Case Report: Lip Augmentation with Injection of a Novel PEG-crosslinked Hyaluronic Acid Hydrogel

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Abstract

BACKGROUND: Lip augmentation with hyaluronic acid (HA) hydrogels is one of the most common esthetic procedures worldwide, but requires products with an optimal balance of elasticity and cohesivity to volumize while integrating with the surrounding tissue. This case report describes the results of lip augmentation with a novel, 24 mg/mL HA hydrogel cross-linked with poly (ethylene glycol) diglycidyl ether (PEGDE-HA 24), and supplemented with l-proline and glycine to limit post-injection swelling.

METHODS: In three separate treatment sessions (Weeks 0, 2, and 10), a 29-year-old woman requesting lip augmentation was injected with PEGDE-HA 24 as multiple superficial injections using a tenting technique. Photographs were taken before treatment and at 2-weeks, 1-month, and 5-months after the initial injection. The subject provided post-treatment updates on her experience with the hydrogel in terms of the results achieved and any adverse events experienced.

RESULTS: A total of 1.0 mL PEGDE-HA 24 was injected: treatment session 1 (0.3 mL); session 2 (0.4 mL); and session 3 (0.3 mL). The day after each injection the subject reported that her lips were sensitive, but not painful. The level of post-injection bruising and swelling diminished with each subsequent injection and healed rapidly. No other adverse events were reported. The subject was very satisfied with the results describing them as attractive and natural looking for up to 5 months.

CONCLUSIONS: This case report demonstrated that 1 mL of PEGDE-HA 24 was effective and well tolerated for volume augmentation of the lip. The subject was very satisfied with her experience of the hydrogel and natural-looking results were achieved.

Introduction

Lip enhancement with injections of hyaluronic acid (HA) hydrogel is one of the most frequently requested esthetic procedures worldwide [1], [2], [3]. This popularity stems from the immediate volumizing and shaping effects the treatment provides, the ability to remove the HA with hyaluronidase in the event of an unwanted result, as well as the requirement for minimal or no downtime [4]. The procedure is popular in all age groups to enhance natural lip volume, correct asymmetries, or to replace lip volume lost with age [5].

HA hydrogels are manufactured with varying rheological properties using proprietary techniques [6]. This is achieved with specific cross-linking technologies and modifications to the amount of cross-linked to non-cross-linked HA, HA concentration, and the size and uniformity of the HA particles [7]. These factors influence product clinical performance and are used to tailor HA hydrogels to specific indications [6]. In particular, the chemical modifications of HA afforded by the chosen cross-linking technology determine the biodegradation rate and modulate the viscoelastic properties of the final product and its compatibility with different tissues [8].

The lips form part of a very dynamic facial area and careful selection of product is required to ensure that treatment provides a natural result both at rest and during animation. To enhance the lips, hydrogels are usually selected that provide low to medium G prime (sufficient elasticity for smoothness and moldability), low water uptake to reduce risk of swelling, and medium-to-high cohesivity for volumization and projection [7]. Several HA fillers have been specifically developed for lip enhancement including those from the Restylane, Juvederm, Belotero, and Teosyal ranges [9]. For these products, the chemical cross-linking agent used is 1,4-butanediol diglycidyl ether (BDDE). While BDDE has been considered the standard cross-linker for the past 20 years, new cross-linking technologies have emerged, potentially bringing novel features to HA fillers. One such strategy utilises poly(ethylene glycol) diglycidyl ether (PEGDE), a water-soluble chemical, widely used in the pharmaceutical and biomaterial sectors to cross-link polymers containing hydroxyl, amine, and carboxyl groups, and now used to crosslink HA in the Neauvia hydrogel product range (PEGDE-HA) [10]. PEGDE is
the longest cross-linker employed and it introduces unequal spacers among the HA chains as opposed to simpler molecules such as BDDE. This renders the three-dimensional molecular HA scaffold less rigidly cross-linked, which enhances tissue integration and provides a long-lasting filler effect [11]. The addition of l-proline and glycine to the hydrogel improves elasticity and controls osmotic balance, preventing excessive swelling during the post-implant phase [12].

In this case report, a physician experienced with the use of PEGDE-HA for lip augmentation, describes her technique for safe and effective injection, and the treatment results that can be achieved.

Methods

A healthy 29-year-old Caucasian female attended the private practice of the author requesting lip augmentation. She reported that she had received two previous lip treatments with a BDDE-based HA filler, the past 5 years previously, but had been disappointed by the duration of the results, stating that the effects had disappeared after only 1 month. The author proposed lip augmentation with PEGDE-HA 24 mg/mL (Neauvia Intense Lips, Matex Lab SA, Switzerland), HA hydrogel specifically developed for lip augmentation.

The subject had received no temporary soft-tissue filler treatment or botulinum toxin injections below the inferior orbital rim in the past 5 years. PEGDE-HA 24 was injected in three separate treatment sessions over a 10-week period. Before injection, topical anesthesia was applied to reduce injection discomfort. PEGDE-HA 24 was injected with a 27G needle as multiple superficial injections using a tenting technique (Figure 1). Photographs were taken before treatment and at 2-weeks and 1 month after the initial injection. Following treatment, the subject was advised to avoid make-up, exercise and saunas for 48 h. The subject used ice to reduce post-treatment swelling and moisturized with the manufacturer’s lip balm.

Written informed consent was obtained from the subject for publication of the case report and any accompanying images.

Results

Injection volume was determined by the physician, but volumes did not exceed 1.0 mL for initial and touch-up treatments combined: treatment session 1 (0.3 mL); treatment session 2 (2 weeks after first visit, 0.4 mL); and treatment session 3 (10 weeks after first visit, 0.3 mL).

The physician solicited regular subject feedback to follow the progress of treatment. 1 day after the first injection the subject reported that no lumps or bumps were palpable and that her lips were sensitive, but not painful. She noted that the level of swelling and bruising was equivalent to that previously experienced with injections of a BDDE-HA filler, but believed the shape of her lips was rounder. One day before the second injection, and 2 weeks after the first, the subject reported that her lips had healed very quickly, but she believed that more shape was required. Images of the subject, before, and at 2 and 4 weeks after initial treatment are shown in Figure 2.

The subject reported no bruising after the second injection and less swelling, which had dissipated within 24 h. Five weeks after the second injection, the subject was still very satisfied with the results. A third injection was performed at 10 weeks. The subject again reported less swelling and bruising and natural-looking results. Injection site bruising and swelling resolved within 24 h. No other adverse events were observed.

Five months after the initial visit, an esthetic difference could still be observed (Figure 3).

Discussion

PEGDE-HA 24 was effective at augmenting lip volume and improving lip shape and profile in this case report. The author’s approach when performing aesthetic treatments is to create a treatment plan that involves two or three visits spaced 1-month apart to allow the products time to achieve their effects and the body time to react to them. In this manner, she is able to create more natural-looking results using less product. This is particularly relevant for the lips, where initial swelling can mask the true treatment result, and where it is important to avoid over filling. In this case study, the
time between injections also allowed the investigator to evaluate the level of product degradation between visits. The subject was satisfied with the shape and volume of her lips at each follow-up visit. The final follow-up photographs show that a difference could still be observed 5 months after the initial treatment. The treatment protocol therefore allows satisfactory results to be achieved with low amounts of filler.

The lips are a highly mobile area and require treatment with HA hydrogels specifically formulated to withstand dynamic movement at the same time as integrating seamlessly with the lip tissue. Following injection with PEGDE-HA 24, the subject was very satisfied with the treatment results, describing them as attractive and natural looking. The author injected superficially in the submucosa of both the upper and lower lip, as anatomical studies have shown that the labial artery is located in this position in <2% of individuals if the midline is avoided [13], and it is therefore the safest zone for application of volumizing material. No adverse events were observed apart from minimal bruising and swelling, which were mostly resolved within 24h of injection.

PEGDE-HAs are a relatively recent introduction to the esthetic field and published clinical data are only just starting to appear [14]. A 3-year retrospective study of clinical experience with PEGDE-HAs for a range of treatment indications reported long-term results with no safety concerns, including no nodules, granulomas, or foreign body reactions [14].

Although the published clinical data are currently limited, the PEGDE-HA range has been subject to extensive molecular, chemical, mechanical, and histological characterization [8], [11], [12], [15], [16]. Two key features distinguish the PEGDE-HA range from other HA hydrogels on the market: PEGDE cross-linking and enrichment with l-proline and glycine. PEGDE consists of a mixture of oligomers of different lengths and consequently introduces unequal spacers between the HA chains, as opposed to more uniform spacing with BDDE. As a result, the fraction of PEGDE molecules that cross-link between two HA chains (effective cross-linker ratio) is lower [8], [16], [17]. This allows the formation of a compact and elastic hydrogel network, which has been suggested to explain the enhanced resistance to degradation by hyaluronidase, and lower swelling rates for PEGDE cross-linked HA as compared to BDDE-cross-linked products [8], [17]. The less rigid cross-linking combined with the relatively high HA concentration (24 mg/mL) also provides the gel with viscoelastic properties that are compatible with lip tissue [16].

Unreacted cross-linkers in HA hydrogels, as well as any by-products released during resorption of the gel, must be degraded into safe and inert products to avoid any potential toxicity at high concentrations [18].

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**Figure 2:** Subject before treatment, immediately before the second injection at 2-weeks, and 4-weeks after the initial injections of PEGDE-HA 24 for lip augmentation

**Figure 3:** Subject before and exactly 5 months after the initial treatment
PEGDE and BDDE have extensive biocompatibility data and a favorable clinical safety profile. Data from in vitro and in vivo studies indicate that PEGDE induces lower levels of dermal toxicity than BDDE [10], [19], and the concentration of residual unreacted PEGDE is estimated at <10 ng/mL; for Food and Drug Administration-approved HA fillers using BDDE as a cross-linker the residual BDDE content must be inferior to 2 ppm [18].

Histological analysis of skin biopsies obtained 8 months after injection of PEGDE-HA into the hypodermis has revealed no inflammatory cells surrounding the implant or closely associated with it [11], [20]. A further distinguishing feature of PEGDE-HA hydrogels is that they are enriched with l-proline and glycine. These comprise a major portion of the primary amino acid sequence of collagen and had the greatest effect on collagen production in a comparison of 20 amino acids added to human dermal fibroblasts [21]. The addition of l-proline and glycine to PEGDE-HA has been shown to improve hydrogel elasticity and osmoregulation in a series of in vitro viscoelastic studies [12].

PEGDE-HA24 has been manufactured with the rheological properties appropriate for safe and effective lip augmentation. This case report demonstrated that natural-looking results can be achieved with 1 mL of product. Further studies are now warranted to investigate efficacy, safety, and longevity in a range of subjects of varying ages. Additional research should focus on potential mechanisms of PEGDE-HA longevity including levels of resistance to hyaluronidase, thermo-degradation, free radical/oxidative metabolism, mechanical stresses, and inflammation.

Conclusion

PEGDE-HA24 was effective and well tolerated for volume augmentation of the lip. Natural results were achieved and subject satisfaction was high.

Declarations

Ethics approval and consent to participate
NA.
The case report was conducted in accordance with the Declaration of Helsinki.

Consent for publication
Informed consent was obtained from the subject involved in the case report. Written informed consent has been obtained from the patient to publish this paper.

Availability of data and materials
The data presented in this case report are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

Authors’ contributions
C Edwards developed, wrote, and approved this case report.

Acknowledgments

The author thanks the patient for agreeing to publication of these data.

Disclosure statement

Dr Cleo Edwards is self-employed in her clinic “Edwards Aesthetics” in the Netherlands. She is a consultant and KOL for Merz Pharma and Matex Lab S.A., and a trainer at UMA Academy Amsterdam. No logistical and financial support for the execution of this study was given.

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