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Main clinical outcomes of orofacial harmonization and choice of appropriate filling: a systematic review

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Abstract

Introduction: Techniques for administering injectable fillers for facial rejuvenation and aesthetic enhancement continue to evolve. Hyaluronic acid (HA) is the most commonly used soft tissue filler. The cross-linking process is also essential to improve the mechanical properties and control the rate of HA degradation. The great challenge lies in the rational choice of the product to be used according to the anatomical area to be corrected. **Objective:** This was to conduct a literature review on the different types of hyaluronic acid crosslinking and the appropriate choice of the product in different regions of the face, especially in areas where the product can be migrated due to the musculature, as the appropriate choice directly interferes with its benefits and results. **Methods:** The systematic review rules of the PRISMA Platform and the methodological quality of AMSTAR 2 were followed. The research was carried out from March to April 2025 in the Web of Science, Scopus, Embase, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 138 articles were found. A total of 32 articles were fully evaluated and 12 were included and developed in the present systematic review study. The clinical studies showed homogeneity in their results, with Chi-Square (X^2) = 72.2%>50%. Considering the Cochrane tool for risk of bias, the overall evaluation resulted in 40 studies with a high risk of bias and 20 studies that did not meet the GRADE. The studies generally showed safe effects, with a high success rate and aesthetic satisfaction with the participants' application of the types of hyaluronic acids. Restylane Defyne hyaluronic acid filler was safe and effective for augmentation of the chin region and was associated with high aesthetic improvement and patient satisfaction. Furthermore, studies have generally shown the beneficial effects of flexible hyaluronic acid fillers in the augmentation and perioral enhancement of the lips, demonstrating a significant improvement in the texture, red color, and fullness of the lips. A substantial increase in surface stretch (dynamic tension) was also observed, indicating tissue expansion and improvement in lip smoothness. The 20 mg/mL hyaluronic acid gel with lidocaine for cheek augmentation was safe and effective using a cannula and was non-inferior to needle injection. The evaluation of the effect of Sardenyashape® with lidocaine demonstrated its efficacy and safety for use in the correction of nasolabial folds. The success of lip filler treatment is the result of the combination of a visually volumizing effect, satisfaction with the anatomical shape, function, recovery, and psychosocial effects.

Keywords: Orofacial harmonization. Hyaluronic acid. Facial aesthetics. Filler. Cross-linking.

Introduction

Techniques for administering injectable fillers for facial rejuvenation and aesthetic enhancement continue to evolve [1]. The use of a slow, careful, and methodical injection technique is imperative in all treatment settings and for all facial areas. Constant attention to local anatomy, particularly arteries, veins, and nerve bundles, is critical to minimize complications [2]. In this context, hyaluronic acid (HA) is the most commonly used soft tissue filler. It is a large, injectable, nonsulfated glycosaminoglycan found in the extracellular matrix of connective tissue, synovial fluid, and other tissues [3].

It is composed of polymeric disaccharides and

forms hydrogen bonds in aqueous solutions. HA binds water and is structurally stable. It is thought that 1 g of HA can bind up to 6 L of water in the native human body. HA has a variety of functions ranging from shock absorption in joints to tissue healing. Furthermore, HA has minimal immunogenicity, making it a favorable option for many patients seeking non-surgical treatment for facial lines and wrinkles [4,5]. In this scenario, the crosslinking process is also essential to improve the mechanical properties and control the rate of HA degradation (DVS) [1,6].

HA can be defined by three rheological properties: viscosity, elasticity, and cohesiveness, which will determine its resistance to deformation during these mechanical stresses. Viscosity and elasticity are related to the resistance to deformation in the horizontal plane (lateral shear or torsion) while cohesiveness defines the resistance in the vertical plane (compression/ stretching) [4].

In this sense, the resistance to lateral shear or torsion forces in the horizontal plane defines the viscous and elastic properties of HA. Cohesiveness can be defined as the resistance to a compression/stretching force in a vertical plane after implantation of the product, reflecting the lifting capacity of the tissues (volumizing effect) and defining the initial vertical projection of the filler product [4,5]. The great challenge lies in the rational choice of the product to be used according to the anatomical area to be corrected. Each region of the face is subject to specific mechanical conditions for HA [6].

Given this, the present study carried out a literature review on the different types of cross-linking of hyaluronic acids and the appropriate choice of the same in different regions of the face for orofacial harmonization, mainly in areas where the product can be migrated due to the muscles since the appropriate choice directly interferes with its benefits and results.

Methods

Study Design and Data Analysis

The present study followed an international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 04/07/2025. The AMSTAR 2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 04/07/2025.

To analyze the data from the results of the articles that comprised the statistical analysis, the chi-square test (X^2) was performed to determine the homogeneity or heterogeneity of the studies in terms of the safety and success of fillers with hyaluronic acids.

Data Sources and Search Strategy

The search strategies for this brief systematic review were based on the keywords (DeCS/MeSH Terms): *"Orofacial harmonization. Hyaluronic acid. Facial aesthetics. Filler. Cross-linking"*. The search was conducted from March to April 2025 in the Web of Science, Scopus, Embase, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar databases, in English and Portuguese. In addition, a combination of keywords with the Boolean operators "OR", "AND" and "NOT" operators were used to target the scientific articles of interest.

Study Quality, Eligibility Criteria, and Risk of Bias

Studies that rigorously presented the results of the search process that presented scientific quality according to the GRADE classification, and that did not present a significant risk of bias, that is, that could compromise the safety of the results, were selected. According to GRADE recommendations, the quality of scientific evidence in the studies addressed was classified as high, moderate, low, or very low, according to the risk of bias of evidence, sample size, clarity of comparisons, precision, and consistency in the effects of the analyses. High quality of evidence was attributed through four criteria: 1) Randomized or prospective controlled clinical trials; 2) Retrospective clinical trials or case series; 3) Sample size greater than 15 participants; 4) Studies with well-designed statistical results; 5) Studies published in indexed journals and with a significant impact factor; 6) descriptive, interpretative, theoretical (credibility of methods) and pragmatic validity.

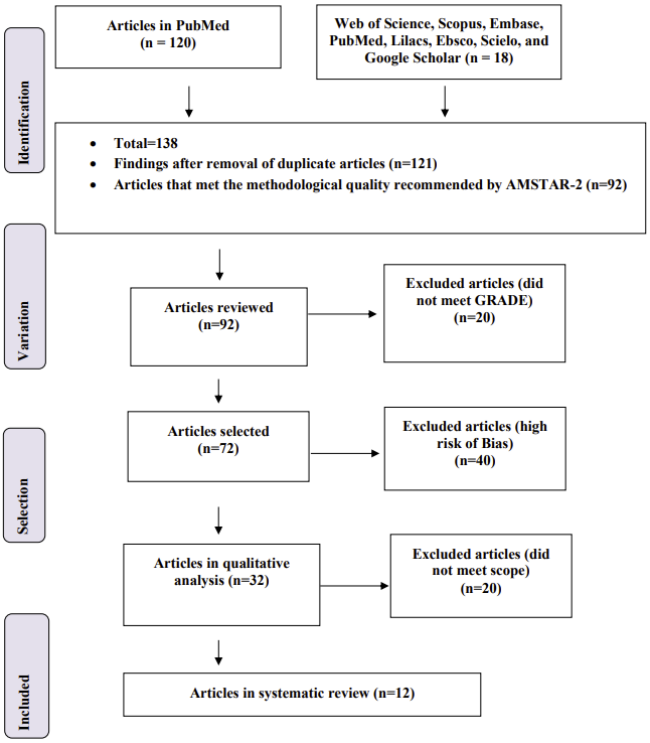
Results and Discussion

Summary of Literature Findings

A total of 138 articles were found. Initially, duplicate articles were excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing articles that did not include the theme of this article, as well as the exclusion of articles that did not meet the methodological quality criteria recommended by AMSTAR 2, resulting in 92 articles. A total of 32 articles were evaluated in full and 12 were included and developed in the present systematic review study (Figure 1). Of the total of 18 articles that make up the list of references, 6 articles are only part of the introduction of this study. The clinical studies presented homogeneity in their results, with Chi-Square (X^2) =

72.2%>50%. Considering the Cochrane tool for risk of bias, the overall evaluation resulted in 40 studies with a high risk of bias and 20 studies that did not meet GRADE and AMSTAR-2.

Figure 1. Screening of articles to the systematic review.



Source: Own authorship.

Main Clinical Findings (n=12 clinical studies)

In the facial aesthetics setting, soft tissue filler augmentation has become increasingly common due to its perceived ease and satisfactory results, despite some potential complications. Injectors must rely on the only strong point that exists in the lip literature to date, which is anatomy. The basis of all successful injections is a mandatory understanding of the normal vital structures and also the variations of an area, combined with meticulous injection techniques, deposition of small aliquots of the product, and the ability to recognize unwanted adverse events early enough to act on them [7].

In this sense, a randomized controlled clinical trial conducted by Beer et al. (2021) [8] evaluated the safety and efficacy of hyaluronic acid (VYC-20L) in patients with chin retrusion. Adults with chin retrusion were randomized (3:1) to receive VYC-20L in the chin at baseline (treatment group) or 6 months later (control group). The primary efficacy endpoint was a ≥1point improvement in the Allergan Chin Retrusion Scale (ACRS) from baseline at Month 6. Safety assessments included injection site responses (ISRs) and adverse events (AEs). As a result, VYC-20L was administered to 192 participants (treatment group, n=144; control group, n=48). At Month 6, significantly more participants had an ACRS response in the treatment versus control group (56.3% vs 27.5%; p=0.0019). Efficacy was also demonstrated by the proportion of participants with improved/much-improved scores on the Global Aesthetic Improvement Scale and responses on the FACE-Q Satisfaction with Chin questionnaire and the FACE-Q Psychological Wellbeing module. Treatment benefits remained evident at Month 12. The most common ISRs were tenderness (81.1%) and firmness (75.1%). One participant (0.5%) discontinued the study due to two serious AEs related to the treatment of facial cellulite and inflammation at the injection site, both of which resolved without sequelae.

In this context, regarding the treatment of the chin, which is important for facial appearance, and affects the overall balance and harmony of the face, a randomized clinical study developed by Marcus et al. (2022) [9] analyzed the efficacy of Restylane Defyne hyaluronic acid filler for chin augmentation and correction of chin retrusion versus a control without treatment. Thus, male and female individuals, 22 years of age or older, with mild to moderate chin retrusion, were randomized in a 3:1 ratio to Restylane Defyne hyaluronic acid filler (n=107) or no treatment (n=33). Assessments included blinded, live assessments of a validated scale of chin retrusion (Galderma Chin Retrusion Scale), aesthetic improvement (Global Aesthetic Improvement Scale), subject-reported FACE-Q chin satisfaction, and safety follow-up. Results showed that the Galderma Chin Retrusion Scale response rate (≥ 1-grade improvement) was higher for Restylane Defyne hyaluronic acid filler (81 percent) than control (6 percent) (p<0.001) at week 12 and remained higher at week 48 (74 percent versus 11 percent; p<0.001). Aesthetic improvement rates were high throughout the study, as reported by both investigators (≥96 percent) and participants (≥85 percent). Participant satisfaction was higher in the Restylane Defyne hyaluronic acid filler group than in the control group at week 12 (p<0.001). On individual items of the FACE-Q scale, 87 to 98 percent of subjects were satisfied at week 12. Treatment-related adverse events were mild to moderate. Efficacy was sustained through 48 weeks.

Additionally, an 8-week, open-label, Phase IV, multicenter study was conducted by Nikolis et al. (2021) [10] who quantitatively evaluated the results of subjects by measuring the change in lip texture, color (redness), lip fullness, and lip and perioral surface stretch (dynamic tension) after treatment with hyaluronic acid. Restylane Kysse (HARK), Restylane Refyne (HARR), and Restylane Defyne (HARD) are HA dermal fillers formulated with XpresHAn technology. Subjects were treated with HA on the lips and HARR and/or HARD on perioral wrinkles and

folds as an add-on treatment. Assessments included 2D photographic analyses of lip texture and color and 3D photographic assessments of lip enhancement and dynamic tension. HARK significantly improved lip texture ($p \leq 0.002$), lip redness ($p < 0.001$), and added fullness to the lips (lip enhancement measures; $p < 0.001$) at week 8 post-treatment. In addition, lower lip wrinkles were significantly reduced ($p = 0.007$) and upper lip wrinkles were reduced (not statistically significant). Surface stretch (dynamic tension) in the lip and perioral region significantly increased post-treatment ($p < 0.001$).

Authors Jones et al. (2021) [11] demonstrated the safety and efficacy of VYC-20L (hyaluronic acid gel 20 mg/mL with lidocaine) via cannula for age-related volume deficit in the midface through a multicenter, evaluator-blinded, randomized, within-subject, controlled study. This study enrolled adults with moderate to severe Midface Volume Deficit Scale (MFVDS) scores. VYC-20L was administered to one cheek via a cannula (with optional use of a needle in the zygomaticomalar region) and to the other cheek via a needle. The primary efficacy outcome was the mean paired difference between treatments in a change in MFVDS score from baseline to month 1. ISRs, procedural pain, and AEs were assessed. Out of 60 total randomized and treated subjects, the mean change in MFVDS score from baseline to month 1 was -1.8 with a cannula and -1.9 with a needle, yielding a paired mean difference (95% CI) of 0.1 (-0.05 to 0.25). Most ISRs were mild/moderate and resolved within 2 weeks. Procedural pain was minimal, and no serious adverse events were reported.

Authors Qiao et al. (2019) [12] evaluated the longevity and diffusion pattern of two hyaluronic acid fillers generated by different cross-linking technologies used in the treatment of nasolabial folds using high-frequency ultrasound. A total of 41 subjects were treated with Restylane 2 and the remaining 41 were treated with Dermalax DEEP. Wrinkle severity scale scoring and high-frequency ultrasound assessment of the nasolabial folds were performed before and after hyaluronic acid filler injection. As a result, at 2 and 24 weeks after baseline, the increase in dermal thickness induced by hyaluronic acid filler treatment was not significantly different between the groups. After 48 weeks, the increase in dermal thickness of the Restylane 2 group (0.14 ± 0.12 mm) was much smaller than that of the Dermalax DEEP group (0.20 ± 0.13 mm). Ultrasound examination revealed that HA materials formed well-demarcated, hypoechoic areas. Restylane 2 tended to form a more diffuse pattern with multiple smaller bubbles, whereas Dermalax DEEP developed a more localized configuration with larger clusters.

A randomized clinical trial with 96 participants was designed by authors Chung and Lee (2021) [13] and compared the tolerability (wrinkle severity rating scale, WSRS), pain (visual analog scale, VAS score), satisfaction (global aesthetic improvement scale, GAIS) and safety of a novel monophasic HA filler (MAH) (Sardenyashape®) containing lidocaine, used to correct nasolabial folds (SNLs), with those of a biphasic HA filler (BAH) (Restylane LYFT®) containing lidocaine. Participants were injected with a novel MAH filler in one SNL and a BAH filler and were reassessed for aesthetic changes at 8 and 24 weeks. Wrinkle severity was assessed using the 5-point WSRS. As a result, at week 24, the mean improvement in WSRS compared to baseline was 1.92 ± 0.75 and 2.24 ± 0.66 for MAH and BAH fillers, respectively, and the corresponding mean pain values using the VAS score 30 minutes after the procedure were 0.04 ± 0.25 and 0.02 ± 0.15, respectively, with no significant difference. The mean GAIS values 8 weeks after the procedure with MAH and BAH fillers were 1.89 ± 0.77 and 1.40 ± 0.82, respectively ($p < 0.001$). Both fillers were well tolerated, with mild adverse reactions.

Furthermore, a multicenter, randomized, controlled, quadruple-blind clinical trial evaluated whether superiority in durability of effect, appearance improvement, quality of life, and safety could be demonstrated among the 4 most commonly used hyaluronic acid dermal filler brands in the Netherlands. A total of 143 adult women requesting lip augmentation were enrolled. Participants were randomized (stratified by physician and product) in a 1:1:1:1 ratio to receive 1.2 mL of any of 4 hyaluronic acid dermal filler brands known as Juvederm Ultra 3, Belotero Intenso, Restylane Kysse, and Stylage M that were injected by 5 physician aestheticians. Outcomes were assessed at baseline, day 14, and week 13. As a result, linear mixed model analysis showed a mean increase in lip height from baseline to follow-up (12.1 mm [118.9%], $p < .01$). With Stylage (12.8 mm [126.3%]), lip height increased more than with Juvederm (11.2 mm [110.9%], $d = 0.73$). Overall, appearance assessment increased from baseline to follow-up (19.4 points on a 10- and 40-point scale [140.7%], P\.01), and increased more with Juvéderm (110.9 points [150.7%]) than with Belotero (17.2 points [129.8%], $d = 0.50$). No serious adverse events were recorded. Overall, social functioning (12.4 points on an 8- and 32-point scale [19.8%], P\.01) and psychological well-being (12.7 points on a 10- and 40-point scale [18.7%], P\.01) scores increased from baseline to follow-up. Social functioning increased more with Stylage (14.6 points [120.1%]) than with Belotero (11.6 points [16.3%]; $d = 0.64$). Overall, lip height increased from baseline to check-up (13.8 mm

[134.4%], P\0.01). Belotero (14.7 mm [141.3%]) resulted in a greater increase than both Juvederm (13.1 mm [127.7%], d = 1.21) and Stylage (13.4 mm [131.1%], d = 0.58). Juvederm was associated with 25.3% higher side effect scores (13.0 points on an 8e32 point scale) than Stylage (12.0 points; d = 0.85). No differences were observed at follow-up for any of these outcomes. Treatment satisfaction and quality of life were high in all groups. Despite this, the absolute difference in lip volume increase from baseline to follow-up between Juvederm versus Stylage was 1.6 mm (15.4%) in this sample of women with relatively small lips (an average of 10.9 mm at baseline), suggesting a clinically relevant longer duration of Stylage. Lastly, the absolute difference in lip enhancement in assessment score between Juvederm versus Belotero was 20.9%, suggesting a clinically relevant effect of Juvederm over time [14].

A recent exploratory and prospective study by Araco, Araco, Raichi (2023) [15] investigated the rationale of sequentially associating Highly Purified Polynucleotide Technology (PN-HPT®) as a first priming agent acting on the skin followed by HA dermal filler injections to correct moderate to severe nasolabial folds (SNLs). The authors examined 10 Caucasian outpatient women aged 40-65 years with SNLs. Selected right-sided SNLs received 4 mL of PN-HPT® intradermally in the initial priming phase ("SNL Rx group"). Selected left-sided SNLs received 4 mL of saline (placebo) ("SNL Lx group"). After 3 and 6 weeks, all patients received 2 mL of cross-linked HA subdermally in both areas. The total study follow-up was at week 1, 6 weeks, and 3 and 6 months. Due to favorable initial results, the authors allowed the inclusion of a total of 20 women and 40 SNLs. All treated women completed the 6-month follow-up without reporting any side effects, even clinically minor. The Antera 3D® device demonstrated that wrinkles and skin texture were significantly improved on the SNL Rx after 6 weeks (monotherapy phase) and 3 and 6 months (PN-HPT® preparation phase + AH phase) compared to baseline. AH levels, measured with Vectra H2® quantitative assessment technology in the right SNLs, were significantly higher than contralaterally at both 3 and 6 months.

A recent 18-month prospective randomized, double-blind study by Braccini et al. (2023) [16] analyzed HA fillers that are ART FILLER® Volume versus the reference product Juvéderm Voluma® in the midface, temple, jaw, and chin. The observations confirmed the non-inferiority of ART FILLER® Volume versus the reference product in the different injected areas. For both fillers, the beneficial effects in restoring volumes were maintained 18 months after injection; however, these effects diminished over time. In addition, Art Filler® Volume injections were well tolerated by the subjects and presented fewer acute side effects compared to the reference product, which can be explained by a lower induction of inflammation.

A study conducted by Hilton et al. (2023) [17] evaluated the safety and efficacy of lip injections with two HA fillers manufactured with different gel technologies. In a study sample of 40 subjects, treatment with two soft tissue fillers (HARK or HAJUS) was randomly assigned. Subjects were injected with 0.5 cc per upper and lower lip using a standardized injection procedure. Early-onset adverse events were assessed by evaluation through day 14. Aesthetic improvement, patient satisfaction, and post-day 14 AEs were assessed over 24 weeks. In subjects treated with HARK, the intensity of early-onset swelling, erythema, and pain/tenderness was less than in subjects treated with HAJUS. Aesthetic improvement was achieved in both groups, and the majority of subjects were satisfied with the appearance of their lips. Aesthetic improvement, subject satisfaction, and adverse event profiles after day 14 were similar between filler groups.

Finally, Xie et al. (2022) [18] analyzed the efficacy and safety of Restylane Defyne (HA_{RD}) compared with Restylane for correction of SNLs in a Chinese population. In this 12-month study, Chinese adults (n=173) with moderate or severe wrinkle severity of both SNLs received treatment with HA_{RD} on one SNL and HA_{RD} on the opposite SNL. The WSRS response rates at month 6 (i.e., improvement ≥1 grade according to the blinded evaluator) were similar (72.9% and 72.8% for HA_{RD} and Restylane, respectively). HA_{RD} was non-inferior to Restylane; the 95% CI for the difference in response rates was -5.7% to 5.5%. Similarly, the products were effective and comparable in terms of reducing SNL wrinkle severity and improving Global Aesthetic Improvement Scale (GAIS) scores (according to the blinded evaluator and the subject) throughout the study. Both products were well tolerated and the injection of the product containing lidocaine (Restylane) was less painful.

Conclusion

It was concluded that the studies generally demonstrated safe effects, with a high success rate and aesthetic satisfaction with the participants' application of the types of hyaluronic acids. The Restylane Defyne hyaluronic acid filler was safe and effective for augmentation of the chin region and was associated with high aesthetic improvement and patient satisfaction. Furthermore, the studies generally showed the beneficial effects of flexible hyaluronic acid fillers in perioral lip augmentation and enhancement, demonstrating a significant improvement in the texture,

red color, and fullness of the lips. A substantial increase in superficial stretch (dynamic tension) was also observed, indicating tissue expansion and improvement in lip smoothness. The 20 mg/mL hyaluronic acid gel with lidocaine for cheek augmentation was safe and effective using a cannula and non-inferior to needle injection. The evaluation of the effect of Sardenyashape® with lidocaine proved its efficacy and safety for use in the correction of nasolabial folds. The success of lip filler treatment is the result of the combination of a visually volumizing effect, satisfaction with the anatomical shape, function, recovery, and psychosocial effects.

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Author contributions **Conceptualization-** Lorena Alves Rezende, Ana Paula Bernardes da Rosa; **Formal Analysis-** Lorena Alves Rezende, Ana Paula Bernardes da Rosa; **Investigation-** Lorena Alves Rezende; **Methodology-** Lorena Alves Rezende; **Project administration-** Lorena Alves Rezende, Ana Paula Bernardes da Rosa; **Supervision-**Ana Paula Bernardes da Rosa; **Writing - original draft-** Lorena Alves Rezende, Ana Paula Bernardes da Rosa; **Writing-review & editing-** Lorena Alves Rezende, Ana Paula Bernardes da Rosa.

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Informed Consent

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No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate®.

Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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