Hyaluronic Acid Dermal Fillers for Treatment of Congenital and Acquired Lip Asymmetries and Deformities

Rellenos Dérmicos de Ácido Hialurónico para el Tratamiento de Asimetrías y Deformidades Labiales Congénitas y Adquiridas

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ABSTRACT: Hyaluronic acid (HA) dermal fillers are widely used in aesthetic treatments for facial and lip modeling. Despite HA fillers has largely known to be use in procedures for augmentation the lip volume, their application to management lip abnormalities is not widespread. This study reviewed the use of HA fillers for reconstruction of congenital and acquired lip asymmetries and deformities, searching to expand knowledge about this treatment modality. To undertake this narrative review, the Medline-Pubmed, Web of Science, Scopus, Embase, Google Scholar e Lilacs databases were searched. Several studies have reported positive results in the use of HA fillers for the treatment of lip deformities caused by different factors such as: Insatisfactory dermal fillers, permanent lip implants, excision of lip carcinoma, post-operative scars and electrical burns. HA fillers are also an alternative for the management of lip asymmetries and residual surgical scars in patients with cleft lip. Moreover, injection of HA fillers in individuals with facial paralysis and facioscapulohumeral muscular dystrophy can also improve lip incompetence. Additionally, HA fillers can be used as a complementary treatment in cases of severe malocclusion associated with skeletal changes, helping to maintain the seal and refine the lip appearance. Therefore, HA fillers can be used as alternative treatment for several types of congenital and acquired lip deformities and asymmetries. However, it is necessary to carry out randomized clinical trials with a greater number of patients and follow-up time, in order to investigate the benefits of the HA fillers for carriers patients of lip abnormalities.

KEY WORDS: hyaluronic acid, dermal filler, lip deformity, lip asymmetry, lip abnormalities.

INTRODUCTION

The overall number of cosmetic minimally invasive procedures has increased by 144% since 2000, according to statistics released by the American Society of Cosmetic Plastic Surgeons. Next to botulinum toxin injection, injection of soft-tissue fillers is the second most frequent minimally invasive procedure performed in the USA (Ballin et al., 2015).

Facial filler is an important nonsurgical modality to management of lip defects. They can be performed in an outpatient setting, with minimal time and low risk of complications (Ballin et al., 2013). In fact, they make it possible to augmentation the volume lips, treat rhytids, scars, lip deformities and asymmetries (Ballin et al., 2013; Stolic et al., 2015; Grablowitz et al., 2020).

The dermal fillers can serve as a stand-alone or adjunctive treatment for lip reconstruction. They can improve oral competence, facial expression, and aesthetics through augmentation of subdermal volume in areas of volume loss (Yamasaki & Lee, 2020).

On the other hand, hyaluronic acid (HA) dermal fillers can help in the treatment of post-operative scars,

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exerting positive effects on the repair of lip scars (Stolic et al., 2015; Franchi et al., 2018) as besides to augmentation the volume, they also provide increased tissue elasticity and flexibility (Franchi et al., 2018). Furthermore, there are case reports showing that HA fillers can be used to treat congenital (Kandhari et al., 2017; Serdar & Karabay, 2018) and acquired lip asymmetries (Kandhari et al., 2017; Rauso et al., 2020).

Despite the HA fillers being widely used in aesthetic procedures, their application to management lip abnormalities is not widespread. In this scenario, our study reviewed the use of HA fillers for repair of lip deformities present in congenital and acquired asymmetries, searching to expanding knowledge about this treatment modality.

MATERIAL AND METHOD

To undertake this narrative review, the Medline-Pubmed, Web of Science, Scopus, Embase, Google Schoolar e Lillacs databases were searched. The search strategy used following keywords: “[hyaluronic acid OR hyalurunan OR dermal filler] AND [lip defect OR lip asymmetry OR cleft lip OR congenital abnormalities OR acquired abnormalities OR birth defects OR congenital defects OR facial asymmetry OR cancer surgery OR facial paralysis]”. Inclusion criteria were full-text articles available and published until February 2022. There was no language restriction. Publications which did not address the topic of this study were excluded. Additionally, a search for articles about the properties of hyaluronic acid dermal fillers was carried out.

RESULTS AND DISCUSSION

Hyaluronic Acid Fillers. HA is a high viscosity glycosaminoglycan which acts as a structural component of the extracellular matrix (Wollina & Goldman, 2011; Brandt et al., 2012). In the human body it is found in almost all biological fluids and tissues, although it is present in higher concentration in the extracellular matrix of soft connective tissues, such as the skin (Wollina & Goldman, 2011). HA is involved in several biological processes such as cell proliferation, signaling and migration; besides to acting in wound repair and regeneration (Volpi et al., 2009). Moreover, as it is a hygroscopic molecule, it also contributes to the maintenance of tissue volume, hydration and structural support (Ballin et al., 2015).

Due to these properties, HA dermal fillers were developed for anti-aging treatments that restore volume, hydration and facial contour (Ballin et al., 2015; Wollina & Goldman, 2020). These fillers cause volume augmentation due to their hydrophilic properties, retaining about 1,000 times of their mass in water, which maintains tissue hydration. They are biodegradable, biocompatible and non-immunogenic (Yamasaki & Lee, 2020). According brand chosen, HA fillers can be available in pre-filled syringes of various sizes and concentrations (Pontes-Quero et al., 2019; Han et al., 2019; Arima et al., 2019) and, in various types of preparations, with differences in molecular weight, origin, viscosity, presence or absence of cross-linking (Walker et al., 2022).

The first HA fillers were derived from avian proteins, and caused allergic reactions in some patients. In 2003, the Food and Drug Administration (FDA) approved the first HA filler of non-animal origin (Restylane, Galderma, Zug, Switzerland) for injection to mid to deep dermis for correction of moderate to severe facial wrinkles and folds. Since October 2011, Restylane has been FDA approved to submucosal implantation in lip augmentations. Only in October of 2013, was the HA filler approved for deep subcutaneous/supraperiosteal injection for cheek augmentation (Juve’derm Voluma, Allergan, São Paulo, Brazil) and, in June 2014 for perioral rhytides (Restylane Silk, Galderma, Zug, Switzerland) (Ballin et al., 2015). The HA dermal fillers available on the market are produced by cultures of Streptococcus species (eg, S. pyogenes and S. zooepidemicus), and are considered gels because they are particles (a solid phase) suspended in the fluid phase (Sundaram et al., 2010; Ballin et al., 2015). In fact, bacterial technology makes it possible to obtain high purity hyaluronic acid with low levels of proteins and endotoxins (Xu et al., 2012; Snetkov et al., 2020).

Naturally occurring HA is non-cross-linked. It is a viscous liquid that can be completely metabolized (few days after injection into the skin) by free radicals and the endogenous enzyme hyaluronidase, naturally present in the skin (Kablik et al., 2009; Ballin et al., 2015). The cross-linking process of the HA filler consists of the formation of a three-dimensional network of AH chains by binding of molecules and by formation of hydrogen bonds between AH chains. This process increases the duration of the gel’s effect, giving
resistance to it degradation by hyaluronidase and also by influencing the consistency and immunological acceptance of the filler (Brandt et al., 2012; Micheels et al., 2016; Salti & Fundarò, 2020). The BDDE (1,4-butanediol diglycidyl ether) is the most widely used cross-linking agent, as it is the safest. The cross-linking of the particles allows the production of more concentrated HA fillers (Walker et al., 2022). Nevertheless, the optimal level of cross-linking should be determined because they decrease the hygroscopicity and therefore the effectiveness of the HA fillers (da Costa et al., 2017).

The HA fillers can be classified as non-crosslinked or cross-linked (Ballin et al., 2015). Monophasic fillers consist of a homogeneous mixture of high- and low-molecular-weight HA. Biphasic fillers have cross-linked particles of HA dispersed in a non-cross-linked HA vehicle; resulting in a heterogeneous mix of HA. Monophasic fillers can also classified as monodensified (cross-linking occurs after molecule mixing) or polydensified (cross-linking occurs separately, before the mixture is produced) (Falcone & Berg, 2008; da Costa et al., 2017).

Several studies have demonstrated safety and efficacy of monophasic monodensified HA fillers (Juvéderm Ultra) for lip filling. This filler has been regarded as the preferred for injection in the lips (Brandt & Cazzaniga, 2008; Ballin et al., 2013; Fagien et al., 2013). They were approved by the FDA in 2006 and they are available as a smooth, soft, viscous and malleable gel, with a homogeneous consistency and easy to apply. It is cross-linked by BDDE in one step and has great longevity due to high concentration of particle cross-link (Brandt & Cazzaniga, 2008; Ballin et al., 2013). On the other hand, Polydensified monophasic HA fillers with variable density (Belotero Balance Lidocaine and Belotero Intense Lidocaine) can also show satisfactory results and long-term durability in lip augmentation (Fischer et al., 2016). They are based on double cross-link technology (known as polydensified cohesive matrix) in two steps and it were approved by the FDA in 2012 (Brandt & Cazzaniga, 2008; Ballin et al., 2013).

Adequate longevity of soft tissue filling is an important requirement for volume correction (Cavallini et al., 2020). Lip filling with HA dermal fillers remain around 3 to 4 months, depending on the patient's metabolism, application volume and depth, adverse effects, and filler properties (Chang et al., 2018; Schweiger et al., 2008). The shelf life of HA depends on the particle size, concentration, viscosity and degree of cross-linking of the product (Born, 2006; Franchi et al., 2018). Patients who have very thin lips, a wide smile or very dynamic and mobile lips may have shorter filling longevity. On the other hand, patients with a more harmonious lip shape and less mobile lips may have greater longevity (Pavicic, 2009).

Fillers containing great particles are effective for increasing volume in large defects or deep lines, such as the mouth commissures, while fillers containing smaller particles are more suitable for thin perioral rhytids and the lip line (Chang et al., 2018). Fillers containing smaller HA particles are considered safe and highly effective for lip augmentation (Solish & Swift, 2011; Glogau et al., 2012).

HA gels are the most popular fillers as they have few adverse effects, reversibility, biocompatibility, durability, and the ability to produce subtle and natural results (Carruthers et al., 2015; Salti & Fundarò, 2020). The most common adverse effects associated with HA fillers are pain, bruising, redness, itching, and swelling. However, they do not last longer than seven days. Extremely rare side effects such as infection, tissue necrosis, granulomatous foreign body, and herpes labialis activation may occur. Contraindications for the use of these fillers are hypersensitivity to hyaluronic acid or to any of the components and to gram-positive bacterial proteins. In fact, after injection of these fillers, an immediate inflammatory process takes place, which fades in 4 to 5 days. When complications occur a hyaluronidase injection, antibiotics, or steroids may be necessary to treat these side effects (Walker et al., 2022).

**Lip Asymmetries And Deformities.** The lip asymmetries and deformities can be congenital or acquired, therefore they have different etiologies (Skoog, 1970; Gay, 1984; Stal & Hollier, 2002; Koshy et al., 2010; Starmer et al., 2015; Wang et al., 2016; Mishra et al., 2020; Rauso et al., 2020). Deformities can be acquired as a result of surgical procedures, such as resection of neoplasms or labial hemangioma, corrective surgery of orofacial clefts or removal of permanent lip implants. In these cases, the great potential for the emergence of lip deformities is not only related to the extent of tissue removal, but also the formation of scars, which can cause morphological, functional and aesthetic damage (Stal & Hollier, 2002; Koshy et al., 2010; Chang et al., 2012; Wang et al., 2016; Chang et al., 2019; Rauso et al., 2020); as changes in the length, tension, seal, thickness and aesthetics lip (Mishra et al., 2020).
Lip deformities may also occur due to electrical burns, which generate tissue sequelae and areas of scar contraction (Skoog, 1970; Gay, 1984). Moreover, lip asymmetries can be caused by facial paralysis or muscular dystrophy, which lead to loss of muscle function and consequent reduction in lip strength and function, resulting in phonetic difficulties and of the food bolus containment (Starmer et al., 2015). In fact, lip incompetence can be a sequela of both facial paralysis and lip surgeries (Starmer et al., 2015; Wollina & Goldman, 2020).

Among the congenital conditions that most affect the face, orofacial clefts encompass a variety of craniofacial anomalies and malformations, which result in phonetic difficulties and lip structure abnormality (Martelli et al., 2012; Shkoukani et al., 2013). In complex cases, cleft lip may be present in patients with Syndromes, such as Treacher-Collins and Goldenhar (Franchi et al., 2018). On the other hand, congenital lip asymmetries can also cause aesthetic deformities that need treatment, as even if they are less apparent, they can have negative psychosocial effects for the patient (Saraç & Pancar, 2019).

For permanent correction of lip deformities, the first choice treatment is the surgical procedure (Stal & Hollier, 2002; Edlich et al., 2005; Starmer et al., 2015). However, in many cases, surgical correction may not be possible or may not achieve the desired results. In these situations, hyaluronic acid (HA) dermal fillers can be used as a non-surgical alternative for the correction of lip asymmetries and deformities.

### Table I. Summary of the main studies which report the treatment of lip asymmetries and deformities with HA dermal fillers.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Methodology</th>
<th>Lip Asymmetry or Deformity</th>
<th>Main Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schweiger et al.</td>
<td>2008</td>
<td>Case report</td>
<td>Lip asymmetry after surgical correction of cleft lip.</td>
<td>HA fillers can satisfactorily use for correction of asymmetry and low volume present after surgery for repair cleft lip, emerging as a novel and less invasive way to improve cosmetic of these patients.</td>
</tr>
<tr>
<td>Belyea et al.</td>
<td>2010</td>
<td>Case report</td>
<td>Whistle deformity following resections for treatment of squamous cell carcinoma of the lower lip.</td>
<td>HA-based filling allowed lip augmentation, improved lip competence and a pleasant aesthetic result. However, after 3 months there was relapse due to HA degradation and autologous microfat transplantation to the lower lip were used for definitive management of the patient’s whistle deformity.</td>
</tr>
<tr>
<td>Stolic et al.</td>
<td>2015</td>
<td>Case report</td>
<td>Post-operative scar after cleft lip surgery.</td>
<td>HA fillers can be successfully used in the treatment of post-operative scars after cleft lip surgery.</td>
</tr>
<tr>
<td>Starmer et al.</td>
<td>2015</td>
<td>Clinical trial (n = 25)</td>
<td>Lip incompetence from facial paralysis or muscle dystrophy.</td>
<td>HA filler injection for augmentation of the lip is a simple and effective means of improving labial strength, bilabial sounds, and anterior spillage in patients with facial paralysis or facial muscular dystrophy.</td>
</tr>
<tr>
<td>Franchi et al.</td>
<td>2018</td>
<td>Clinical trial (n = 32)</td>
<td>Scars in patients carriers cleft lip and palate, Treacher-Collins syndrome, Goldenhar syndrome, lip hemangioma or electrical burn in the lip.</td>
<td>HA fillers offered very subtle cosmetic results, enhancing the lip volume and improving softness and elasticity of the scarring tissues.</td>
</tr>
<tr>
<td>Kandhari et al.</td>
<td>2017</td>
<td>Case report</td>
<td>Congenital lip asymmetry and acquired lip asymmetry after resection of basal cell carcinoma of the upper lip.</td>
<td>HA filler may be used successfully when lip asymmetry is evident and is a relatively simple nonsurgical alternative.</td>
</tr>
<tr>
<td>Serdar &amp; Karabay</td>
<td>2018</td>
<td>Case report</td>
<td>Congenital lip asymmetry and lip asymmetry after dermal filler application to the lips.</td>
<td>HA fillers are considered to be gold standard treatment for congenital, acquired, and postsurgical asymmetries.</td>
</tr>
<tr>
<td>Dall’Magro et al.</td>
<td>2019</td>
<td>Clinical trial</td>
<td>Lip asymmetry in case of severe malocclusion associated with skeletal changes.</td>
<td>HA fillers can be used as adjuvant treatment in cases of severe malocclusion associated with skeletal changes. Lip filling can be performed in the same session of the orthognathic surgery; helping to maintain the seal and restore the lip appearance, besides to patient satisfaction.</td>
</tr>
<tr>
<td>Saraç &amp; Pancar</td>
<td>2019</td>
<td>Case report</td>
<td>Congenital lip asymmetry</td>
<td>HA dermal fillers are an effective tool in correction of lip asymmetries. Although a temporary solution, HA injections provided an immediate improvement in the appearance of the lips and resolution of resting lip incompetence.</td>
</tr>
<tr>
<td>Rauso et al.</td>
<td>2020</td>
<td>Case report</td>
<td>Lip incompetence following surgical excision of nonresorbable filler.</td>
<td></td>
</tr>
</tbody>
</table>
Hyaluronic acid fillers for treatment of lip asymmetries and deformities. HA fillers are widely used in aesthetic treatments for facial reconstruction and modeling (Stolic et al., 2015). However, they have been increasingly used to correct congenital and acquired lip deformities and asymmetries (Rauso et al., 2010; Kandhari et al., 2017; Serdar & Karabay, 2018; Saraç & Pancar, 2019). They promote immediate and aesthetically satisfying clinical results and, in addition to restoring symmetry and volume, they also improve lip function (Schweiger et al., 2008). A summary of the main studies that report the treatment of lip asymmetries and deformities with HA fillers can be seen in Table I.

Several studies have reported positive results in the use of HA fillers for the treatment of lip asymmetries caused by different factors such as: Insatisfactory dermal fillers (Serdar & Karabay, 2018), permanent lip implants (Rauso et al., 2020), excision of lip basal cell carcinoma (Kandhari et al., 2017), post-operative scars (Stolic et al., 2015; Franchi et al., 2018), scars after excision of lip hemangioma and electrical burns (Franchi et al., 2018).

In a similar way, patients with cleft lip undergo numerous reconstructive surgeries throughout their lives to correct this deformity and dysfunction. However, aesthetic and scar imperfections are common and inherent sequelae of these surgical procedures (Schweiger et al., 2008). These conditions leave patients dissatisfied with their appearance, causing aesthetic, psychological and social harm. Faced with so many challenges, HA fillers have emerged as an alternative for the treatment of lip asymmetries and residual surgical scars (Stolic et al., 2015; Franchi et al., 2018). On the other hand, congenital lip asymmetries not associated with syndromes have also been successfully treated with injections of HA-based gels (Kandhari et al., 2017; Serdar & Karabay, 2018; Saraç & Pancar, 2019).

HA fillers have positive effects on scar repair, as they are able to stimulate the production of elastin and collagen, resulting in increased flexibility and elasticity of fibrous scar tissue. Therefore, they provide aesthetic and functional results that could not be achieved even by the most subtle surgical techniques (Franchi et al., 2018). In addition, they are an alternative that does not lead to hospitalization, excessive postoperative swelling and long recovery periods (Stolic et al., 2015).

Injection of HA fillers in individuals with facial paralysis may also aid in the treatment of lip incompetence by providing an increase of the lip strength in the paralyzed side. Although the filler does not directly change the strength of the perioral muscles, its mechanical properties influence the lip strength by providing greater rigidity to the lip. This allows better containment of the food bolus and improves word articulation. Moreover, lip fillers can also improve lip strength and function in patients with facioscapulohumeral muscular dystrophy (Starmer et al., 2015).

Additionally, HA fillers can be used as a complementary treatment in cases of severe malocclusion associated with skeletal changes, whose predictive orthognathic planning shows the establishment of a correct skeletal position, but with a less lip aspect than desired. In these cases, lip filling can be performed in the same surgical session of the osteotomy; helping to maintain the seal and refine the lip appearance, besides to patient satisfaction (Dall’Magro et al., 2019).

Literature reports demonstrate that filling with HA gels offers positive results for the patient, being a well-tolerated procedure with minimal discomfort (Saraç & Pancar, 2019; Rauso et al., 2020) and, that can be used to management congenital or acquired deformities (Kandhari et al., 2017; Franchi et al., 2018; Serdar & Karabay, 2018). Associated to this, the volume increase with HA can be performed gradually (in different sessions), so that the patient can more accurately assess their satisfaction with the result and also allows repairs easily performed by additional applications of the filler (Kandhari et al., 2017; Serdar et al., 2018; Saraç & Pancar, 2019).

In a similar way, patients with cleft lip undergo numerous reconstructive surgeries throughout their lives to correct this deformity and dysfunction. However, aesthetic and scar imperfections are common and inherent sequelae of these surgical procedures (Schweiger et al., 2008). These conditions leave patients dissatisfied with their appearance, causing aesthetic, psychological and social harm. Faced with so many challenges, HA fillers have emerged as an alternative for the treatment of lip asymmetries and residual surgical scars (Stolic et al., 2015; Franchi et al., 2018). On the other hand, congenital lip asymmetries not associated with syndromes have also been successfully treated with injections of HA-based gels (Kandhari et al., 2017; Serdar & Karabay, 2018; Saraç & Pancar, 2019).
Another advantage is related to application reversibility, either through the natural degradation of HA by the body over time or through the administration of hyaluronidase, in case of dissatisfaction or adverse effects (Belyea et al., 2010; Chang et al., 2018; Vidic & Bartenjev, 2018; Rauso et al., 2020). Therefore, from the beginning, the patient must be aware of the need for maintenance appointments (Schweiger et al., 2008). Furthermore, the number of studies on the use of HA as an auxiliary measure in the treatment of the lip deformities that were described in this study is still little explored in the literature (Kandhari et al., 2017). Therefore, it is necessary to carry out randomized clinical trials with a greater number of patients and follow-up time, in order to investigate the benefits of the HA fillers for this group of patients.

CONCLUSION

The HA fillers can be used as alternative treatment for several types of congenital and acquired lip deformities and asymmetries. They are reversible, biocompatible and can produce subtle and natural results. These fillers also have few adverse effects and are able to stimulate the production of elastin and collagen, resulting in increased flexibility and elasticity of fibrous scar tissue. However, they are temporary and require new applications every 3 or 4 months to maintain aesthetic results. There are several reports showing that HA fillers result in excellent effects on the repair of lip deformities, but it is necessary to carry out randomized clinical trials with a greater number of patients and follow-up time, in order to investigate the benefits of the HA fillers for carriers patients of lip abnormalities.

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REFERENCE


