

# Filling procedures for lip and perioral rejuvenation: A systematic review

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## Abstract

The ideal perioral and lip rejuvenation technique provides the longest period of efficacy, lowest complication rate, and best aesthetic results. Genetics, intrinsic aging, sun exposure and repetitive muscle twitching of the orbicularis oris produce angular, radial, and vertical lines of the perioral lines and, for this reason, the needs of patients in the treatment of this anatomical area can range from simple lip enhancement to a broader and more comprehensive treatment with simultaneous correction of perioral wrinkles.

A myriad of materials have been described for rejuvenation of this area. At present, the most popular and commonly used lip enhancers are dermal fillers, but there is still no agreement on what the best material for filling soft tissue of the face, and in particular of the perioral region is.

This systematic review will focus on the various dermal fillers, of different materials approved by the US Food and Drug Administration (FDA) namely poly-L-lactic acid, calcium hydroxylapatite and hyaluronic acid and also different grafts, for perioral rejuvenation, with the goal of determining the optimal approach.

A systematic search for English studies involving perioral rejuvenation was performed using these databases: PubMed, Google Scholar, and Ovid, using a combined keyword search or medical subject headings. At the end of our study selection process, 17 relevant publications were included. For each study, year of publication, type of material used for filling, number of patients, subject of study assessment, efficacy of the filler procedure for lips rejuvenation were analyzed.

## Introduction

The rejuvenation of lips and the perioral area is of prime concern to many patients, indeed, in the aesthetics of the face, lips have a significant role for their shape and fullness.

In youthful lips of white patients, the ideal ratio of the upper to lower lip is 1:1.6.<sup>1</sup> However, the properties of lips change with age, resulting in lengthening of the cutaneous portion of the upper lip and the upper lip vermilion gradually losing volume and becoming thinner.

Genetics, intrinsic aging, sun exposure and repetitive muscle twitching of the orbicularis oris produce angular, radial, and vertical lines of the perioral lines and, for this reason, the needs of patients in the treatment of this anatomical area can range from simple lip enhancement to a broader and more comprehensive treatment with simultaneous correction of perioral wrinkles. Furthermore, there is no univocity of the ideal target to be achieved, rather, only the size of the lips is often seen as the goal, neglecting the harmony and the anatomical symmetry to be respected. Therefore, we can find, among the media and not, many examples of unnatural results, caused by an uncontrolled increase in the volume of the lips, without respecting these anatomical limitations or using incongruous materials.

To avoid this, the complete knowledge of the anatomical characteristics of the lower third of the face and injection techniques are essential information for physicians who practice in this area. Similarly, the knowledge and consequently the choice of the right filling material contributes to the success of the treatment, for a safe, effective and natural result.

Over the years, numerous compounds available have been tested and used to correct the signs of aging in the perioral and lip area, including permanent and non-permanent dermal fillers, implants, neurotoxins, lasers, and micropigmentation without arriving to determine which the best is. At present, the most popular and commonly used lip enhancers are dermal fillers, but there is still no agreement on what the best material for filling soft tissue of the face, and in particular of the perioral region is .

Ideally, the characteristics of the ideal filler should be able to guarantee a long-term aesthetic result, with low rates of complications at an affordable price, getting the most natural result. Among the difficulties in establishing the best product usable we find a great variety of materials on the market available to the physician.

With the above considerations in mind, we designed the current study to systematically review all the heretofore-published quality studies regarding filling procedures for lip and perioral rejuvenation.

The review included studies evaluating dermal fillers of different materials approved by the US Food and Drug Administration (FDA) namely poly-L-lactic acid, calcium hydroxylapatite and hyaluronic acid and also different grafts.

The goal was to evaluate good quality data regarding the various fillers for the rejuvenation of the lips and perioral region in order to determine the optimal approach.

## **Materials and methods**

### *Literature search*

Relevant published studies were searched for in PubMed, Google Scholar, and Ovid using either the following keywords or, in case of the PubMed database, medical subject headings: (“lip” and “filler”), (“perioral” and “filler”), (“lip” and “dermal graft”), (“perioral” and “dermal graft”), (“lip” and “collagen graft”), (“perioral” and “collagen graft”), (“lip” and “hyaluronic acid”), (“perioral” and “hyaluronic acid”), (“lip” and “poly-L-lactic acid”), (“perioral” and “poly-L-lactic acid”), (“lip” and “calcium hydroxylapatite”), (“perioral” and “calcium hydroxylapatite”), with a limit selected for works published before 2000. Our initial search identified 349 publications. The reference lists of articles that meet the first criteria were fully reviewed to identify useful articles that were not included in the initial electronic search.

Excluding studies not involving humans or discussing a different topic, and excluding studies discussing cleft lip, other lip pathologies, and lip rejuvenation techniques not using fillers further reduced the articles to 17.

### *Selection criteria*

The following inclusion criteria were used to select appropriate studies: 1) human patients; 2) lips without pathology; 3) lip augmentation techniques using fillers; 4) at least 5 patients in the study.

The exclusion criteria were as follows: 1) use of fillers for the nasolabial fold or marionette fold; 2) resurfacing, peeling, laser, botulinum toxin injection or tattoos; 3) languages other than English; 4) literature reviews, technical notes and letters to editors; 5) publications older than 2000.

### *Data extraction*

The following data were extracted from the full-text version of each selected study: year of publication, type of material used for filling, number of patients, subject of study assessment, efficacy of the filler procedure for lips rejuvenation.

## **Results**

Features of each single study are reported in Table 1.

### Dermal graft

Two studies on dermal grafts have been selected.

Rohrich et al.<sup>2</sup> have published in his work the results obtained in 2 years on a group of 47 patients who underwent treatment of volumetric increase of the lips by means of insertion of 94 grafts (Alloderm sheets). It shows a certain degree of satisfaction, with 53% of satisfied patients with the result and 71% of patients would repeat the procedure in the future.

Scalfani et al.<sup>3</sup> focused their study on rejuvenating the aging and atrophic lip comparing Cymetra (a suspension of particulate dermal matrix) with Zyplast (a glutaraldehyde cross-linked bovine collagen). To do this, they conducted a study on 44 patients treated with Cymetra (19 patients) or Zyplast (25 patients) and, from the results obtained at 12 months 85% of patients treated with Cymetra had an increased percentage of red lip in the midline

and 85% exhibited an increased vermilion height in the midline. Resulting with significantly more Cymetra-treated patients with improved lip aesthetics than those treated with Zyplast.

### Collagen

As to rejuvenation through collagen we find four works.

Landau<sup>4,5</sup> published two works, in 2008<sup>6</sup> and 2009<sup>4</sup>, which showed the qualities of an increase in the volume of the lips with collagen, and more specifically with Evolence Breeze and Dermicol P-35 (a collagen gel for soft-tissue cosmetic correction). In both works we found a high satisfaction of patients. Of the 15 patients (2008) who used Dermicol- P35 (Evolence Breeze) 86% considered the result "very good" or "good", and the same result was achieved by 86.6% of the 16 patients (2009) who received the same treatment.

De Boule et al.<sup>7</sup> have also conducted a study on the treatment of lips with Dermal P-35 and found a high satisfaction by patients. Specifically, 57 patients were treated, at 3 cosmetic clinics in Europe. Efficacy outcome measures included subjective impression of improvement by the clinic investigator who performed the injections, and subjective satisfaction of both the investigator and patient with treatment. As a result, 90% of clinicians were satisfied or very satisfied with the results; 94% of patients were satisfied or very satisfied; and 98% of patients had improved lip enhancement.

Downie et al.<sup>8</sup> compared four fillers, two porcine-collagen based (PRI 1 and PRI 2), one purified bovine collagen-based (Zyplast) and one hyaluronic acid-based (Perlane), for treatment of wrinkles in the upper lip line border. 19 patients were treated with PRI 1, 19 patients with PRI 2, 23 patients with Perlane, 18 patients with Zyplast for a total of 79 females. A double-blind clinical evaluation of lip augmentation was performed using mathematically-derived facial volume and shape measurements obtained by 3D stereophotogrammetry, and ratings of 2D images using the validated CKC scale. This scale contains five ordinal categories for the size of the lips, the vermilion body, and the vermilion border. All treatments produced larger, less wrinkled, more prominent lips. PRI 1, PRI 2 and Zyplast showed similar lip volume gains, with Perlane showing the greatest

upper lip volume increase. All treatments were comparable for rates of decrease in upper lip volume post-treatment, however, Perlane maintained higher lip volume gains at each time point.

### CaHA

Only 1 item on the rejuvenation of the lips with CaHA fillers, respected the inclusion and exclusion criteria of this review.

Jacovella et al.<sup>9</sup> using the CaHA filler Radiesse found 80% 'very good' and 20% 'good' results in a 3-point patient satisfaction survey at 18 months follow-up. Noticeably, the categories for this scale were 'very good', 'good', and 'acceptable', so poor outcomes could not be identified.

### Hyaluronic acid

Finally, hyaluronic acid fillers are probably the most important and vast section.

We have selected three works that evaluate the effectiveness of Restylane used for tissue augmentation, this kind of filler consisted of nonanimal stabilized hyaluronic Acid (NASHA), 20 mg / mL, in physiologic sodium chloride solution buffered to pH 7 in a gel form (250- $\mu$ m gel bead size and 100,000 U / mL) preloaded in 0.7-mL glass syringe with a Luer-Lok fitting.

Bosniak et al.<sup>10</sup> injected a total of 1446 consecutive patients (1029 women and 417 men) of commercially available non-animal stabilized hyaluronic acid (2242 treatments) for the enhancement of lip volume and contour and the reduction of visible facial rhytids. After 3 months, 87.88% of participants were satisfied or very satisfied with their treatment result. After 6 and 9 months, 72.73% and 60.67% of participants, respectively, were satisfied or very satisfied.

A mean patient satisfaction of 4.5 (out of 5) was reported by Jacono et al.<sup>11</sup> In his work a total of 137 NASHA treatments were performed on the lips of 66 patients (62 women and 4 men). After injection, patients were given a follow-up questionnaire that asked them to quantitate in 2-week intervals when their lips returned to pretreatment appearance, and

their satisfaction with the results in shape and size with the treatment without consideration for longevity on an integral scale of 1 (dissatisfied) to 5 (most satisfied).

Beer et al.,<sup>12</sup> to compare the safety and effectiveness of small particle hyaluronic acid plus lidocaine (SPHAL) versus no treatment for lip augmentation and perioral rhytides, randomized adults with thin or very thin lips (on the Medicis Lips Fullness Scale) to SPHAL or no treatment. In their results there was an evidence on that more patients were treated successfully with SPHAL (upper lip [80.2% vs 11.9%], lower lip [84.2% vs 18.4%], and upper and lower lips combined [76.1% vs 11.6%]), compared with no treatment. Furthermore, patients treated for both lip augmentation and perioral rhytides were rated as having an aesthetically meaningful improvement in perioral rhytides. Thus, concluding that small particle hyaluronic acid plus lidocaine was effective and well tolerated and significantly more effective when both lips and perioral rhytides were treated, we found improvement evident up to 6 months after treatment.

Most recent studies have suggested that positive results after Juvederm Volbella and Juvederm Ultra injection persist longer than after Restylane.

In 2012, Eccleston et al.<sup>13</sup> published results on about 60 subjects treated with Juvederm Volbella injectable gel in the perioral area, 59 of these subjects returned to the clinic at 1, 3, 6, 9, and 12 months for follow-up. By analyzing the questionnaires it finds that 94.6%, 93%, 90%, and 83% of patients reported overall satisfaction at 3, 6, 9, and 12 months after injection of JuvedermVolbella, using an 11-point non-validated scale.

Scarano et al.<sup>14</sup> reviewed the results of 46 cases undergone to lip augmentation and perioral rejuvenation in 1 year. In all patients both lips were treated with a cross-linked hyaluronic acid (ALIAZIN FL-LIPS IBSA-Lodi, Italy) injected in a single session and the aesthetic evaluation was performed at 3, 6, 9, and 12 months after injection. After 3 months, 87.88% of participants were satisfied or very satisfied with their treatment result. After 6, 9 and 12 months, 52.73%, 40.67% and 10.67% of participants, respectively, were satisfied or very satisfied.

Fagien et al.<sup>15</sup> evaluated the safety and effectiveness of Juvéderm Ultra injectable gel for lip enhancement and assessed the utility of 3 new lip-specific effectiveness scales. 50



patients received lip enhancement with Juvéderm Ultra injectable gel. The subjects were observed by the treating investigator and results were evaluated by a blinded independent rater and by subject self-assessment for up to 48 weeks to determine the durability of the effects. An 80% improvement in lip fullness scale at 12 weeks after the injection of Juvederm Ultra and a 56% improvement at 24 weeks was found. Patient satisfaction rates were 82% and 81% at 3 and 6 months, respectively.

Philipp-Dormston et al.<sup>16</sup> recorded the results from 2 centers. The study population included 62 subjects (30 from Center 1 and 32 from Center 2) who had been selected by the site physician, signed an informed consent form and underwent treatment with the hyaluronic acid dermal filler. Two end-points were analyzed, the primary endpoints defined were patient satisfaction with improvement in lips and satisfaction with the natural look and feel of lips immediately after injection and at the follow-up visit within 4 weeks post-treatment, the secondary endpoints were defined to provide a complete overview of subject and physician experience. For the primary endpoints, 83.6% of subjects were at the first visit Extremely Satisfied, Very Satisfied or Satisfied with the improvement in their lips which increased to 94.1% and 93.0% of subjects with/without top-up treatment at follow-up, respectively. After injection at first visit, 61.7% of subjects rated the look and feel of their lips as Extremely Natural or Very Natural, which increased to 75.0% and 93.0% of subjects with/without top-up treatment, respectively.

In 2015 Raspaldo et al.<sup>17</sup> randomized 280 subjects desiring lip enhancement to Juvéderm Volbella with Lidocaine or Restylane-L. The results showed that Juvéderm Volbella with Lidocaine was non-inferior to Restylane-L at 3 months, highlighting significant improvements in lip fullness, perioral lines, and oral commissures with Juvéderm Volbella with Lidocaine versus Restylane-L at months 6 to 12.

Similar Dayan et al.<sup>6</sup> randomized 213 subjects to the treatment group (n = 157) or concurrent no-treatment control group that received delayed treatment (n = 56), to assess safety and effectiveness of Juvéderm Ultra XC, a 24 mg/mL hyaluronic acid gel containing 0.3% (wt/wt) lidocaine (HYC-24L), for augmentation of the lips. An investigator's assessment of the subject's overall lip fullness (or fullness of the eligible lip) using the

validated Allergan 5-point Lip Fullness Scale was used to evaluate results. More than half of subjects (56.4%) maintained treatment response for 12 months, resulting safe and effective for aesthetic lip augmentation, with outcomes lasting up to 1 year.

A recent study by Fischer<sup>18</sup> in 2016 assessed the handling and outcome of lip augmentation of monophasic polydensified hyaluronic acid products with variable density, CPM-HAL1 (Belotero Balance Lidocaine, Merz Aesthetics, Raleigh, NC) and CPM-HAL2 (Belotero Intense Lidocaine, Merz Aesthetics, Raleigh, NC) for the perioral rejuvenation. A total of 146 patients from 21 German centers participated. Physicians rated natural outcome and evenness as good or very good for more than 95% of patients. Distribution, fluidity, handling, and malleability were assessed for both fillers as good or very good in more than 91% of patients. At every evaluation point, more than 93% of patients were very or very much satisfied with the product.

## Discussion

The first dermal injections for tissue augmentation were described in the late 19th century, Franz Neuber used autologous fat as a filler to correct facial depressions. Afterwards, Robert Gersuny introduced paraffin for tissue augmentation, paraffine fillers were the most common filler for several years until their high incidence with severe side effects was detected.

Towards the end of the last century numerous injectable dermal fillers were developed, which have evolved or disappeared over time.

Soft-tissue augmentation using acellular allograft dermis has also been described<sup>1</sup> for facial volume reconstruction. Acellular connective tissue matrix of human cadaver origin has been used in lip augmentation, either as sheets (Alloderm),<sup>2</sup> particulates or particulate form (Cymetra).<sup>3</sup>

Alloderm and Cymetra, are terminally sterilized, so they contain no infectious agents and they elicit no immunologic response from host tissue and they require no skin testing prior to use.<sup>19-21</sup>

In 1997, porcine type I collagen was introduced on the market and offered the advantages of a longer life after injection (ranging from 6 to 24 months) and there was no need to perform skin tests prior to use because of its high structural similarity to human collagen. Since 2010, no collagen fillers have been available in the US.

Currently, three dermal fillers, namely poly-L-lactic acid, calcium hydroxylapatite and hyaluronic acid are FDA approved to complete the rejuvenation of the lips and the perioral region.

Poly-L-lactic acid is currently used as soft tissue fillers. It is a biodegradable, reabsorbable polymer that belongs chemically to the alpha-hydroxy-acid group.

Injected poly-L-lactic acid hydrogel (Sculptra) induces a foreign body reaction, leading to local collagen production, dermal fibrosis, and substantial increase of subcutaneous tissue.<sup>22,23</sup> It has been used in the nasolabial folds of unhealthy individuals and in the medial cheek fat compartment in patients with HIV.<sup>24</sup> No studies in lip augmentation have been reported yet.

For more than 20 years CaHA has been used as a bio-compatible alloplast that induces the neo-formation of bone material. Therefore, it is widely used in dentistry as well as in reconstructive surgery as a filler substance to replace amputated bone material. Despite its application in surgery, CaHA was introduced by Thomas Tzikas<sup>25</sup> and Patrick Flaherty in 2004 for use in aesthetic medicine. This kind of filler is a subdermal implant composed of synthetic calcium hydroxylapatite (CaHA) microspheres suspended in a carrier of carboxymethylcellulose.<sup>26</sup> The gel structure dissipates *in vivo* and is subsequently replaced by soft-tissue, so that the CaHA remaining at the site of injection is surrounded by connective tissue. In several studies Calcium hydroxylapatite (Radiesse) has been used for lip rejuvenation, but a high rate of nodularity has been also found.<sup>9</sup>

Hyaluronic acid is an anionic, non-sulfated glycosaminoglycan comprising of repeating disaccharides of D-glucuronic and N-acetyl-D-glucosamine linked by beta-1,4-glycosidic bonds. Due to its highly viscoelastic and extremely hygroscopic properties Hyaluronic acid further acts as a ground and filling substance of the skin dermis and water retainer.<sup>27-30</sup>

Despite these general commonalities the various hyaluronic acid fillers differ in characteristics such as the concentration and degree of cross-linking, gel hardness, viscosity and concentration.

It was developed in 1989<sup>31,32</sup> and first used as a facial filler in the year 1995.<sup>33</sup>

The majority of hyaluronic acids used in cosmetic surgery is produced by fermentation of strains of the bacteria *Streptococcus equi*.

The dermal injection with hyaluronic acid is generally considered to be safe and the risk for severe side effects is low. However, very common side effects are bruising, pain and redness as well as tenderness, swelling and firmness. These side effects are usually of mild to moderate severity, related to the injection sites, and resolve spontaneously between 1 and 7 days post-injection.

Finally, also autologous dermal strips used in cosmetic or reconstructive facial volume rejuvenation have been described<sup>34</sup> but they have had a limited role due to donor-site morbidity, graft bulk, and the need for open-access incisions.

## Conclusions

The rejuvenation of the perioral region and lips has become a frequently performed treated issue in aesthetic medicine in the recent years.

Theoretically, autologous dermis grafts seem attractive because they replace “like with like,” but nowadays, it has not been possible to efficiently process injectable dermis. Furthermore, they have had a limited role due to donor-site morbidity, graft bulk, and the need for open-access incisions.

Many materials have been used, in the form of fillers, over the years but only three dermal fillers, namely poly-L-lactic acid, calcium hydroxylapatite and hyaluronic acid are FDA approved. For the perioral region, poly-L-lactic acid does not seem to be indicated, and the calcium hydroxylapatite is little used. Instead, the hyaluronic acid is mostly used for the rejuvenation of this area.

The use of hyaluronic acid fillers is supported by several advantages, including: high patient satisfaction, longer lasting overall effect, lower side effects and complications.

With the above considerations we conclude that hyaluronic acid filler has proven to be a reliable and predictable treatment for lip and perioral rejuvenation.

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TABLE 1 – Features of each study

AUTHOR	YEAR	PATIENTS	MATERIAL	TREATMENT	EVALUATION CRITERIA	RESULTS
			<b>DERMAL GRAFT</b>			
Rohrich et al.	2000	47 pt	Alloderm (94 graft)	Volumetric increase of the lips	<ul style="list-style-type: none"> <li>- overall satisfaction</li> <li>- desire to repeat treatment</li> <li>- discomfort</li> </ul>	<ul style="list-style-type: none"> <li>- 53% of satisfied patients</li> <li>- 71% of patient would repeat the procedure in the future</li> <li>- 23% of patient discomfort more than a week</li> </ul>
Scaflani et al.	2002	44 pt	Cymetra (19 pt)	Rejuvenating of aging and atrophic lip	<ul style="list-style-type: none"> <li>- change in vermillion (midline from baseline)</li> </ul>	<ul style="list-style-type: none"> <li>- 84% (Cymetra)</li> <li>- 39% (Zyplast)</li> </ul>

			Zyplast (25 pt)		- change in vermillion (height from baseline)  - change in vermillion (surface area from baseline)	- 84% (Cymetra) - 38% (Zyplast)  - 69% (Cymetra) - 33% (Zyplast)
			<b>COLLAGEN</b>			
Landau	2008  2009	15 pt  16 pt	Dermacol P53	Lip rejuvenation using a porcine collagen-derived filler	Patient satisfaction survey (3 point scale)	- 53% very good (2008) - 53,3% verygood (2009)  - 33% good (2008) - 33,3% good (2009)

						- 14% satisfactory (2008) -13,4% satisfactory (2009)
De Boulle et al.	2009	57 pt	DermaCol P53	Perioral correction with a ribose cross-linked collagen dermal filler	- improvement survey clinician  - satisfaction survey clinician  - satisfaction survey patient	- 98% improvements  - 90% satisfied results  - 94% satisfied results
Downie et al.	2009	79 pt	PR-1 (19 pt)  PR-2 (19 pt)	Treatment of the wrinkles in the upper lip line border	- average upper lip volume (3D stereophotogrammetry)  - upper lip size (2D	- Perlane (Significantly higher average in volume compared to the other group)

			Zyplast, (18 pt)  Perlane (23 pt)		analysis)  - lower vermillion body (2D analysis)  - upper vermillion border (2D analysis)	- Perlane (Largest average changes)  - Perlane / PR-1 (Longevity of effect compared to the other groups)  - Perlane (More longevity than PR-1)
			<b>CaHA</b>			
Jacovella et al.	2006	10 pt	Radiesse	Calcium hydroxylapatite as a facial soft-tissue filler for the perioral lines	Patient satisfaction survey (3 point scale)	- 80% of patients (very good satisfaction)  - 20% pf patients (good satisfaction)  - no patients unsatisfied

			HYALURONIC ACID			
Bosniak et al.	2004	1446 pt	Restylane	Nonanimal stabilized hyaluronic acid as an injectable filling agent for perioral rejuvenation	Patient satisfaction (3 point scale) at 3, 6 and 9 month follow up	<p>- 3 months: 87.88% of patients were satisfied or very satisfied</p> <p>- 6 months: 72.73% of patients were satisfied or very satisfied</p> <p>- 9 months: 60,67% of patients were satisfied or very satisfied</p>
Jacono	2008	66 pt	Restylane	Lip augmentation	Patient satisfaction (5 point scale)	4.5 $\pm$ 0,6
Beek et al.	2015	178 pt	Restylane (135pt)	Treatment for lip augmentation and perioral rhytides	MLFS and perioral rhytides were assessed using the 6-point Wrinkle Assessment	- 80,2% (SPHAL) vs 11,9% (no treated) good satisfaction upper lip

			No treated control group (43 pt)		Scale of Upper Lip Lines	<p>- 84,2% (SPHAL) vs 18,4% (no treated) good satisfaction lower lip</p> <p>- 76,1% (SPHAL) vs 11,6% (no treated) good satisfaction upper and lower lips</p>
Eccleston et al.	2012	60 pt	Juvederm Volbella	Perioral area rejuviantion	Overall satisfaction (11 point scale) at 3, 6, 9, 12 months follow up	<p>- 3 months: 94,6% of patients were satisfated</p> <p>-6 months: 93,2% of patients were satisfated</p> <p>- 9 months: 89,8% of patients were satisfated</p>

						- 12 months: 82,8% of patients were satisfied
Scarano et al.	2012	46 pt	Aliazin FL-LIPS	Perioral rejuvenation and lip augmentation	Aesthetic evaluation was at 3, 6, 9, and 12 months follow up	- 3 months: 87,88% of participants were satisfied or very satisfied  - 6 months: 52,73% of participants were satisfied or very satisfied  - 9 months: 40,67% of participants were satisfied or very satisfied  - 12 months: 10,67% of participants were satisfied or very satisfied
Fagien et al.	2013	50 pt	Juvederm Ultra	Lip enhancement	- Lip fullness improvement (4 point	- 12 week: 80% improvement in lip fullness scale



					<p>scale) at 12 and 24 weeks follow up</p> <p>- Patient satisfaction (11 point scale) at 3 and 6 months follow up</p>	<p>- 24 weeks: 56% improvement in lip fullness scale</p> <p>- 3 months: 82% of patient satisfied</p> <p>- 6 months: 81% of patient satisfied</p>
Philipp-Dormston et al.	2014	62 pt	Juvederm Volbella	Three-dimensionally restoring of the lips and perioral area	<p>Patient satisfaction with improvement in lips and satisfaction with the natural look</p>	<p>- 83,6% of patient were at the first visit extremely/very satisfied</p> <p>&gt; 94,1% of patient with top-up treatment were at follow-up extremely/very satisfied</p> <p>&gt; 93% of patient without top-up treatment were at the first visit extremely/very satisfied</p> <p>- 61,7% of subjects rated their lips as</p>

						<p>extremely/very natural</p> <p>&gt; 75% of subjects with top-up treatment were at follow-up extremely/very natural</p> <p>&gt; 93% of subjects without top-up treatment were at follow-up extremely/very natural</p>
Raspaldo et al.	2015	280 pt	<p>Juvederm Volbella (139 pt)</p> <p>Restylane-L (142 pt)</p>	<p>Lip volume enhancement and perioral rejuvenation</p>	<p>- Lip fullness (5 point scale) at 3 months follow up</p> <p>- Perioral lines (4 point scale) at 3 months follow up</p>	<p>- Lip fullness responder rates, based on subject assessments, were significantly greater with Juvéderm Volbella with Lidocaine versus Restylane-L 73.8% vs 59.8%</p> <p>- Both treatments reduced the severity of perioral lines (47,6% vs 44,9%) and oral commissures (31,8%</p>

					- Oral commissures (4 point scale) at 3 months follow up	vs 30,4%)
Dayan et al.	2015	213 pt	Juvederm Ultra XC (157 pt)  No treated control group (56 pt)	Lip augmentation at 12 months follow up	Subject's overall lip fullness (5 point scale)	More than half of subjects (56.4%) maintained treatment response for 12 months with results lasting up to 1 year
Fischer et al.	2016	146 pt	CPM-HAL1  CPM-HAL2	Lip rejuvenation with a monophasic polydensified hyaluronic acid filler	- Natural outcome and evenness	- 95% of patients rate natural outcome and evenness as good or very good  - 91% of patients assessed

					- Distribution, fluidity, handling, and malleability	distribution, fluidity, handling, and malleability for both fillers as good or very good
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