboptimal augmentation of the folds. Folds were never overcorrected. None of the patients received topical or local anesthetics.

After injection, the treated areas were gently massaged, so they conform to the contour of the surrounding tissue if necessary. If the treated area was swollen directly after the injection, an ice pack was applied on the site for a short period. Subjects were instructed to minimize exposure of the treated areas to excessive sun, UV lamp, and extreme cold weather until initial redness and swelling had resolved.

Evaluation

The subjects returned at 1, 3, 6, 9, and 12 months after initial treatment. At the 1-month follow-up visit, photographs of the nasolabial area were taken and were assessed by the physician to determine whether a touch-up treatment in one or both folds was necessary. This is the only time during the duration of the study that touch-up was allowed and a maximum of one touch-up per site was permitted. If a touch-up application was administered, the photograph and Global Aesthetic Improvement Scale (GAIS) assessment were completed prior to the touch-up injection. At 3, 6, 9, and 12 months visits, the subjects returned for physician evaluation. For the assessment of safety and efficacy, photographs of the nasolabial area were taken. The evaluation was carried out using the GAIS and WSRS for efficacy. Safety was assessed by recording any medication changes or adverse events (AEs) during the 12-month follow-up.

Statistics

For statistical analysis of WSRS scores, the Mann–Whitney *U*-test was performed. Data presented are mean ± standard deviation. *P*-values < 0.05 were considered statistically significant.

Results

Efficacy

Global Aesthetic Improvement Scale assessments (GAIS; 3 = very much approved, 2 = much improved, 1 = improved, 0 = no change, and −1 = worse)[22] were performed by the evaluating investigator. GAIS ratings are expressed as percentages of the total amount of patient's, where total much improvement (TMI) is the total GAIS rating of "very much improved" (VMI) + "much improved" (MI, Table 1) together. In summary, GAIS ratings show 85% (6 months post-treatment), 41% (9 months post-treatment), and 20% (12 months post-treatment) PCL-treated NLFs as TMI, compared to 64% (6 months post-treatment) and 0% (9 and 12 months post-treatment) TMI of NASHA-treated folds, respectively (Table 1).

Furthermore, assessment of the severity of the NLFs was performed according to the WSRS scoring system (1 = absent, 2 = mild, 3 = moderate, 4 = severe, and 5 = extreme).[23] Before treatment (baseline), the mean WSRS score of NLFs rated by the evaluating investigator was 3.55 ± 0.5 for the patients treated with the PCL-based filler and 3.53 ± 0.5 NASHA-based dermal filler. All post-treatment time points show improvements in mean WSRS scores (Fig. 1). Interestingly, significantly higher improvements in mean WSRS scores were found for the NLFs treated with the PCL-based filler compared to the NLFs treated with the NASHA-based filler at 6 (2.00 ± 0.55 *vs.* 2.29 ± 0.76, $P = 0.0472$), 9 (2.16 ± 0.64 *vs.* 2.87 ± 0.67, $P = 0.002$), and 12 (2.57 ± 0.43 *vs.* 3.05 ± 0.46, $P = 0.002$) months

Table 1 Global Aesthetic Improvement Scale distribution: PCL *vs.* NASHA at 6, 9, and 12 months

	6 months (n = 34)		9 months (n = 32)		12 months (n = 30)	
	PCL	NASHA	PCL	NASHA	PCL	NASHA
VMI (%)	53	29	16	0	0	0
Much improved (MI, %)	32	35	25	0	20	0
Improved (%)	9	29	56	56	33	10
No change (%)	6	6	3	41	47	90
Worse (%)	0	0	0	3	0	0
TMI (%)	85	64	41	0	20	0

NASHA, nonanimal stabilized hyaluronic acid; PCL, polycaprolactone; TMI, total much improvement; VMI, very much improved.

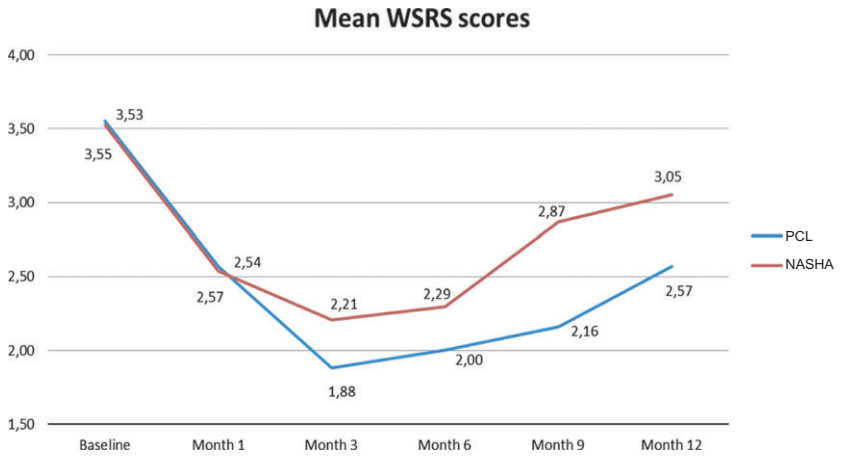

Figure 1 Mean WSRS scores over a 12-month period. At 1 month post-treatment, a touch-up was performed when needed to give an optimal cosmetic correction. WSRS, Wrinkle Severity Rating Scale.

post-treatment (Table 2). Figure 2 shows a representative serial photographic image of NLFs treated with a PCL-based filler compared to the a NASHA-based filler taken at baseline, 6, and 12 months post-treatment (Fig. 2).

Injected volumes

At initial treatment, the mean volume of the PCL-based dermal filler that was injected into the NLFs was 17.4% less than the mean volume of the NASHA-based dermal filler. Furthermore, for both groups, 59.5% of the patients received a touch-up to full correction. For these patients, the mean volume of the PCL-based dermal filler that was injected into the NLFs for touch-up was 13% less than the mean volume of the NASHA-based dermal filler.

Table 2 Mean ± standard deviation scores according to the WSRS. WSRS scores were obtained by the evaluating investigator at baseline, 1, 6, 9, and 12 months post-treatment

	PCL based	NASHA based	*P*-value†
Baseline	3.55 ± 0.50	3.53 ± 0.50	0.999
1 months	2.54 ± 0.69	2.57 ± 0.60	0.752
3 months	1.88 ± 0.64	2.21 ± 0.59	0.052
6 months	2.00 ± 0.55	2.29 ± 0.76	0.047*
9 months	2.16 ± 0.64	2.87 ± 0.67	0.002*
12 months	2.57 ± 0.43	3.05 ± 0.46	0.002*

NASHA, nonanimal stabilized hyaluronic acid; PCL, polycaprolactone; WSRS, Wrinkle Severity Rating Scale.
*$P < 0.05$.
†Mann–Whitney *U*-test.

Safety

Following initial treatment, 48% of the patients reported mild treatment related AE's which all resolved without intervention. No AE's were reported at touch-up, or at 3, 6, 9, or 12 months post-treatment.

Discussion

To our knowledge, it is for the first time that a PCL-based dermal filler has been compared with a NASHA-based filler for efficacy and safety in the treatment of NLFs. Efficacy of the fillers was determined using the WSRS and GAIS rating system.

Results from our GAIS ratings show that the PCL-based dermal filler has greater esthetic improvements in the treatment of NLFs over the NASHA-based filler at 6, 9, and 12 months after initial treatment. The largest improvements of the PCL-treated NLFs over the NASHA-treated NLFs were seen at month 9 and 12. At these time points, results showed 41% (9 months post-treatment) and 20% (12 months post-treatment) TMI for the NLFs treated with the PCL-based dermal filler while at the same time points, 0% TMI in GAIS scores were found for the NASHA-treated NLFs. These results indicate that the PCL-based dermal filler has prolonged esthetic improvement over this commonly used NASHA-based dermal fillers.

In addition, similar results were found with our obtained mean WSRS scores showing significantly higher esthetic improvement for PCL-treated NLFs compared with NASHA-treated NLFs at 6, 9, and 12 months after initial treatment.

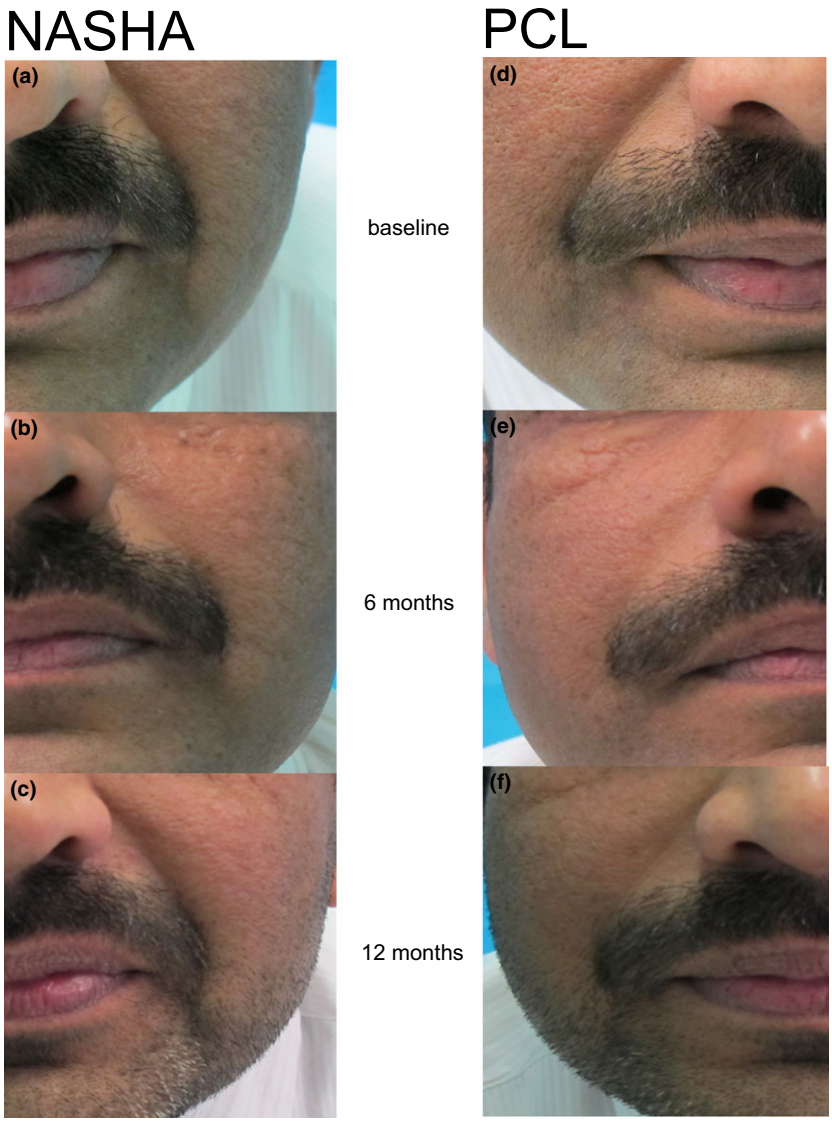

Figure 2 Photograph of nasolabial folds (NLFs) of a male representative patient at baseline (a, d), 6 months (b, e), and 12 months (c, f) post-treatment. NLFs were treated on contralateral sides of the face, with a PCL-based filler on the patients right side (d–f) and a NASHA-based filler on the patients left side (a–c). NASHA, nonanimal stabilized hyaluronic acid; PCL, polycaprolactone.

Treatment was well tolerated for all patients for both PCL- and NASHA-treated NLFs. Reported AE disappeared approximately 2 weeks after initial treatment and resolved without intervention.

Another interesting point to address is the amount of injection volume needed for initial treatment, and when needed, for touch-up. These results show that less injection volume was required with the PCL-based filler compared to the NASHA-based filler to reach optimal cosmetic effect.

Together, based on these results, we conclude that the PCL-based dermal filler offers advantages over the NASHA-based dermal filler, in terms of both cosmetic longevity and efficiency.

In conclusion, patient willing to undertake a nonpermanent dermal filler treatment for NLFs correction, with a long-lasting cosmetic effect, may consider choosing a PCL-based dermal filler over a NASHA-based dermal filler.

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