Efficacy and Safety of Cross-Linked Carboxymethylcellulose Filler for Rejuvenation of the Lower Face: A 6-Month Prospective Open-Label Study

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BACKGROUND Cross-linked carboxymethylcellulose (CMC) filler is a biosynthetic filler with very low antigenic risk.

OBJECTIVE To assess the efficacy and safety of CMC filler in the rejuvenation of the lower face.

MATERIALS AND METHODS Two hundred eighty-seven procedures were performed in 174 patients: 115 nasolabial folds, 86 marionette lines, 29 bar codes, 14 cheek rhytides, and 43 lip rejuvenations. Results were evaluated at 3 (T1) and 6 months (T2) with photographic evaluation, Global Aesthetic Improvement Scale (GAIS), Modified Fitzpatrick Wrinkle Scale (MFWS) for nasolabial folds, Marionette Lines Grading Scale (MLGS), and Medicis Lip Fullness Scale (LFS).

RESULTS GAIS was ≥2 in >91.05% of patients both in T1 and T2. MFWS score significantly improved at T1 (86.9% class ≤1, $p < .001$) and T2 (82.6% class ≤1, $p < .001$); in all patients in T1 and T2, median amelioration of MLGS was 2 ± 1 and there was a significant amelioration of at least 1 grade in LSF in both upper and lower lips.

CONCLUSION The use of CMC filler resulted in a significant and satisfactory amelioration of lower face aging signs with very low incidence of adverse events. Therefore, it should be considered a valid alternative to cross-linked hyaluronic acid fillers.

The authors have indicated no significant interest with commercial supporters.

In Europe and United States, aesthetic medicine is on the rise and injectable fillers are one of the cornerstones of treatment of aging signs. The first use of heterologous implant of paraffin in humans was reported in 1889 and the use of liquid silicone started in late 1960s.[1,2] Since then, many dermal fillers have been used for reducing facial skin lines and wrinkles and for providing lip augmentation and hyaluronic acid (HA) is one of the most widely used agents.[3,4] In 2003, the first hyaluronic acid filler was approved by the FDA in the United States for soft tissue augmentation and since then its use has increased by 70%. Although HA fillers are nontoxic and nonimmunogenic, hypersensitivity and granulomatous foreign body reaction have been reported.[5] Carboxymethylcellulose (CMC) is a biosynthetic substance used in food science as a viscosity modifier or thickener already present in some dermal fillers as carrier or filling.[6,7] The nonanimal, nonbacterial nature of CMC confers to this product's unique properties.[8–10] Since 2012, CMC hydrogel cross-linked by 1,4-butanediol diglycidyl ether (BDDE) has been approved for tissue augmentation and wrinkles correction.[11] The aim of the present study was to prospectively evaluate the efficacy and safety of the use of CMC for the correction of aging signs of the lower face.

Materials and Methods

All patients who had clinical evidences of moderate or severe nasolabial folds (Zone 1), marionette lines (Zone 2), bar code (Zone 3), moderate-to-severe cheek

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rhytides (Zone 4), or loss of lips fullness (Zone 5) were prospectively enrolled in the study over a period of 6 months. Exclusion criteria were: pregnancy, breast-feeding, age <18 years, ongoing anticoagulant or antiplatelet therapy, previous radiotherapy or burn scars in the region of treatment, ongoing local infections or inflammations, and use of injectable fillers in the previous 6 months or previous use of permanent fillers at any time. All patients gave their written informed consent and agree to refrain from using other aesthetic procedures for the period of the study and were followed up for 6 months after the procedure. Skin type was classified according to Fitzpatrick skin type classification.

An eutectic mixture of lidocaine 15% was applied at least 30 minutes before the injection using an occlusive dressing. The procedures were preceded by asepsis with 70% alcohol solution.

CMC filler was injected in the mid-deep dermis through a sharp needle packaged with the syringe. Needles were sized relative to the cross-linking and concentration of the filler. Lower cross-linked CMC filler was injected through smaller bore needle (30 gauge), whereas higher cross-linked CMC fillers required a 27-gauge needle. After insertion through the skin, the bevel was positioned downward so as to minimize unwanted deposition of the filler in a more superficial plane. Based on the area being treated, one or more of several different techniques were employed for proper placement of CMC filler.

Nasolabial folds were treated with linear threading technique. In cases where a particular deep fold was present, layering the parallel lines was used to achieve the desired results. In order to effectively efface this area, the needle was placed medial to the fold. If placed within the deepest aspect of the fold or more laterally, there is a high likelihood of further deepening upon injection. The needle was typically inserted at the inferior border of the fold and advanced superiorly toward the alar facial junction. In many patients, the superior aspect of the fold required a layered injection because of more volume deficiency in this area.

Marionette lines were done with linear threading or serial puncture technique. The injection plane was deep dermal. In many cases, there was not only a deep line extending from the commissure but also loss of volume in the surrounding area. In these cases, a cross-hatching technique was used to add more volume.

Bar code was mostly treated with serial puncture technique followed by a post-treatment massage to blend the filler. Some patients had very shallow wrinkles visible only during the contraction of the oris muscle: in these patients, bar code was corrected with cross-hatching technique. Cheek rhytides were treated with a radial fanning technique using a very tiny amount of filler.

Lip enhancement in the younger population involves straightforward volume enhancement. Injection was typically done with a linear threading or serial puncture technique, proceeding from medial to lateral. Lip enhancement in the more senescent population typically requires submucosal injection along the entire length of the lip with serial puncture or linear threading technique rather than just the central aspect. In this study, a tiny amount of CMC filler was injected to add more volume in the vermillion in order to stretch the vertical lip lines as they extend from the mucosal lip resulting in decreased visibility.

Before and after treatment, photographs were taken in the same light conditions with a high-resolution 14 megapixel camera. The subjects rated the global improvement for every procedure with separation between upper and lower lip at the 3-month (T1) and at 6-month (T2) follow-up visit according to the Global Aesthetic Improvement Scale (GAIS) ranging from very much improved,[3] much improved,[2] improved,[1] no change (0), worse (−1), much worse (−2), to very much worse (−3).

Moreover, validated objective scales were used, at the same time points, to evaluate correction of nasolabial folds, marionette lines, and lip fullness. The 7-point Modified Fitzpatrick Wrinkle Scale (MFWS) was used to quantify the nasolabial folds severity: no wrinkle (Class 0), very shallow wrinkle (0, 5), fine wrinkle,[1]

wrinkle less than 1 mm depth,[1,5] moderate wrinkle with 1 to 2 mm depth,[2] prominent wrinkle 2 to 3 mm depth,[2,5] and deep wrinkle more than 3 mm depth.[3,12] Marionette Lines Grading Scale (MLGS) with photoguide was used to classify severity of marionette lines in 5 scores: no visible folds (0), shallow but visible folds with slight indentation,[1] moderately deep folds − clear feature at normal appearance but not when stretched,[2] very long and deep folds − prominent facial feature,[3] and extremely long and deep folds − detrimental facial appearance.[4,13]

Medicis Lip Fullness Scale (MLFS) with photoguide was applied separating upper and lower lip and divided in 5-point scale the lip appearance ranging from very thin,[1] thin,[2] medium,[3] full,[4] to very full.[5,14]

To avoid the nonoptimal agreement between in-person and photographic assessments, the MFWS, MLGS, and MLFS were applied exclusively on photographic documentation and 2 independent investigators (one expert and one nonexpert) blinded to the treatment reviewed the photographs and gave their scores. Finally, MFWS, MLGS, and MLFS scores were given as mean of the 3 observers' evaluations. Adverse events were recorded immediately after the treatments and at every time (T1 and T2) of follow-up.

Statistical Analysis

Qualitative data were described using frequencies and percentages. Quantitative data were described using median values and interquartile ranges (IQR). In comparison with different subgroups, quantitative variables were handled by using Student or Wilcoxon rank-sums tests, and categorical variables using χ^2 or Fisher exact tests or Friedman test for correlated nonparametric categorical variables as appropriate. Statistical significance was set at $p < .05$. The calculations were performed with the JMP package (1989–2003 SAS Institute Inc.).

Agreement between observers was analyzed by calculating the overall proportion of observed agreement (the sum of the ratings in complete agreement divided by the total number of observations). Agreement was also measured using the k coefficient, which express the degree of agreement among 2 different sets of observations between 2 observers. To assess agreement between raters, pairwise weighted k coefficients were calculated for MFWS and MLFS.

Results

Between June 2013 and December 2013, 174 participants were prospectively enrolled and 287 procedures were performed. Study population comprehended 165 females and 9 males with median age was 52 ± 13. Sixty-nine percent of patients had Fitzpatrick skin Type 3, followed by 21% of Type 2, 9% of Type 4%, and 1% of Type 1.

One hundred fifteen patients underwent correction of nasolabial folds; before the procedure, 88/115 (76%) were classified in MFWS ≥1.5. Eighty-six patients had treatment of marionette lines: 75% of them (67/86) were Class 3 or 4 in MLGS before treatment. Twenty-nine had treatment of bar code, 14 had correction of cheek rhytides, and 43 had lip enhancement. In this last group, before the procedure, median LFS class was 3 ± 1 in both upper and lower lip. Thirty-five among 43 patients (81%) were in Classes 2 or 3 for superior lip and 37/43 (86%) were classified as classes between 1 and 3 for inferior lip.

The injected volume depended on the severity of the aging sign and was different for each treated zone (Table 1). The mean volume injected to achieve a significant improvement in the nasolabial folds was 0.5 mL (range 0.3–1 mL) per side (Figure 1) and 0.3 mL (range 0.2–0.5 mL) per side to correct marionette lines (Figure 2). The mean volume injected into the bar code was 0.3 mL (range 0.2–0.4 mL) of filler (Figure 3). Cheek wrinkles were injected with 0.2 mL (range 0.2–0.6 mL) of filler per side (Figure 4). A total of 0.5 (range 0.3–1 mL) and 0.3 (range 0.2–0.8 mL) volume were sufficient to achieve the desired lip size and shape in young and older patients, respectively (Figure 5).

Three months after the treatment (T1), all patients self-reported a significant improvement, being GAIS ≥2 in 92% of the subjects. This amelioration

TABLE 1. Injected Volume by Treatment Zone

Zone	No. Procedures	Mean Volume and Range Per Side, mL
Nasolabial folds	115	0.5 (0.3–1)
Marionette lines	86	0.3 (0.2–0.5)
Bar code	29	0.3 (0.2–0.4)
Cheek rhytides	14	0.2 (0.2–0.6)
Lip rejuvenation	43	
Subjects <40 yrs		0.5 (0.3–1)
Subjects >40 yrs		0.3 (0.2–0.8)

remained constant at 6 months with 90.1% of patients with GAIS ≥2. Percentage of patients in different classes of GAIS at T1 (3 months) and T2 (6 months) is represented in Figure 6. There was no statistical difference in the perceived satisfaction between zone 1, 2, 3, and 4.

Patients who underwent lip enhancement reported satisfaction of the procedure with GAIS ≥2 in 93% of patients both at T1 and T2 for upper lip and in 93% at T1 and 95% at T2 for lower lip. Percentage of patients in different classes is represented in Figure 7.

The initial median MLFS significantly (Zone 5) increased from 3 ± 1 to 4 ± 1 for both upper and lower lip ($p < .001$) at both T1 and T2 without significant loss of fullness at the last follow-up of the study (Figure 8). All patients had increased of at least 1 point of the scale at T1 and 85% of patients in T2 (Figure 8).

Median MFWS of 2 ± 1 (Zone 1) increased after procedure at T1 to 0.5 ± 1 ($p < .001$) and 0.5 ± 0.5 at T2 ($p < .001$), being stable over 6 months (Figure 9). After treatment number of patients with MFWS >1.5 increased from 29/115 (25%) to 100/115 (86.9%) were classified in MFWS <1.5 at T1 and 95/115 (82.6%) ($p < .001$) (Figure 9).

Marionette Lines Grading Scale at T1 and at T2 respectively score 0 to 1 in 61% procedures (54/86) and in 53% (47/86) ($p < .001$). Median grade of amelioration of MLGS was 2 ± 1 and 87% of procedures classified as 0 to 1 at T1 maintained the same score at T2.

Interobserver agreement weighted k for MLFS was 0.82 between injector and expert independent reviewer and 0.74 between injector and nonexpert independent reviewer and 0.76 between the nonexpert independent reviewer and the expert independent reviewer. Interobserver agreement weighted k for MFWS was 0.82 between injector and expert independent reviewer and 0.74 between injector and nonexpert independent reviewer and 0.77 between the nonexpert independent reviewer and the expert independent reviewer. K value of MLGS was 0.85 between injector and expert reviewer and 0.83 between inject and the nonexpert reviewer.

Only 14 treatments result in adverse events that were all small ecchymosis immediately after treatment which disappeared in 24 to 36 hours. No local erythema or edema was recorded immediately after procedure. During the follow-up, there was no appearance of nodules, infections, migrations, or Tyndall effect.

Discussion

The ideal filler should be efficacious in reducing wrinkles and plumping the tissues without looking unnatural, be easy and safe to introduce into the tissues, have a long duration of action, be relatively inert, and not incite a painful or bulky tissue response.[4,15]

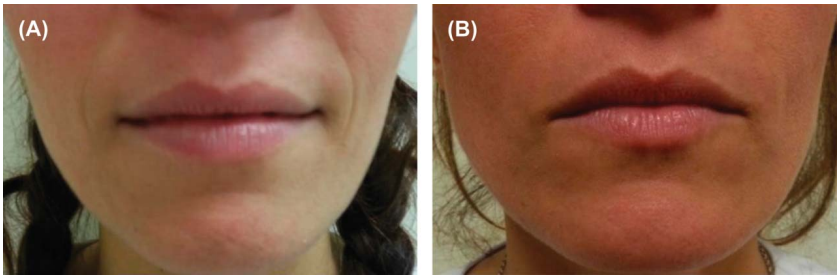

Figure 1. (A and B) correction of nasolabial folds: pretreatment MFWS Class 2 (A) and at 6 months Class 0 (B).

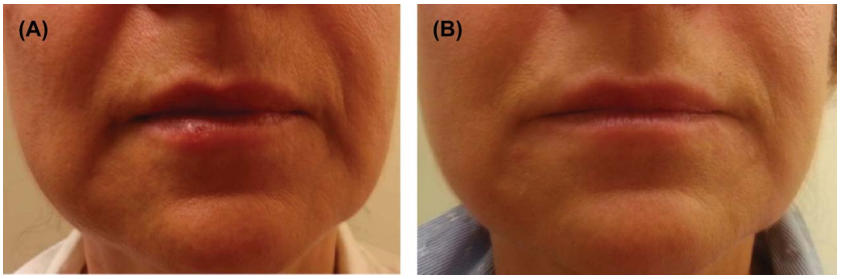

Figure 2. Marionette lines: before treatment MLGS Score 3 (A) and at 6 months Score 1 (B).

Nonpermanent or degradable fillers are made up of naturally occurring biological agents such as collagen or hyaluronic acid that undergo degradation at variable rates.[4] Collagen dermal fillers are available in the form of bovine collagen and human-based collagen.[16] HA is a nonsulfated glycosaminoglycan polysaccharide, which is a natural component of the extracellular matrix in all animal tissues produced by mesenchymal cells without specificity of species; as such, there is no risk for immunogenicity and it is nontoxic and biocompatible. It is highly hydrophilic and this property helps it to retain water and occupy larger volumes relative to its mass.[17,18]

HA fillers may be obtained from both animal and nonanimal sources, and at the beginning of its aesthetic clinical use, there were 2 main commercial forms of HA: Hyaloform (Biomatrix, Ridgefield, NJ), derived from rooster combs, no longer used nowadays, and Restylane (Q Med, Uppsala, Sweden), which is produced by microbiologic engineering techniques (generated by streptococcus equi).[19] This latter product is more resistant to early degradation by hyaluronidase and rendered more water insoluble because of cross-linkage. As novelty, since 2006, CMC has been used as main component of filler to correct wrinkles. First, the CMC was used in the non–cross-linked free form combined with polyethylene oxide (Laresse, FzioMed Inc., San Luis Obispo, CA) and showed good efficacy and safety with long-lasting results. From 2012, CMC has then been marketed a single component as cross-linked filler. In this study, for the first time, we prospectively evaluated efficacy and safety of CMC filler for the correction of aging signs of the third lower face in a wide cohort of patients.

All patients experienced a very high rate of satisfaction of treated regions at 3 months, which persisted at a very high rate at 6 months with more than 80% have high and very high satisfaction with the procedure independently from the treated region. This rate of satisfaction was even higher in the lip enhancement group. These results compare favorably with those of HA and to Restylane in a Brazilian study of 1,446 consecutive patients treated in up to 4 areas of the face.[20]

Of the 685 patients who received Restylane for lip augmentation, 77.8%, 50.8%, and 36.6% were satisfied at 3, 6 and 9 months, respectively. Moreover, in a systematic review, response rate for the GAIS ranged from 73% to 90% for small and as low as 64% for large-gel-particle HA.[21]

Cross-linked reversible CMC filler demonstrated a very good safety profile, with only 5% of ecchymosis immediately after the procedure, in keeping

Figure 3. Treatment of bar code: before (A) and at 6 months (B).

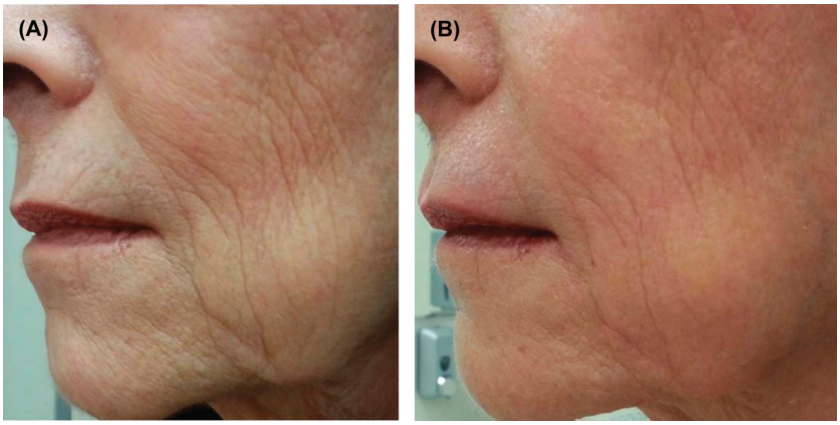

Figure 4. Cheek rhytides: before (A) and at 6 months (B).

with the previous studies by Leonardis et al.[11,22] This percentage of collateral effect seems lower than that reported with HA.[23,24] Postmarketing 5-year analysis with HA by FDA described 930 adverse events being inflammation, allergy, and infection within the first 5 causes.[25] The lack of allergic reactions to CMC can be due to the nonbacterial, nonanimal nature of this filler; moreover, this characteristic can be responsible to the very low total number of adverse events with this filler along with the absence of some peculiar effects of HA such as bluish discoloration. CMC has also antibacterial properties and no episodes of infections have been reported up to know although the commercialization of the product is recent.

Delayed adverse reactions of HA include hypersensitivity and granulomatous foreign body reaction that occur in up to 0.6% of cases[26,27] likely due to the reactivity of some patients to the protein residues of bacterial or avian origin or impurities and residual 1,4-butanediol diglycidyl ether (BDDE) from the cross-linking process. Up to now, few cases of hypersensitivity and foreign body reaction have been documented within 6 to 24 months from implantation.[28,29]

If nodules of CMC had appeared during the follow-up, they would have been treated by cellulase, an enzyme absent in humans, which cleaves the beta 1,4-glycosidic bonds along the cellulosic backbone.

Cellulase has been shown to be safe and to dissolve the cross-linked CMC filler in the dermis in 2 days since its injection.[30] Moreover, the ability of cellulase to degrade redox-polymerized CMC hydrogels was investigated by another paper by monitoring the degree and rate of degradation of 2% and 4% gels over 72 hours in the presence of 0.02 U mL–1 cellulase solution. The 2% hydrogels completely degraded within 2 hours. In contrast, the 4% hydrogels gradually lost structure over time with complete degradation observed at 72 hours.[31]

The galenic cellulase is prepared from Celluplast, which is cold sterilized and diluted at concentration of 35

Figure 5. Lip rejuvenation: pretreatment MLFS Grade 3 (A) and at 6 months Grade 4 (B).

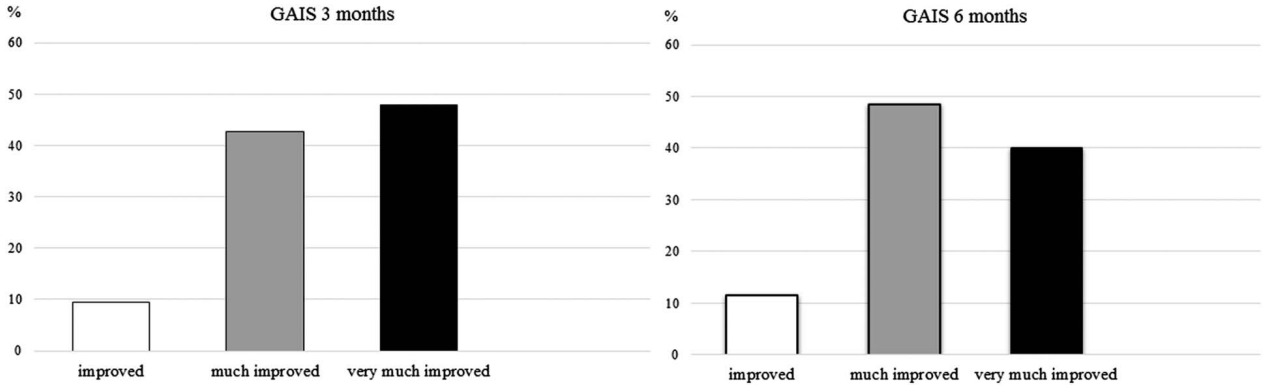

Figure 6. Global aesthetic improvement scale at 3 and 6 months for evaluation of nasolabial folds, marionette lines, bar code, and cheek rhytides.

UI/mL in physiological solution. It can be injected through a 30-gauge needle directly in the implanted filler in the dermis. The absence of cellulose in humans eliminates the risk of cellulase enzymatic action on native tissue at the injection site, nevertheless in vivo testing is necessary.

Another peculiarity of CMC may be the nature of the synthetic polymer that is characterized by a very low concentration of residual BDDE[32] which is lower than 0.5 PPM in all the 3 forms of cross-linked CMC, compared to 1 to 2 PPM of hyaluronic acids. Despite BDDE has been recently discussed to be completely broken

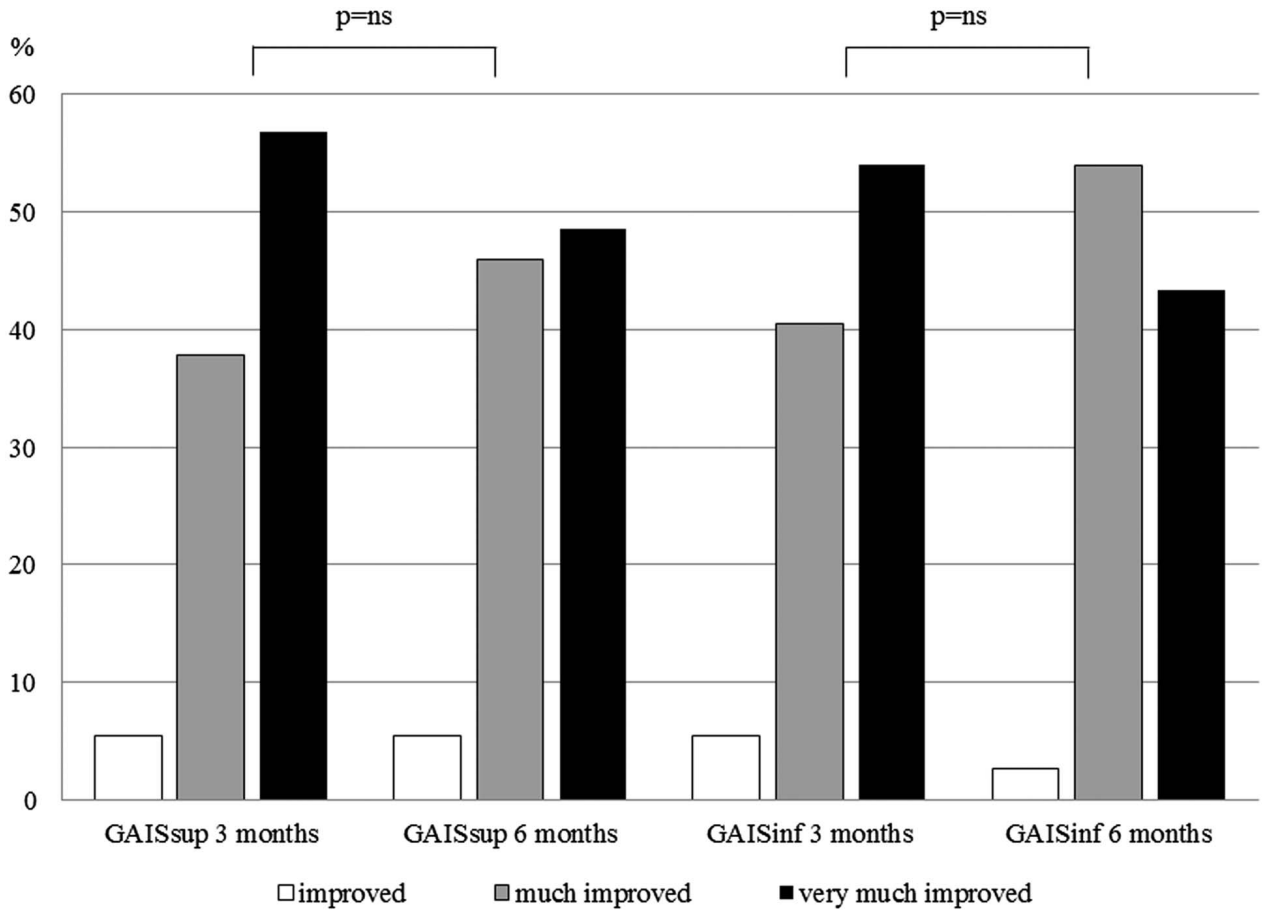

Figure 7. Global aesthetic improvement scale at 3 and 6 months for evaluation of upper (left) and lower (right) lip rejuvenation.

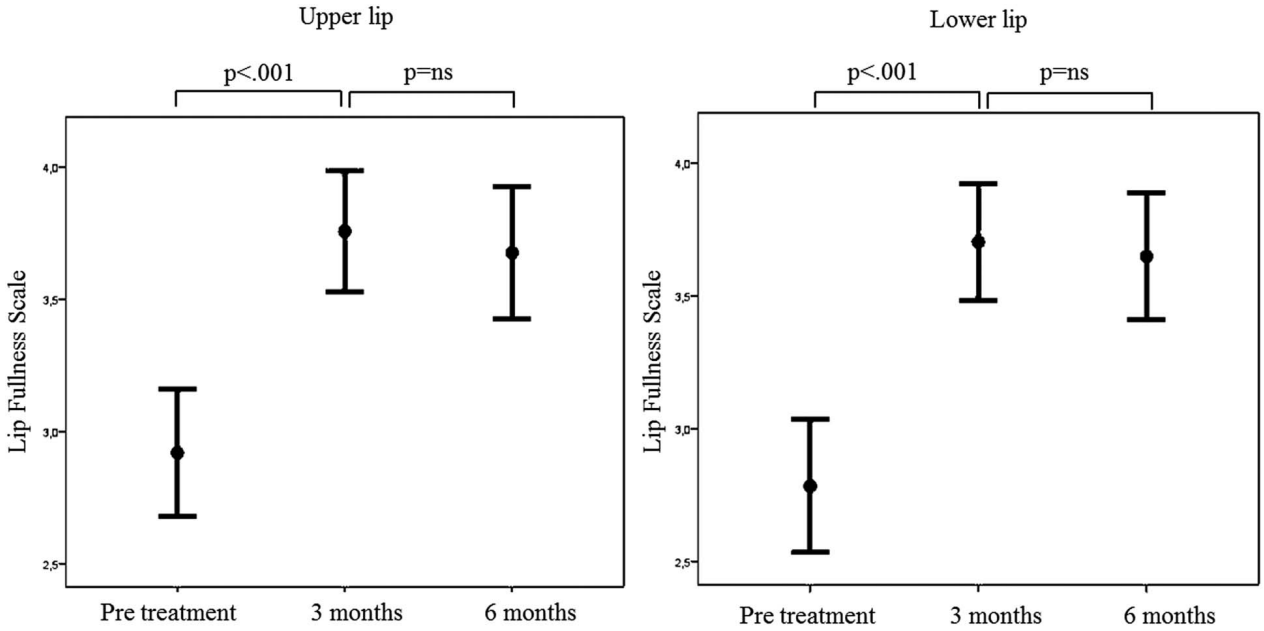

Figure 8. Medicis lip fullness scale for upper and lower lip pretreatment at 3 and 6 months.

down into biodegradable products, it has an intrinsic carcinogenic risk although consider minimal.[33,34]

The limitation of this study is the open label nature; however, to try to overcome the obvious possible bias, independent reviewers were enrolled and they have been blinded to the treatments when giving the scores of MFWS, MLGS, and MLFS according to photographs. The injector evaluated the results of the procedures on photographs as well to avoid the low interobserver agreement with $K < 0.6$ described in the validation of the MFWS.[13]

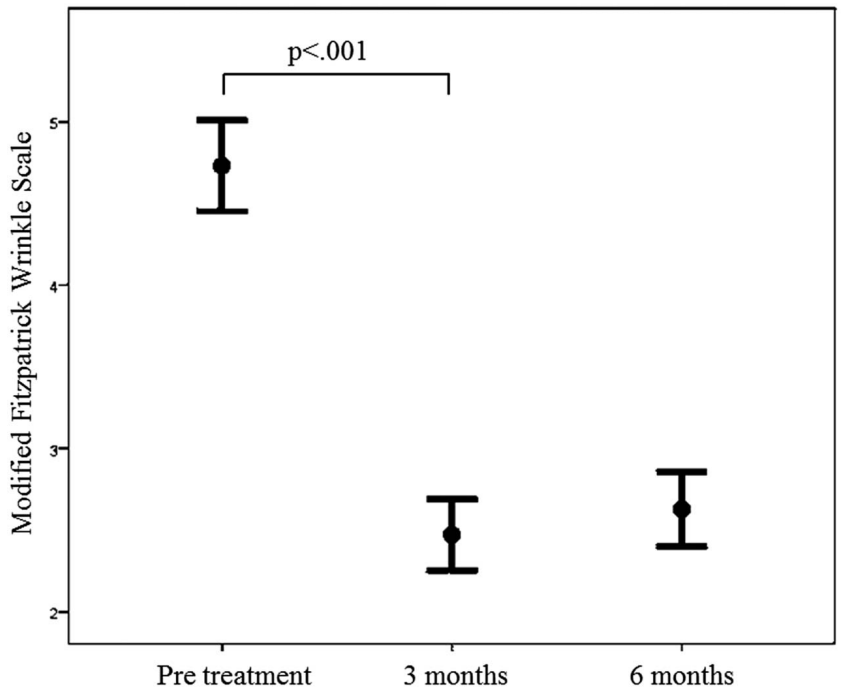

Figure 9. Modified Fitzpatrick wrinkle scale pretreatment, at 3 and 6 months.

In conclusion, CMC filler has been demonstrated in this cohort of patients to be very effective in the correction of aging signs of the lower face with a very high rate of satisfaction and good safety profile. Therefore, cross-linked CMC filler can be a promising candidate to be used by professionals in their everyday clinical practice.

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