

# 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

Isabela Campbell Santos<sup>1</sup>; Romero Gomes da Silva<sup>2</sup>; Gustavo Leite Coelho Martins de Oliveira<sup>1</sup>; Mônica Regina Pereira Senra Soares<sup>1</sup> & Alexa Magalhães Dias<sup>1</sup>

**SANTOS, I. C.; GOMES DA SILVA, R.; MARTINS DE OLIVEIRA, G. L. C.; SOARES, M. R. P. S. & DIAS, A. M.** Hyaluronic acid dermal fillers for treatment of congenital and acquired lip asymmetries and deformities. *Int. J. Odontostomat.*, 17(4):392-399, 2023.

**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 Lillacs 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,

<sup>1</sup> Cirujano dentista, Universidade Federal de Juiz de Fora, Campus GV, Governador Valadares, Minas Gerais, Brasil.

<sup>2</sup> Cirujano dentista, Centro Universitário de Belo Horizonte (uniBH), Belo Horizonte, Minas Gerais, Brasil.

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 Scholar e Lillacs databases were searched. The search strategy used following keywords: “[hyaluronic acid OR hyaluronan OR dermal filler] AND [lip deformity 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 its 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 be classified as monodensified (cross-linking occurs after molecular 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 was 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.*,

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

Authors	Year	Methodology	Lip Asymmetry or Deformity	Main Outcomes
Schweiger <i>et al.</i>	2008	Case report	Lip asymmetry after surgical correction of cleft lip.	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.
Belyea <i>et al.</i>	2010	Case report	Whistle deformity following resections for treatment of squamous cell carcinoma of the lower lip.	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.
Stolic <i>et al.</i>	2015	Case report	Post-operative scar after cleft lip surgery.	HA fillers can be successfully used in the treatment of post-operative scars after cleft lip surgery.
Starmer <i>et al.</i>	2015	Clinical trial (n = 25)	Lip incompetence from facial paralysis or muscle dystrophy.	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.
Franchi <i>et al.</i>	2018	Clinical trial (n = 32)	Scars in patients carriers cleft lip and palate, Treacher-Collins syndrome, Goldenhar syndrome, lip hemangioma or electrical burn in the lip.	HA fillers offered very subtle cosmetic results, enhancing the lip volume and improving softness and elasticity of the scarring tissues.
Kandhari <i>et al.</i>	2017	Case report	Congenital lip asymmetry and acquired lip asymmetry after resection of basal cell carcinoma of the upper lip.	HA filler may be used successfully when lip asymmetry is evident and is a relatively simple nonsurgical alternative.
Serdar & Karabay	2018	Case report	Congenital lip asymmetry and lip asymmetry after dermal filler application to the lips.	HA fillers are considered to be gold standard treatment for congenital, acquired, and postsurgical asymmetries.
Dall'Magro <i>et al.</i>	2019	Clinical trial	Lip asymmetry in case of severe malocclusion associated with skeletal changes.	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.
Saraç & Pancar	2019	Case report	Congenital lip asymmetry	HA dermal fillers are an effective tool in correction of lip asymmetries.
Rauso <i>et al.</i>	2020	Case report	Lip incompetence following surgical excision of nonresorbable filler.	Although a temporary solution, HA injections provided an immediate improvement in the appearance of the lips and resolution of resting lip incompetence.

2015; Rauso *et al.*, 2018, 2020, 2022). However, due to its invasive nature, need of additional corrective surgeries, occurrence of scars, fear and preference of the patient; alternative or complementary treatment methods have been increasingly sought after (Starmer *et al.*, 2015; Rauso *et al.*, 2020). Among these, dermal fillers are highlighted as one of the best minimally invasive treatment options. In this context, the HA filler was recognized in 2018, as the gold standard non-surgical treatment for the correction of lip asymmetries (Serdar & Karabay, 2018). In fact, some studies have reaffirmed its importance as an alternative method for the management of postoperative scars and the treatment of apparent lip asymmetries (Schweiger *et al.*, 2008; Rauso *et al.*, 2010; Stolic *et al.*, 2015; Kandhari *et al.*, 2017).

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

& Karabay, 2018). 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).

Despite the advantages, this treatment offers a temporary solution, which is conditioned to the time of HA degradation by the body, require consultations for new applications every 3 or 4 months (Belyea *et al.*, 2010; Chang *et al.*, 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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**SANTOS, I. C.; GOMES DA SILVA, R.; MARTINS DE OLIVEIRA, G. L. C.; SOARES, M. R. P. S. & DIAS, A. M.** Rellenos dérmicos de ácido hialurónico para el tratamiento de asimetrías y deformidades labiales congénitas y adquiridas. *Int. J. Odontostomat.*, 17(4):392-399, 2023.

**RESUMEN:** Los rellenos dérmicos de ácido hialurónico (AH) son muy utilizados en tratamientos estéticos para el modelado facial y de labios. A pesar de que se sabe en gran medida que los rellenos de HA se utilizan en procedimientos para aumentar el volumen de los labios, su aplicación para el tratamiento de anomalías labiales no está muy extendida. Este estudio revisó el uso de rellenos de HA para la reconstrucción de asimetrías y deformidades labiales congénitas y adquiridas, buscando ampliar el conocimiento sobre esta modalidad de tratamiento. Para realizar esta revisión narrativa, se realizaron búsquedas en las bases de datos Medline-Pubmed, Web of Science, Scopus, Embase, Google Scholar y Lillacs. Varios estudios han reportado resultados positivos en el uso de rellenos de HA para el tratamiento de deformidades labiales causadas por diferentes factores tales como: rellenos dérmicos insatisfactorios, implantes labiales permanentes, escisión de carcinoma labial, cicatrices postoperatorias y quemaduras eléctricas. Los rellenos de HA también son una alternativa para el manejo de asimetrías labiales y cicatrices quirúrgicas residuales en pacientes con labio hendido. Además, la inyección de rellenos de HA en personas con parálisis facial y distrofia muscular facioescapulohumeral también puede mejorar la incompetencia de los labios. Además, los rellenos de HA se pueden usar como un tratamiento complementario en casos de maloclusión severa asociada con cambios esqueléticos, lo que ayuda a mantener el sellado y refinar la apariencia de los labios. Por lo tanto, los rellenos de HA se pueden utilizar como tratamiento alternativo para varios tipos de deformidades y asimetrías labiales congénitas y adquiridas. Sin embargo, es necesario realizar ensayos clínicos aleatorizados con mayor número de pacientes y tiempo de seguimiento, para investigar los beneficios de los rellenos HA para pacientes portadores de anomalías labiales.

**PALABRAS CLAVE:** ácido hialurónico, relleno dérmico, deformidad labial, asimetría labial, anomalías labiales.

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Corresponding author:  
Alexa Magalhães Dias  
Adjunct Professor  
Dentistry Department  
Federal University of Juiz de Fora  
Campus Governador Valadares  
Av. Moacir Paleta, 1167 São Pedro  
Governador Valadares  
Minas Gerais, CEP: 35020-360  
BRAZIL

Email: alexa.magalhaes@ufff.br

Isabela Campbell Santos  
Romero Gomes da Silva  
Gustavo Leite Coelho Martins de Oliveira  
Mônica Pereira Senra Soares  
Alexa Magalhães Dias Brazil.

<https://orcid.org/>  
0000-0002-5409-1660  
0000-0002-7435-7710  
0000-0002-0214-9955  
0000-0002-2074-5232  
0000-0002-3351-6586