ABSTRACT

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

Materials and methods: 154 procedures were performed in 73 patients: 63 nasolabial folds, 39 marionette lines, 16 bar codes, 9 cheek rhytides and 27 lip rejuvenations. All patients were evaluated immediately after the procedure (T1) and at 3 months (T2) with photographic evaluation, Global Aesthetic Improvement Scale (GAIS), Modified Fitzpatrick Wrinkle Scale (MFWS) for nasolabial folds and Medicis Lip Fullness Scale (LFS) for lips. Side effects were recorded.

Results: GAIS was significantly satisfactory in all patients in both T1 and T2, as it was ≥ 2 in 70%. Before treatment, MFWS was class 1.5 or 2 in 41/63 and significantly improved in both T1 and T2 (class ≤ 1 in 53/63 and 49/63 respectively, p < 0.001). Treatment of lips produced an improvement ≥ 1 grade of MLFS in all cases in T1 and in 25/27 cases in T2 (p < 0.001). 11 cases of ecchymosis were recorded after the procedures, no local oedema, erythema or nodules.

Conclusions: The use of CMC filler resulted in a significant and satisfactory amelioration of lower face aging signs with very low incidence of adverse events.

Keywords
Cross-linked carboxymethylcellulose, tissue augmentation, lip augmentation, efficacy, safety

Correspondence
Maria Cristina D’Aloiso, Superior Postgraduate School of Aesthetic Medicine of Sapienza University of Rome, Padua, Italy.
E-mail: cristina.daloiso@gmail.com

Accepted for publication 29 January 2015

© 2015 Editrice Salus Internazionale srl
Introduction

In Europe and the United States, aesthetic medicine is on the rise, and injectable fillers are one of the cornerstones of the treatment of signs of aging. The first heterologous human implant of paraffin was performed in 1889 and the use of liquid silicone started in the late 1960s1,2. Since then many dermal fillers have been employed to reduce facial wrinkles and to enhance lip volume. Hyaluronic acid (HA) is one of the most widely used3-4.

In 2003 the first HA filler was approved in the US by the FDA for correction of soft tissue, and since then its use has grown by 70%. Although HA fillers are non-toxic and non-immunogenic, hypersensitive reactions and foreign body granulomatous reactions have been reported5.

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 thickener already present in some dermal fillers6-7.

The non-bacterial, non-animal origin of CMC and its anti-inflammatory activity confer unique properties on this product8,9,10.

Since 2012 a transparent CMC hydrogel crosslinked by 1,4-butanediol diglycidyl ether (BDDE) has been approved for soft tissue augmentation and wrinkle correction11.

The aim of the present study was to prospectively evaluate the efficacy and safety of cross-linked CMC filler for rejuvenation of the lower face.

Materials and Methods

All patients with moderate to severe nasolabial folds (zone 1), marionette lines (zone 2), bar code (zone 3), cheek rhytides (zone 4) or loss of lip volume (zone 5) were enrolled in this study for a 3-month period.

Exclusion criteria were pregnancy or breastfeeding, age under 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 during the previous 6 months or previous use of permanent fillers at any time. All patients gave their written informed consent and agree to avoid to undergo other aesthetic procedures in the treated area for the period of the study.

Procedures were preceded by asepsis with 70% alcoholic solution. A conservative approach was performed to avoid hypercorrection.

CMC filler was injected in the mid-deep dermis with the needle packed with the syringe. CMC filler was injected in the mid-deep dermis through a sharp needle packaged with the syringe. Needles were sized relative to the crosslinking and concentration of the filler. As CMC can be cross_linked by varying pH, temperature, concentration and BDDE concentration, three formulations of CMC filler differing in degree of crosslinking and concentration of CMC were used. Lower cross-linked CMC filler was injected through a smaller bore needle (30 gauge) whereas higher cross-linked CMC fillers required a 27 gauge needle.

Nasolabial folds (zone 1) were treated with a linear threading technique. The needle was typically inserted at the inferior border of the fold and advanced superiorly toward the alar-facial junction. When the fold was very deep, two layering parallel lines were injected.

Marionette lines (zone 2) were treated by a linear or serial puncture technique with injection in the deep dermis. When loss of volume was found in the area surrounding labial commissures, a cross-hatching technique was performed to restore volume in this area.

Bar code (zone 3) was treated by a serial puncture technique followed by a massage to precisely distribute the filler. Some patients had a very superficial bar code, only visible during the contraction of orbicular muscle: in these cases injection was deep in the dermis.

Cheek rhytides were treated with a fan technique with a very tiny amount of filler.

Lip treatment (zone 5) in young patients is often related to volume enhancement of this region: a linear technique was performed, or serial puncture from medial parts to lateral.

In the older population lip rejuvenation was performed: contour redefinition with Paris lip technique and restoration of the normal anatomy of labial commissures. A minimal volume was used in order to maintain a natural appearance of the area.

Before and after pictures of all patients were taken in the same lighting conditions with a 14 megapixel photocamera.

Patients were evaluated for amelioration of every treated area, with a separate evaluation for upper and lower lip, with the Global Aesthetic Improvement Scale (GAIS) giving a score of very much improved (+3), much improved (+2), improved (+1), no change (0), worse (-1), much worse (-2) or very much worse (-3).

Validated scales were used to evaluate nasolabial folds and lips. The Medicis Lip Fullness Scale (MLFS) with photoguide was applied separately for upper and lower lip, with a 5-point score for lip volume: very thin (1), thin (2), medium (3), full (4) and very full (5)12.

The Modified Fitzpatrick Wrinkle Scale (MFWS) was used to quantify depth of nasolabial folds: no wrinkle (class 0), very shallow wrinkle (class 0.5), shallow wrinkle (class 1), wrinkle less than 1 mm
deep (class 1.5), wrinkle 1-2 mm deep (class 2), wrinkle 2-3 mm deep (class 2.5), or wrinkle more than 3 mm deep (class 3)\(^1\).

To avoid non-optimal concordance between photographic evaluation and \textit{in vivo} evaluation, MFWS and MLFS were uniquely applied to the analysis of photographic documents.

Adverse events (oedema, erythema, ecchymosis and nodules) were recorded immediately after the procedure (T1) and at 3 months (T2).

**Statistical Analysis**

Qualitative data were described using frequencies and percentages. Quantitative data were described using median values and interquartile ranges (IQR). In the comparison among different subgroups, quantitative variables were handled by using Student’s or Wilcoxon Rank Sums tests, and categorical variables using \(\chi^2\) or Fisher’s exact tests or Friedman’s test for correlated non-parametric categorical variables as appropriate. Statistical significance was set at \(p < 0.05\). The calculations were performed with the JMP package (1989–2003 SAS Institute Inc.).

**Results**

Between June and September 2013, 73 patients were prospectively enrolled and 154 procedures were performed. The study population comprised 70 females and 3 males, whose median age was 54 ± 11.

63 patients underwent correction of nasolabial folds (zone 1) (figure A). 39 patients had treatment of marionette lines (zone 2) (figure B), 16 bar code (zone 3) (figure C), 9 cheek rhytides (zone 4) (figure D) and 27 lips (zone 5) (figure E).

Three months after the treatment (T2) all patients self-reported a significant improvement, being GAIS ≥ 2 in 92% of the subjects in zone 1, 2, 3 and 4.

GAIS was ≥ 2 at T1 and T2 for upper lip in 91% of patients and GAIS was ≥ 2 in 93% of patients at T1 and 91% of patients at T2 for lower lip.

Before the procedure, the median MLFS was 3 ± 1 for upper and lower lip; after the procedure it was 3 ± 1 and 4 ± 1 at T1 and T2. 21 out of 27 patients (77.8%) were classified as class 2 and 3 for upper lip and 18 out of 27 (66.7%) were between class 1 and 3 for lower lip. Lip correction produced an amelioration of ≥ 1 grade in all cases in T1 and in 25 out of 27 cases (92.6%) in T2 (\(p < 0.001\)).

Immediately after the procedure 11 cases of ecchymosis were recorded which lasted up to 24-36 hours. No local oedema or erythema after the procedure. No nodules, infections, migration or Tyndall effect were reported during the follow-up.
The ideal filler should be efficacious in reducing wrinkles and plumping the tissues without making them look unnatural, be easy and safe to introduce into the tissues, have a long-lasting effect, be relatively inert and not incite a painful or bulky tissue response. Non-permanent or degradable fillers are generally made up of naturally-occurring biological agents such as collagen or hyaluronic acid that undergo degradation at variable rates. Collagen dermal fillers are available in the form of bovine collagen and human-based collagen. HA is a non-sulphated glycosaminoglycan polysaccharide composed of repeating disaccharide units of glucuronic acid and N-acetylglucosamine. HA is a major and natural component of the extracellular matrix in all animal tissues produced by mesenchymal cells with no organ or species specificity; as such, there is no risk of immunogenicity and it is non-toxic and biocompatible. It is highly hydrophilic and this property helps it to retain water and occupy larger volumes relative to its mass.

Non-permanent or degradable fillers are generally made up of naturally-occurring biological agents such as collagen or hyaluronic acid that undergo degradation at variable rates. Collagen dermal fillers are available in the form of bovine collagen and human-based collagen. HA is a non-sulphated glycosaminoglycan polysaccharide composed of repeating disaccharide units of glucuronic acid and N-acetylglucosamine. HA is a major and natural component of the extracellular matrix in all animal tissues produced by mesenchymal cells with no organ or species specificity; as such, there is no risk of immunogenicity and it is non-toxic and biocompatible. It is highly hydrophilic and this property helps it to retain water and occupy larger volumes relative to its mass.

HA fillers have been used to eliminate skin aging signs such as nasolabial fold and cheek wrinkles, as well as perioral rhytides and marionette lines. Such fillers may also be used for lip filling or contouring.
and chin and cheek augmentation.

At the beginning of its aesthetic clinical use there were two main commercial forms of HA: Hyaloform (Biomatrix, USA), derived from cocks’ combs and Restylane (Q Med, Uppsala, Sweden) which is produced by microbiologic engineering techniques (generated by Streptococcus equi). This latter product is more resistant to early degradation by hyaluronidase and rendered more water-insoluble because of cross-linkage. Since then, many other commercial forms of cross-linked bacteria-derived HA fillers have been developed.

As an innovation, since 2006, CMC has been used as the main component of filler to correct wrinkles. First, the CMC was used in the non-crosslinked free form combined with polyethylene oxide (Laresse, FzioMed Inc, USA) and showed good efficacy and safety with long-lasting results. From 2012 CMC has been marketed a single component as cross-linked filler. In this study, for the first time we prospective-ly evaluated the efficacy and safety of CMC filler for the correction of signs of aging of the lower third face in a cohort of patients.

All patients experienced a very high rate of satisfaction of treated regions at 3 months which persist- ed at a very high rate at 6 months with more than 80% having 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 were comparable with those of new HA and are much superior to Restylane in a Brazilian study of 1446 consecutive pa-tients treated in up to four areas of the face

By using objective assessment, cross-linked CMC filler showed 100% of at least 1 point of increase in MLFS at 3 months (T2). A less effective response of 70% was seen on the 5-point MLFS at week 24 with Restylane and of 80% with the Volbella™ study and of 40% with Juvederm®

Cross-linked CMC filler demonstrated a very good safety profile, with 0.7% of ecchymosis immediate-ly after the procedure, in keeping with the previous study by Leonardis et al. This very low percentage of collateral effects is lower than usually reported with HA. Adverse reactions to HA consisting primarily of localised hypersensitivity reactions and injection site inflammation are uncommon and local, and transient side effects are injection site reactions such as pain, mild to moderate oedema, ecchymoses and haematoma; palpability, hypercorrection, and bluish discoloration may also occur secondary to super-perficial injection of the implant and inappropriate technique. The incidence of such reactions has been documented in approximately 2% of treatments for HA. The most common early or immediate, non-al-lergic reaction to CMC compared to HA can be due to the non-bacterial non-animal nature of this filler, and this can be responsible for 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. Post-marketing 5-year analy-sis with HA by the FDA up to 2008 described 930 adverse events, inflammation, allergy and infection being among the top 5 causes. Lack of inflammation and hypersensitivity occur in 0.05–0.15% of cases.

Delayed adverse reactions to HA include hyper-sensitivity and granulomatous foreign body reaction that occur in up to 0.6% of cases. This may result from the reactivity of some patients to protein residues of bacterial or avian origin or impu-rities and residual 1,4-butanediol diglycidyl ether (BDDE) from the cross-linking process. Few cases of hypersensitivity and foreign body reaction have been documented, usually developing within 6–24 months. To date, 3 cases of nodule formations after Restylane injection have been reported in the literature. Such persistence may be related to the cross-linking process, which makes Restylane more resistant to breakdown.

Another advantage of CMC over HA may be the nature of the synthetic polymer, which is character-ised by a very low concentration of residual BDDE which is used for crosslinking. Residual concentra-tion of BDDE in all the three forms of cross-linked CMC is lower than 0.5 PPM, compared to 1-2 PPM of hyaluronic acids.

In conclusion, CMC filler has been demonstrated to be very effective in the correction of signs of aging of the lower face with a very high rate of satisfaction compared to the cross-linked HA fillers and a long-lasting effect. Safety profile seems to be an-other advantage of this filler, with a lack of some side effects which are peculiar to cross-linked HA fillers, and a reduced dose of BDDE.

Therefore cross-linked CMC filler can be a perfect candidate for use by professionals in their everyday clinical practice.

References
6. Courtois JE, Bui Khac Diep. Research on the de-


Contents

Modern concept of skin aging problem correction 3
Vladimir Tsepkolenko

Enhancement of photodynamic therapy after peeling with glycolic acid: observational study 11
Elena Mari, Enzo Palese, Marta Carlesimo, Alfredo Rossi, Emanuele Bartoletti

Soft tissue augmentation with cross-linked carboxymethylcellulose filler: efficacy and safety profile 15
Maria Cristina D’Aloiso

Nutrition in women between prevention and wellness 21
Barbara Paolini, Irene Del Ciondolo

Endolaser soft lift: from theory to practice 27
Luca Scrimali, Giuseppe Lomeo

Courses and Congresses 31