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(54) Title: IMPLANTS FOR SCULPTING, AUGMENTING OR CORRECTING FACIAL FEATURES SUCH AS THE CHIN

(57) Abstract: An injectable device, comprising a hyaluronic acid-based composition, useful for long lasting facial sculpting and correction of facial features, for example, for augmenting and shaping the profile, including for example, the chin, jawline or the nose, in a human being is provided. Methods of treatment are also provided.

IMPLANTS FOR SCULPTING, AUGMENTING OR CORRECTING FACIAL FEATURES SUCH AS THE CHIN

by Jean Xavier Roca Martinez and Aurore Ayglon

[0001] The present invention generally relates to injectable compositions and more specifically relates to injectable implants for adding structure and contour to the lower face.

[0002] Dermal fillers are injectable, biocompatible compositions which are well known to correct wrinkles and folds and add volume to the face. Hyaluronic acid (HA) is still considered by many to be one of the most desirable dermal fillers in that it does not pose the risk of an allergic reaction and it is temporary and reversible. The great majority of hyaluronic acid -based dermal fillers have been specifically developed for treating wrinkles and folds in skin. To be useful for facial contouring or substantial volumizing, it would be advantageous to increase the bulking effect of the compositions, also referred to as “lift”. It would also be advantageous to maximize resistances of the compositions to shear and normal deformation happening in the soft tissues of the face. One of the drawbacks of maximizing these resistances, for example, elasticity and cohesivity, is that it is expected that in doing so, the viscosity of the compositions will increase to the point that they become difficult to inject with a thin needle.

[0003] There is therefore a great need for an injectable HA based implant that is specifically designed to be effective in adding substantial volume to the face, for example, for contouring the lower face, for example, for augmenting or correcting the chin, for example, for correction of chin retrusion, or for example, for augmenting or correcting the nose. It would be highly advantageous if such an implant, despite, its high viscosity, would remain easy to inject with a thin needle.

[0004] The shape of the chin has long been recognized as an important feature of the face that elicits a strong aesthetic perception that tends to be associated with personality traits of an individual. A deficient chin that lacks projection is commonly labeled a “weak chin” while prominent chins are labeled “strong chins”, both implying strength of personality.

[0005] Several studies have suggested that faces with average proportions are viewed as the most attractive and that small features including a small chin are interpreted as attractive in females while the expanded chin and jaw, as a result of maturation, are interpreted as attractive in males. The appearance of the chin is a determinant of perceived attractiveness and can even influence an individual's psychosocial well-being.

[0006] Chin augmentation is conventionally performed by surgically placing a permanent implant above the jaw. The procedure is currently among the top aesthetic surgical procedures performed, based on the American Society for Aesthetic Plastic Surgery (ASAPS), and has increased 71% since 2010.

[0007] A retrusive chin can be the result of changes in growth of the lower third of the face during maturation, trauma, or facial aging, the latter of which may exacerbate the deformities or asymmetries caused by the former two. The shape of the mandible affects the mouth, chin, and neck. As an individual ages, the reduction in skeletal support of this region makes soft tissue atrophy prominent, exaggerating jowls, decreasing chin protrusion, and making the jawline look weak. Chin deformities are among the most common bony abnormalities of the face, the most common of which is horizontal microgenia characterized by the presence of normal vertical height with a retruded bony chin.

[0008] As the mandible and chin make up the framework of the lower face, augmentation methods to treat age-related chin retrusion and contour changes of the chin area or to treat microgenia have been explored for decades. Where the approach in correcting chin retrusion is to add volume, treatment methods have included chin implants, genioplasty, and injection of silicone and semi-permanent fillers, such as polymethylmethacrylate microspheres, and calcium hydroxyapatite. However, all of these treatment methods have drawbacks. For example, chin implants and genioplasty involve painful surgery that may not result in correction of chin retrusion and aesthetic blending of the area. This approach may exacerbate bone resorption and infection, resulting in the need for implant removal. Injection of semi-permanent fillers have trade-offs between volumizing capacity and adverse events associated with semi-permanent fillers.

SUMMARY OF THE INVENTION

[0009] Accordingly, an injectable implant is provided for facial sculpturing, for example, for augmenting, correcting, restoring or creating volume in the chin and other facial features in a human being.

[00010] The present invention provides temporary, reversible, HA-based structural gels manufactured specifically to provide a safe, minimally invasive method to create facial volume or facial contours. The present implants provide improved volumizing and lift properties relative to other HA-based injectables, due to a combination of mechanical properties including high elasticity and high cohesivity, while still being easily injectable with a thin needle. The present implants may be used for injection into the subcutaneous and/or supraperiosteal space. In many embodiments the implants are moldable after injection, and therefore permit sculpting, contouring, and shaping across the injected areas, for example, the chin and jaw area.

[00011] The implants generally comprise a composition comprising a hyaluronic acid (HA) crosslinked with a crosslinking agent selected from the group consisting of 1,4-butanediol diglycidyl ether (BDDE), 1,4-bis(2,3-epoxypropoxy)butane, 1,4-bisglycidyloxybutane, 1,2-bis(2,3-epoxypropoxy)ethylene and 1-(2,3-epoxypropyl)-2,3-epoxycyclohexanethe. In some embodiments, the implants generally comprise a composition comprising a hyaluronic acid (HA) crosslinked with BDDE. The compositions are suitable for injection, for example, through a fine gauge needle, and are capable of augmenting, correcting, or creating volume or lift in the face, for example, the lower face, for example, the chin or jaw, or for the midface, for example, the nose.

[00012] In some embodiments, the HA concentration is greater than 20 mg/g. In some embodiments, the HA concentration is about 21 mg/g, or about 22 mg/g, or about 23 mg/g, or about 24 mg/g, or about 25 mg/g, or about 26 mg/g, or about 27 mg/g, or about 28 mg/g, or about 29 mg/g, or about 30 mg/g or greater. In other embodiments, the composition has an HA concentration of between 22.5 mg/g to 27.5 mg/g, for example, 25.0 mg/g.

[00013] In some embodiments the method adds volume and lift to the chin or jawline or nose of the patient for a period of time in the range of about 9 months to

about 24 months after the administration or injection into the chin or jawline of the patient. The composition may be moldable, for example, by physical manipulation of the tissue near the implant for a period of time after injection. The compositions may have a setting time, when the composition is no longer moldable and substantially retains its shape for the duration of the implant, within about 24 to about 48 hours after being implanted or injected.

[00014] In some embodiments, the compositions further include an anesthetic agent, for example, lidocaine HCl. For example, the compositions may include about 0.3% w/w lidocaine HCl.

[00015] In preferred embodiments, the compositions comprise a hyaluronic acid gel, preferably in an amount of about 25 mg; and lidocaine hydrochloride, preferably in an amount of about 3 mg, in a phosphate buffer (pH 7.2), preferably in a volume q.s. 1 mL.

[00016] In some embodiments, compositions are made with a mixture of low molecular weight hyaluronic acid and high molecular weight hyaluronic acid. For example, the crosslinked hyaluronic acid may be made from about 50% and about 100% of a low molecular weight hyaluronic acid prior to being crosslinked with the crosslinking agent. In some embodiments, the crosslinked hyaluronic acid is made from about 70% to about 90% of a low molecular weight hyaluronic acid prior to being crosslinked with the crosslinking agent. In some embodiments, the crosslinked hyaluronic acid is made from about 90% of a low molecular weight hyaluronic acid prior to being crosslinked with the crosslinking agent.

[00017] Using primarily a low molecular weight HA prior to crosslinking, for example about 50% or greater, for example, about 70% or about 90% low molecular weight HA, rather than using primarily a high molecular weight HA, produces a more robust, longer lasting, moldable hydrogel, having a higher cohesivity and elasticity, and more specifically suitable for facial sculpturing and augmentation by means of subcutaneous or supraperiosteal injection.

[00018] In some embodiments, the HA has a degree of crosslinking of between about 4% and about 12%. For example, the HA has a degree of crosslinking of about 4%, or about 6%, or about 8%, or about 10%. In some embodiments the HA has a

degree of crosslinking of about 6.5%. In other embodiments, the HA has a degree of crosslinking of about 7.5%, or about 8.5%, or about 9.5%, or about 10.5%.

[00019] In another aspect of the invention, methods for correcting chin retrusion in a patient are provided. The methods generally comprise supraperiostally administering in the chin of the patient, an effective amount of a composition comprising BDDE-crosslinked hyaluronic acid (HA), the HA having a degree of crosslinking of about 10%, and having a HA concentration of greater than 20 mg/g. For example, in a preferred embodiment, the HA concentration is about 25 mg/g.

[00020] In a specific embodiment, the compositions comprises low molecular weight hyaluronic acid (NaHA) crosslinked with about 10% BDDE (w/w), and formulated to a concentration of about 25 mg/g with 0.3% lidocaine hydrochloride (w/w) in a phosphate buffer, pH 7.2, and supplied in a 1 mL COC (cyclic olefin copolymer) syringe.

[00021] The compositions are extrudable through a fine gauge needle, for example, a needle having a gauge of 25G, 26G, 27G, 28G, 29G or 30G. In a specific embodiment, the needle is a needle of 27 gauge X 13 mm / 27 G1/2 X 26mm.

[00022] An extrusion force is the force (in Newtons N) needed to extrude the composition from its syringe at a certain rate. For example, with the supplied 1 mL COC syringe and a TSK 27G X 13mm needle, the extrusion force of some of the compositions of this invention can be between about 4N and about 15N at 13 mm/min, which is considered as very low. For example, the extrusion force can be between about 7N and about 12N, and preferably between about 8N and about 10 N.

[00023] In another aspect of the invention, methods are provide for contouring or correcting a facial feature, for example, a retruded chin, of an individual. The methods comprise, for example, the step of subdermally administering into a treatment area of the patient, an effective amount, for example, about 1.0 ml, or more, for example, about 2.0 ml or more, for example, about 3.0 ml or more, for example, 4.0 mL, of a composition of the invention. The facial feature to be improved or contoured may be a chin, for example, a retruded chin of a patient. The

treatment area may include an area selected from the group consisting of the pogonion, the mentum, the left pre-jowl sulcus, the right pre-jowl sulcus, and the sublabial crease. The treatment may comprise administering the composition into two or more of the treatment areas.

[00024] Each and every feature described herein, and each and every combination of two or more of such features, is included within the scope of the present invention provided that the features included in such a combination are not mutually inconsistent.

BRIEF DESCRIPTION OF THE DRAWINGS

[00025] Figure 1 shows a facial profile and landmarks for calculating G-Sn-Pog angle of a patient.

[00026] Figure 2 shows the Burstone Angle of an average chin.

DETAILED DESCRIPTION

[00027] Certain terms as used in the specification are intended to refer to the following definitions, as detailed below. Where the definition of terms departs from the commonly used meaning of the term, applicant intends to utilize the definitions provided below, unless specifically indicated.

[00028] The term “about” in the context of numerical values will be readily understood by a person skilled in the art, and preferably means that specific values may be modified by +/- 10%. As regards endpoints of ranges, the modifier “about” preferably means that the lower endpoint may be reduced by 10% and the upper endpoint increased by 10%. It is also contemplated that each numerical value or range disclosed in this application can be absolute, i.e. that the modifier “about” can be deleted.

[00029] All numbers herein expressing “molecular weight” of HA are to be understood as indicating the weight average molecular weight (Mw) in Daltons.

[00030] The molecular weight of HA is calculated from an intrinsic viscosity measurement using the following Mark Houwink relation:

Intrinsic Viscosity (L/g) = 9.78 x 10-5 x Mw0.690

[00031] The intrinsic viscosity is measured according to the procedure defined European Pharmacopoeia (HA monograph N°1472, 01/2009).

[00032] Unless stated otherwise, the molecular weight refers to the weight average molecular weight (Mw). The HA used to make the present compositions may comprise a mixture of high molecular weight HA, low molecular weight HA, and/or medium molecular weight HA, wherein the high molecular weight HA has a molecular weight greater than about 2,000,000 Da (or an intrinsic viscosity greater than 2.2 L/g) and wherein the low molecular weight HA has a molecular weight of less than about 1,000,000 Da (or an intrinsic viscosity lower than 1.4 L/g). For example, the high molecular weight HA in the present compositions may have an average molecular weight in the range about 2 MDa to about 4.0 MDa, for example, about 3.0 MDa (2.9 L/g). In another example, the high molecular weight HA may have an average molecular weight of between about 2.4 MDa to about 3.6 MDa, for example, about 3.0 MDa. The high molecular weight HA may have an intrinsic viscosity greater than about 2.2 L/g, for example, between about 2.5 L/g to about 3.3 L/g.

[00033] Low molecular weight HA can have a molecular weight of between about 200,000 Da (0.2 MDa) to less than 1.0 MDa, for example, between about 300,000 Da (0.3 MDa) to about 750,000 Da (1.1 L/g), up to but not exceeding 0.99 MDa (1.4 L/g). The low molecular weight HA may have an intrinsic viscosity of less than about 1.40 L/g, for example, between about 0.6 L/g and about 1.2 L/g.

[00034] Preferably, there is no overlap between the molecular weight distribution of the low and high molecular weight HA materials.

[00035] Preferably, the mixture of the low molecular weight HA and high molecular weight HA has a bimodal molecular weight distribution. The mixture may also have a multi-modal distribution.

[00036] In one aspect of the invention, the compositions comprise HA having a high molecular weight component and a low molecular weight component, and the

high molecular weight component has a weight average molecular weight at least twice the weight average molecular weight of the low molecular weight component.

[00037] "Degree of crosslinking" as used herein refers to the intermolecular junctions joining the individual HA polymer molecules, or monomer chains, into a permanent structure, or as disclosed herein the soft tissue filler composition. Moreover, degree of crosslinking for purposes of the present disclosure is further defined as the percent weight ratio of the crosslinking agent to HA-monomeric units within the crosslinked portion of the HA based composition. It is measured by the weight ratio of crosslinker to HA monomers.

[001] "Uncrosslinked HA" as used herein refers to individual HA polymer molecules that are not crosslinked. Uncrosslinked HA generally remains water soluble. An uncrosslinked HA fraction may optionally also be included in the compositions, for example, to act as a lubricant and facilitate injection into the facial tissues. Such a composition may comprise an uncrosslinked HA fraction where the added uncrosslinked HA is present at a concentration between about 0.1 mg/g and about 3 mg/g. Preferably, the uncrosslinked HA may be present at a concentration between about 0.2 mg/g and about 1.5 mg/g.

[002] In other embodiments, no uncrosslinked HA is present in the gels, or at least no uncrosslinked HA is added to the gels to act as a lubricant.

[00038] The compositions described herein display a high level of elasticity, expressed as a value of elastic modulus (G') measured by oscillation rheology with a strain of 0.8%, using a cone-plate system and measured over a range of frequencies. In some embodiments, the elastic modulus of the compositions measured at 5Hz frequency are from about 500 Pa to about 900 Pa. This is considered as high elasticity in the context of HA-based dermal fillers and contributes to the lifting effect by making the implant more resistant to shear deformation.

[00039] Cohesivity refers to the capacity of the gel to stay attached to itself, for example, meaning the resistance to cutting and the ability to elongate or compress the gel without it separating into pieces. The cohesivity of the gels according to the present invention can be quantified as follows (cf. Derek Jones "Injectable Filers:

Principles and Practice", Wiley, 2011, Chapter 3). A small sample of the gel (e.g. 1 mL) is placed onto the plane surface of a rheometer. The sample is placed such that it forms a little heap. A moveable upper plate is placed onto the sample so that the sample is fully covered, e.g. when looking at the plate in a direction perpendicular to the surface of the rheometer, the sample cannot be seen. In order to ensure this, one must chose a plate size that is larger than the sample size. Ideally, the center of the plate is placed over the sample. Typically, for 1mL of gel material, a 25mm diameter upper plate is used.

[00040] In the next step of the measurement, one then adjusts the gap between the moveable plate and the surface to 2.5 mm. While slowly and steadily moving the plate from this initial position towards a gap width of 0.9 mm within 2 min one records the force (Fn) exerted by the sample in normal direction on the plate.

[00041] Once a gap width of 0.9 mm is reached, the system is allowed to relax for 12 minutes. During this time, the measurement is continued. Five measurements are done. To normalize the forces measured, all 5 initial Fn values measured when the test starts are averaged (arithmetic mean) and this resulting average is subtracted from all other data points. The maximum force at the end on the compressive part of this test (when reaching the minimal 0.9mm gap width between the upper plate and the plane) is called the compression force and is the characteristic value for determining the cohesivity of the gel.

[00042] Specifically, a force of 20 gmf (0.1962 N) or more indicates a cohesive material in the sense of the present invention. Gels with lower compression force values are generally not considered cohesive in the context of the present invention. The accuracy of this measurement is in the order of ±5 gmf. In the context of this invention, the injectable formulation has a high cohesivity of at least about 60 gmf, for example about 60 to about 200 gmf. For example, in a preferred embodiment, cohesivity is between about 60 and about 100 gmf, which will give to the implant a high resistance to pressure and normal forces in the soft tissues of the face.

[00043] In the context of a dermal filler, the cohesivity as defined above will contribute to the lift capacity (clinically called the volumizing / bulking effect) provided by the gel clinically, along with its elastic modulus G'. While cohesive gels can show

a good volumizing effect, non-cohesive or weakly cohesive materials with a similar elastic modulus exhibits lower lift capacity due to the non-cohesive gel material spreading more than a more cohesive material when submitted to vertical compression. In the context of this invention, the compositions exhibit both high levels of elastic modulus and high levels of cohesivity, to maximize the lifting effect upon implantation.

[00044] In certain advantageous, exemplary embodiments, the present implants or fillers generally comprise a cohesive, sterile composition which is implantable subdermally or supraperiostially into the chin area, nose or jawline of the patient in need thereof, for example a patient desiring an improved facial profile or stronger chin. The composition generally comprises a crosslinked hyaluronic acid (HA) crosslinked with 1,4-butanediol diglycidyl ether (BDDE); and the HA concentration of the composition is greater than 20 mg/g. For example, in some embodiments, the HA concentration is about 22.5 mg/g, or about 25 mg/g, or about 27.5 mg/g. The HA used for crosslinking may be made with a mixture of low molecular weight hyaluronic acid and high molecular weight hyaluronic acid. In some embodiments, the compositions have an elastic modulus between about 500 Pa and about 900 Pa at 5Hz, and a cohesivity above about 60 gmf. Advantageously, in some embodiments, the compositions exhibit an extrusion force between about 4N and about 15N, for example, between about 8N and about 10 N, at 13 mm/min using a 1 mL COC syringe and a 27G x 13mm needle.

[00045] In one aspect of the invention, injectable HA-based implants having an improved lift capacity, relative to commercial HA-based dermal fillers, are provided. The present implants are, in some instances in the present disclosure, referred alternatively as dermal fillers and subdermal fillers. The implants and fillers of the present invention are based on hyaluronic acids (HA) and pharmaceutically acceptable salts of HA, for example, sodium hyaluronate (NaHA). Methods of making these compositions, and methods of use of these compositions, are also provided.

[00046] As used herein, hyaluronic acid (HA) can refer to any of its hyaluronate salts, and includes, but is not limited to, sodium hyaluronate (NaHA), potassium hyaluronate, magnesium hyaluronate, calcium hyaluronate, and combinations

thereof. Both HA and pharmaceutically acceptable salts thereof can be used in this invention.

[00047] In addition, in embodiments with anesthetics, the concentration of one or more anesthetics is in an amount effective to mitigate pain experienced upon injection of the composition. The at least one local anesthetic can be selected from the group of ambucaine, amolanone, amylocaine, benoxinate, benzocaine, betoxycaine, biphenamine, bupivacaine, butacaine, butamben, butanilicaine, butethamine, butoxycaine, carticaine, chloroprocaine, cocaethylene, cocaine, cyclomethycaine, dibucaine, dimethisoquin, dimethocaine, diperodon, dicyclomine, ecgonidine, ecgonine, ethyl chloride, etidocaine, beta-eucaine, euprocin, fenalcomine, formocaine, hexylcaine, hydroxytetracaine, isobutyl p-aminobenzoate, leucinocaine mesylate, levoxadrol, lidocaine, mepivacaine, meprylcaine, metabutoxycaine, methyl chloride, myrtecaine, naepaine, octocaine, orthocaine, oxethazaine, parethoxycaine, phenacaine, phenol, piperocaine, piridocaine, polidocanol, pramoxine, prilocaine, procaine, propanocaine, proparacaine, propipocaine, propoxycaine, pseudococaine, pyrrocaine, ropivacaine, salicyl alcohol, tetracaine, tolycaine, trimecaine, zolamine, and salts thereof. In one embodiment, the at least one anesthetic agent is lidocaine, such as in the form of lidocaine HCl. The compositions described herein may have a lidocaine concentration of between about 0.1% and about 5% by weight of the composition, for example, about 0.2% to about 1.0% by weight of the composition. In one embodiment, the composition has a lidocaine concentration of about 0.3% by weight (w/w %) of the composition. The concentration of lidocaine in the compositions described herein can be therapeutically effective meaning the concentration is adequate to provide a therapeutic benefit without inflicting harm to the patient.

[00048] The present compositions may be manufactured by the steps of providing purified HA material for example, in the form of NaHA fibers; the HA material having a desired molecular weight, for example, a mixture of low molecular weight and high molecular weight HA at a desired ratio, hydrating the HA material; and crosslinking the hydrated HA material with a suitable crosslinking agent at the desired ratio to form a crosslinked HA-based gel. The gel may then be neutralized and swollen. If desired, a solution containing lidocaine, preferably an acidic salt of lidocaine

chlorohydrate, may be added to form a HA/lidocaine gel. The gel may be homogenized, for example, by beating or mixing with a shear force. The homogenized composition may then be packaged in syringes. The syringes are then sterilized by autoclaving at an effective temperature and pressure. For example, the compositions are sterilized by autoclaving, for example, being exposed to temperatures of at least about 120°C to about 130°C and/or pressures of at least about 12 pounds per square inch (PSI) to about 20 PSI for a period of at least about 1 minute to about 15 minutes. The sterilized syringes are packaged along with a fine gauge needle for use by a physician.

[00049] More specifically, the initial raw HA material may comprise fibers or powder of NaHA, for example, bacterial-sourced NaHA fibers. Alternatively, the HA material may be animal derived, for example, from rooster combs. It is contemplated that the HA material may be a combination of raw materials including HA and at least one other polysaccharide, for example, another glycosaminoglycan (GAG).

[00050] In one method of manufacturing the compositions, pure, dry NaHA fibers are hydrated in an alkaline solution to produce an uncrosslinked NaHA gel. Any suitable alkaline solution may be used to hydrate the NaHA in this step, for example, but not limited to aqueous solutions containing sodium hydroxide (NaOH), potassium hydroxide (KOH), sodium bicarbonate (NaHCO3), lithium hydroxide (LiOH), and the like. The resulting alkaline gel will have a pH above 7.5. The pH of the resulting alkaline gel can have a pH greater than 9, or a pH greater than 10, or a pH greater than 12, or a pH greater than 13.

[00051] The next step in the manufacturing process may include the step of crosslinking the hydrated, alkaline NaHA gel with a suitable crosslinking agent. The crosslinking agent may be any agent known to be suitable for crosslinking polysaccharides and their derivatives via their hydroxyl groups. One particular suitable crosslinking agent is 1,4-butanediol diglycidyl ether (BDDE).

[00052] In another embodiment, the crosslinking of the HA is accomplished during hydration of the HA fibers, by hydrating the combined high and low molecular weight fibers in an alkaline solution containing a crosslinking agent, for example, BDDE.

[00053] The degree of crosslinking in the HA component of the present compositions is at least about 4% and is up to about 12% BDDE/HA, w/w, for example, about 10%, for example, about 8%, for example, about 6%, for example, about 4%. In a specific embodiment, the degree of crosslinking is about 6.5%. In some embodiments the HA has a degree of crosslinking of about 6.5%. In other embodiments, the HA has a degree of crosslinking of about 7.5%, or about 8.5%, or about 9.5%, or about 10.5%.

[00054] The hydrated crosslinked, HA gels may be swollen to obtain the desired HA concentration. This step can be accomplished by neutralizing the crosslinked, hydrated HA gel, for example by adding an aqueous solution containing of an acid, such as HCl. The gels are then swelled in a phosphate buffered saline (PBS) solution for a sufficient time and at a low temperature.

[00055] The gels may now be purified by conventional means such as, dialysis against a phosphate buffer, or alcohol precipitation, to recover the crosslinked material, to stabilize the pH of the material and to remove any un-reacted crosslinking agent. Additional water or a slightly alkaline aqueous solution can be added to bring the concentration of the HA in the composition to a desired concentration. In some embodiments, the HA concentration of the compositions is adjusted to above 20 mg/g, for example, to about 25 mg/g. In other embodiments, the HA concentration is adjusted to yield an HA concentration of about 21 mg/g, about 22 mg/g, about 23 mg/g, about 24 mg/g, about 26 mg/g, about 27 mg/g, about 28 mg/g, about 29 mg/g, or about 30 mg/g.

[00056] In embodiments in which an anesthetic agent is to be included in the final composition, such as lidocaine, the pH of the purified crosslinked HA gels may be adjusted to cause the gel to become slightly alkaline such that the gels have a pH of greater than about 7.2, for example, about 7.5 to about 8.0. This step may be accomplished by any suitable means, for example, by adding a suitable amount of dilute NaOH, KOH, NaHCO3 or LiOH, to the gels or any other alkaline molecule, solution and/or buffering composition.

[00057] An effective amount of the anesthetic, for example, lidocaine, such as lidocaine HCl, is then added to the purified crosslinked NaHA gels. For example, in

some embodiments, the lidocaine HCl is provided in a powder form which is solubilized using water for injection (WFI). The gels are kept neutral with a buffer or by adjustment with diluted NaOH in order that the final HA/lidocaine composition will have a desired, substantially neutral pH. The final compositions including lidocaine may have a lidocaine concentration of between at least about 0.1% and about 5%, for example, about 2% by weight of the composition, or in another example about 0.3%.

[00058] After the addition of the lidocaine HCl, or alternatively, during the addition of the lidocaine HCl, the HA/lidocaine gels, or compositions, are homogenized to create highly homogenous HA/lidocaine gels having a desired consistency and stability. Preferably, the homogenization step comprises mixing, stirring, or beating the gels with a controlled shearing force obtaining substantially homogenous mixtures.

[00059] After homogenizing the HA composition, an amount of uncrosslinked HA solution or gel may be added to the composition to increase lubricity.

[00060] In some embodiments, no solution of uncrosslinked HA is added to the composition after homogenization.

[00061] The compositions may then be introduced into syringes and sterilized. Syringes useful according to the present description include any syringe known in the art capable of delivering viscous dermal filler compositions. The syringes generally have an internal volume of about 0.4 mL to about 3 mL, more preferably between about 0.5 mL and about 1.5 mL or between about 0.8 mL and about 2.5 mL. This internal volume is associated with an internal diameter of the syringe which plays a key role in the extrusion force needed to inject high viscosity dermal filler compositions. The internal diameters are generally about 4 mm to about 9 mm, more preferably from about 4.5 mm to about 6.5 mm or from about 4.5 mm to about 8.8 mm. Further, the extrusion force needed to deliver the HA compositions from the syringe is dependent on the needle gauge. The gauges of needles used generally include gauges between about 18G and about 40G, more preferably about 25G to about 33G, or from about 25G to about 30G. For example, in some embodiments, the compositions are packaged in a 1 mL syringe and injected using a 27 G needle.

[00062] One preferable method of sterilization of the filled syringes is by autoclave. Autoclaving can be accomplished by applying a mixture of heat, pressure and moisture to a sample in need of sterilization. Many different sterilization temperatures, pressures and cycle times can be used for this step. For example, the filled syringes may be sterilized at a temperature of at least about 120°C to about 130°C or greater. Moisture may or may not be utilized. The pressure applied is in some embodiments depending on the temperature used in the sterilization process. The sterilization cycle may be at least about 1 minute to about 20 minutes or more.

[00063] Another method of sterilization incorporates the use of a gaseous species which is known to kill or eliminate transmissible agents. Preferably, ethylene oxide is used as the sterilization gas and is known in the art to be useful in sterilizing medical devices and products.

[00064] A further method of sterilization incorporates the use of an irradiation source which is known in the art to kill or eliminate transmissible agents. A beam of irradiation is targeted at the syringe containing the HA composition, and the wavelength of energy kills or eliminates the unwanted transmissible agents. Preferable energy useful include, but is not limited to ultraviolet (UV) light, gamma irradiation, visible light, microwaves, or any other wavelength or band of wavelengths which kills or eliminates the unwanted transmissible agents, preferably without substantially altering of degrading the HA composition.

[00065] Preferably, the present compositions also remain stable when stored for long periods of time. For example, many of the present compositions have a shelf life of about 6 months, about 12 months, about 18 months, or about 24 months or greater, when stored at a temperature between about 2 to 25 degrees C. In a specific embodiment, the compositions are stable at a temperature of between 2 to 25 degrees C for a period of at least 18 months. In another specific embodiment, the compositions are stable at a temperature or between 2 to 25 degrees C for a period of at least 24 months.

[00066] The technique for injection of the present compositions may vary with regard to the angle and orientation of the bevel, and the quantity administered. In general, the present compositions are injected subcutaneously and/or

supraperiosteally to increase chin projection, limiting treatment to the pogonion, the mentum (inferior aspect of the chin), pre-jowl sulci (left and right), and sublabial (mental) crease to achieve optimal correction and aesthetic chin contour. The appropriate injection volume will be determined by the investigator but is generally not to exceed a maximum total volume of about 4.0 mL for initial and top-up treatments combined. Up to about 4.0 mL total is allowed for repeat treatment. No more than about 2.0 mL is permitted to be injected into a single treatment area at any treatment session, where treatment areas are defined as the pogonion, the mentum, the pre-jowl sulci (left and right), and the sublabial (mental) crease.

[00067] Prior to injection of the present compositions, the treatment area has to be thoroughly disinfected to ensure that there is no contamination of the injectable filler with bacteria or a foreign body (e.g., make-up, talc from gloves).

[00068] Next, the 27G 1/2"/27 G x 13 mm needle supplied should be attached to the syringe (according to Directions for Use). Prior to injecting the present compositions, the plunger rod has to be depressed until the product visibly flows out of the needle and wipe any excess on sterile gauze.

[00069] The present compositions are injected as follows: Inject the present compositions slowly, and observe the skin for signs of colour change or discolouration. Observe the subject for pain or discomfort. Inject the present compositions in a smooth and measured manner. Insert the needle being mindful of the local vascular anatomy at the injection site. Aspirate to ensure there is no blood backflow to suggest an intravascular location of the tip of the needle.

[00070] Pogonion may be injected supraperiosteally using multiple small boluses. Mentum may be injected supraperiosteally using multiple small boluses. Pre-jowl sulci (left and right) may be injected using a deep subcutaneous fanning technique. Sublabial (mental) crease may be injected using linear, retrograde or anterograde superficial subcutaneous threading.

[00071] When treatment is completed, the treated site may be gently massaged to assure that the product is evenly distributed and conforms to the contour of the surrounding tissues. If overcorrection occurs, gently massage the area between your fingers or against an underlying bone to obtain optimal results.

[00072] The present compositions are not to be injected into the blood vessels (intravascular). Introduction of hyaluronic acid into the vasculature may occlude the vessels and could cause infarction or embolization. Symptoms of vascular

occlusions and embolization include pain that is disproportionate to the procedure or remote to the injection site, immediate blanching that extends beyond the injected area and that may represent vascular tributary distribution, and colour changes that reflect ischemic tissue such as a dusky or reticular appearance.

[00073] Injecting the product too superficially or in large volumes over a small area may result in visible and persistent lumps and/or discoloration.

[00074] When using a retrograde technique, inject the present compositions applying even pressure on the plunger rod while slowly pulling the needle backward. It is important that the injection be stopped just before the needle passes the subcutaneous/dermal interface to prevent material from leaking out or ending up too superficially in the skin. When using an anterograde technique, be sure the needle is in the subcutaneous tissue before the injection is started.

[00075] If the needle is blocked, do not increase the pressure on the plunger rod but stop the injection and replace the needle.

[00076] If the treated area is swollen immediately after the injection, an ice pack may be applied to the site for a short period. If subjects report inflammatory reactions which persist for more than 1 week, or any other side effect which develops, the medical practitioner should use an appropriate treatment.

[00077] In preferred embodiments, the present compositions comprise a hyaluronic acid gel, preferably in an amount of about 25 mg; and lidocaine hydrochloride, preferably in an amount of about 3 mg, in a phosphate buffer (pH 7.2), preferably in a volume q.s. 1 mL, prefilled in e.g. a 1 mL single-use syringe, wherein the hyaluronic acid gel is crosslinked with BDDE. This prefilled e.g. 1 mL single-use syringe may be contained in a kit (blister pack) along with two single use needles (e.g. 27G 1/2"/27 G x 13 mm needles) . The content of the syringe may be sterilised by moist heat. The single-use needles may be sterilised by radiation.

[00078] The present compositions are injectable implants intended for restoration and creation of facial volume, e.g. in the chin and jaw area. The presence of lidocaine is meant to reduce the subject's pain during treatment.

EXAMPLE 1

MANUFACTURE OF AN INJECTABLE IMPLANT IN ACCORDANCE WITH AN EMBODIMENT OF THE INVENTION

[00079] Predried fibers of sodium hyaluronate (NaHA) (0.9 g) having a molecular weight of about 0.9 MDa is weighed out into a first receptacle.

[00080] Predried fibers of NaHA (0.1 g) having a molecular weight of about 3.0 MDa is weighed out into a second receptacle.

[00081] The two different grades of NaHA are combined and diluted into a 1% sodium hydroxide solution and mixed for one to two hours at between 20ºC and 50°C to obtain a substantially homogenous, alkaline HA gel.

[00082] In a separate receptacle, the chosen crosslinking agent, 1,4-butanediol diglycidyl ether (BDDE), is diluted into a 1% sodium hydroxide solution to a final concentration of 10% BDDE (wt/wt).

[00083] To the alkaline HA gel was added 10% (wt/wt) BDDE (1 g of the previously prepared BDDE solution). The resulting mixture is mechanically homogenized.

[00084] The mixture is then maintained at 50ºC for 3 to 4.5 hours.

[00085] The resulting crosslinked HA polymer is then immersed in a phosphate buffer (PB) containing hydrochloric acid to stabilize the pH.

[00086] The crosslinked HA polymer so obtained is then immersed in baths of phosphate buffer to remove unreacted crosslinking agent and HA, providing the purified hydrogel, wherein the degree of crosslinking is about 6.5%.

[00087] Optionally, dry HA material having a high molecular weight is hydrated in 1 liter of phosphate buffer to obtain an uncrosslinked HA gel. This uncrosslinked HA gel can be added to the crosslinked HA composition to represent up to 5% (w/w) of the total HA concentration.

[00088] The hydrogel obtained is then homogenized mechanically to ensure the final homogeneity, and packed into syringes which are sterilized in an autoclave.

[00089] The gel obtained is an injectable composition that can be administered subdermally or supraperiostally through a fine gauge needle (e.g. 27 Gauge). The composition is useful for restoring, contouring, or creating facial volume, for example, in the chin, jaw area, or nose of a person, as described elsewhere herein.

[00090] In one aspect of the invention, methods are provided for improving a patient's facial profile. For example, in some embodiments, methods are provided for changing a person's G-Sn-Pog facial angle, for example, for increasing a person's G-Sn-Pog facial angle. For example, in some embodiments, methods of treatment are provided for correcting chin retrusion in a patient. In some embodiments of the invention, the patient treated an initial pre-treatment G-Sn-Pog facial angle of less than about 165°. After the treatment, the patient has an increased G-Sn-Pog facial angle, that is, a facial angle greater than the initial pre-treatment facial angle. In one embodiment, the patient has a G-Sn-Pog angle of about 169° or greater after the step of administering. The G-Sn-Pog angle may be measured using conventional equipment and calculations, for example, may be based on calculations of facial angle derived from digital images of the patient, for example, using Canfield scientific facial imaging equipment. Figure 1 shows facial profile and landmarks for calculating G-Sn-Pog angle of a patient, which can be used to diagnose or determine the presence and/or degree of chin retrusion, using know methods.

[00091] The methods generally comprise administering into at least one treatment area of the face of the patient, an effective amount of a composition comprising BDDE-crosslinked hyaluronic acid (HA), the HA having a degree of crosslinking of about 6.5%, or about10%, and having a HA concentration of greater than 20 mg/g.

[00092] In some embodiments, treatment methods are provided, the methods comprising supraperiostally administering a composition, such as described herein, into at least one treatment area of the face of a patient, wherein the patient has a G-Sn-Pog facial angle of 145° to 165°. The facial angle value may be based on calculations of facial angle derived from digital images of the patient, or using other techniques. In accordance with some embodiments, the step of administering results in the patient having an increased G-Sn-Pog angle relative to the patient's G-Sn-Pog facial angle prior to the treatment, for example, immediately prior to the administering step. In some embodiments, the patient has an increased G-Sn-Pog angle for a period of time in the range of at least about 3 months, or more preferably, for at least about 6 months, for example, for about 9 months to about 24 months, after the step of administering. For example, the patient has an increased G-Sn-Pog angle for at least about 6 months, or for at least about 9 months, or for at least

about 12 months or for at least about 18 months or for at least about 24 months for after the step of administering.

[00093] In some embodiments, the treatment area is an area selected from the group consisting of the pogonion, the mentum, the left pre-jowl sulcus, the right pre-jowl sulcus, and the sublabial crease. The treatment may comprise administering the composition into two or more of the treatment areas. The administration comprises supraperiostally or subdermally injecting the compositions in an amount of between about 0.5 mL and about 3.0 mL per treatment area. In some embodiments, the amount injected into a given treatment area is no greater than 2.0 mL. In some embodiments, the total amount injected in a single treatment session, over all treatment areas, is between 2.0 mL to about 6.0 mL, for example, about 2.5 mL, about 3.0 mL, about 3.5 mL. about 4.0 mL, about 4.5 mL, about 5.0 mL, about 5.5 mL, or about 6.0 mL. In some embodiments, the amount administered into a single treatment session is about 4.0 mL or less.

Restoration and Creation of Volume in the Chin and Jaw

[00094] In one aspect, the present invention provides methods for restoring and creating volume in the chin and jaw, for example, in sculpting, shaping, and contouring across specific treatment areas of the face. The treatment areas may include one or more of the pogonion (the most projecting point on the anterior surface of the chin), mentum, (the lowest point on the chin), left and right pre-jowl sulci (left antigonion notch and right antigonion notch), and sublabial (mental) crease (the crease between the lower lip and the mentum).

[00095] The shape and projection of the chin contribute to the proportional balance of the face that underlies attractiveness. A chin lacking projection is commonly labeled a “weak chin” whereas prominent chins are labeled “strong chins” and imply strength of personality. Several studies have suggested that faces with average proportions are viewed as the most attractive and that juvenile features including a small chin are interpreted as attractive in females while a strong chin and jaw are interpreted as attractive in males. The appearance of the chin is a determinant of perceived attractiveness and can influence an individual’s psychosocial well being

[00096] Average proportions are dictated by analysis of a representation of facial profiles in a population and include the distances and angles between the nose, lip, and mentum. Several soft tissue landmarks have been used in cephalometric analysis to measure and diagnose chin protrusion and retrusion deviations from average facial parameters. The intersection of the upper facial and anterior lower facial components and the angle formed by the point on the glabella, subnasale, and pogonion (G-Sn-Pog) has been extensively analyzed to understand the average chin projection common among populations. The Burstone angle (Figure 2) has been defined as approximately 169º for the average chin, and the approximate angle (168º to 169º) has been confirmed in several studies.

[00097] Incrementally, deviations from the average chin result in the perception of facial unattractiveness. Analyzing the relationship between facial profile and perception of attractiveness shows that chin prominence plays a major role in this perception. To understand the relationship between the degree of chin prominence and attractiveness, a series of profile images altered in 2-mm increments from an idealized profile image was presented to a group of pretreatment orthognathic patients, clinicians, and laypeople. Subjects were asked to rate each image on a 7-point Likert scale ranging from extremely unattractive to extremely attractive. Ratings of perceived attractiveness decreased an average of 0.15 on the Likert Scale for each 2 mm of chin retrusion and were apparent after 4 mm of change. The degree of chin retrusion at which surgery was desired was 11 mm for patients and clinicians and 10 mm for laypeople. The most attractive image was that which displayed an ideal orthognathic profile with the soft tissue pogonion resting on the true vertical line.

EXAMPLE 2

METHOD FOR INCREASING THE G SN POG FACIAL ANGLE IN A SUBJECT HAVING CHIN RETRUSION OR A WEAK CHIN

[00098] A composition of the invention is administered as an injectable implant, by subdermal or supraperiosteal injection in the chin and/or jaw area of a 32 year old male subject. The subject complains he has a “weak chin”. The doctor measures the subject’s facial angle and determines that the a G-Sn-Pog angle of about 150°,

which is substantially lower than the classic Burstone angle of the average chin (approximately 169º). The measurement is based on calculations of facial angle derived from digital images obtained using Canfield imaging equipment and software.

[00099] The doctor considers the subject's chin/jaw retrusion to be amenable to correction with a treatment goal consistent with increasing chin projection horizontally (in the profile view), not chin lengthening or widening.

[000100] The doctor believes that he can provide the subject with a more attractive facial profile and a stronger jawline by using the implantable compositions described herein.

[000101] The subject undergoes three treatment sessions, including initial treatment, top-up treatment, and repeat treatment, as described below.

[000102] For each treatment, the treatment areas include at least one or more of the following treatment areas: the pogonion (the most projecting point on the anterior surface of the chin), the mentum (the lowest point on the chin), the left pre-jowl sulcus (left antigonion notch), the right pre-jowl sulcus (right antigonion notch), and/or the sublabial crease (the crease between the lower lip and the mentum).

[000103] The doctor implants no more than 2.0 mL into a single treatment area at any of the treatment sessions.

[000104] The initial treatment is performed on the subject as follows. The doctor uses aseptic skin preparation and administers anesthesia following his standard practice. The application of ice and topical anesthesia may reduce injection discomfort. Injectable anesthesia is limited to the treatment areas only is and administered with certainty not to distort the planned treatment areas.

[000105] Using needles (27 gauge x 13 mm / 27G ½") supplied with a kit, the doctor injects the compositions described herein subcutaneously and/or supraperiosteally to increase chin projection (horizontally in the profile view), as well as to aesthetically sculpt, contour, and shape, limiting treatment to the pogonion, mentum, pre-jowl sulci, and sublabial (mental) crease. Suitable injection techniques have been

described above. The treatment goal is to increase chin projection (horizontally in the profile view) and achieve aesthetic chin contour. The doctor determines the appropriate injection volume up to about 4.0 mL for initial and possible top-up treatments combined.

[000106] The doctor gently molds the treated area using manual manipulation of the overlying tissue to achieve the desired facial contour.

[000107] A top-up treatment occurs approximately 30 days after the initial treatment if desired by the subject, or if in the doctor's opinion, optimal (full) increase in chin projection and/or aesthetic contouring was not achieved by the initial treatment. If a top-up treatment is performed, the volume of the administered composition as a combined total (initial treatment and top-up treatment) is between about 2.0 mL to about 4.0 mL.). During this visit, the doctor evaluates the treatment areas for any localized reaction and discusses any reported symptoms. 3D facial digital images (frontal and profile images) are captured for objective calculation of the angle of chin retrusion. If the doctor determines at top-up follow-up visit that optimal (full) increase in chin projection or aesthetic contouring was not achieved after the initial treatment, then subject is advised that he may receive a top-up treatment.

[000108] A single repeat treatment is administered at a scheduled visit between months 18 and 24 if repeat treatment is warranted in the doctor's opinion and/or is desired by the subject. Injection volume for the chin does not exceed a total volume of 4.0 mL for the repeat treatment.

[000109] Although the invention has been described and illustrated with a certain degree of particularity, it is understood that the present disclosure has been made only by way of example, and that numerous changes in the combination and arrangement of parts can be resorted to by those skilled in the art without departing from the scope of the invention, as hereinafter claimed.

[000110] Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are

approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[000111] Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements. Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

[000112] Specific embodiments disclosed herein may be further limited in the claims using consisting of or consisting essentially of language. When used in the claims, whether as filed or added per amendment, the transition term “consisting of” excludes any element, step, or ingredient not specified in the claims. The transition term “consisting essentially of” limits the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristic(s). Embodiments of the invention so claimed are inherently or expressly described and enabled herein.

[000113] In closing, it is to be understood that the embodiments of the invention disclosed herein are illustrative of the principles of the present invention. Other modifications that may be employed are within the scope of the invention. Thus, by way of example, but not of limitation, alternative configurations of the present invention may be utilized in accordance with the teachings herein. Accordingly, the present invention is not limited to that precisely as shown and described.

What is claimed is:

1. A sterile composition, implantable subdermally or supraperiostially into the chin area, jawline or nose of a patient in need thereof, the composition comprising a crosslinked hyaluronic acid (HA) crosslinked with 1,4-butanediol diglycidyl ether (BDDE);

wherein the HA concentration of the composition is greater than 20 mg/g;

wherein the HA used for crosslinking is made with a mixture of low molecular weight hyaluronic acid and high molecular weight hyaluronic acid,

where the HA used for crosslinking is a mixture containing at least 50% by weight of low molecular weight HA, based on the total weight of the HA;

wherein the composition has an elastic modulus between about 500 Pa and about 900 Pa at 5Hz

wherein the composition has a cohesivity above 60 gmf;

wherein the composition exhibits an extrusion force between about 4N and about 15N at 13 mm/min using a 1 mL COC syringe and a 27G x 13mm needle.

2. The composition of claim 1 where the HA concentration is about 22.5 mg/g.

3. The composition of claims 1 or 2 where the HA concentration is about 25 mg/g.

4. The composition of any one of claims 1-3 where the HA concentration is about 27.5 mg/g.

5. The composition of any one of claims 1-4 where the HA used for crosslinking is a mixture containing at least 70% by weight of low molecular weight HA, preferably at least 90% of low molecular weight HA, based on the total weight of the HA.

6. The composition of any one of claims 1-5 where the HA used for crosslinking is a mixture containing about 90% by weight of low molecular weight HA and about 10% by weight of high molecular weight HA, based on the total weight of the HA.

7. The composition of any one of claims 1-6 wherein the cohesivity is between about 60 gmf and about 200 gmf.

8. The composition of any one of claims 1-7 wherein the cohesivity is between about 60 gmf and about 100 gmf.

9. The composition of any one of claims 1-8 where the extrusion force is between about 7 and about 12N at 13 mm/min using a 1 mL COC syringe and a 27G x 13mm needle.

10. The composition of any one of claims 1-9 where the extrusion force is between about 8 and about 10N at 13 mm/min using a 1 mL COC syringe and a 27G x 13mm needle.

11. The composition of any one of claims 1-10 wherein the composition further includes an anesthetic agent.

12. The composition of any one of claims 1-11 wherein the composition further includes lidocaine hydrochloride.

13. The composition of any one of claims 1-12 wherein the composition further includes about 0.3% by weight lidocaine hydrochloride, based on the total weight of the composition.

14. The composition of any one of claims 1-13 wherein the HA has a degree of crosslinking of between about 4% and about 10%.

15. The composition of any one of claims 1-14 wherein the HA has a degree of crosslinking of about 4%.

16. The composition of any one of claims 1-15 wherein the HA has a degree of crosslinking of about 6%.

17. The composition of any one of claims 1-16 wherein the HA has a degree of crosslinking of about 8%.

18. The composition of any one of claims 1-17 wherein the HA has a degree of crosslinking of about 10% or about 6.5%.

19. The composition of any one of claims 1-18 wherein the composition comprises about 25 mg of crosslinked HA and 3 mg of lidocaine in a phosphate buffer pH 7.2 q.s. 1 mL, and wherein the crosslinked HA preferably has a degree of crosslinking of about 6.5%.

20. A method for correcting chin retrusion in a patient comprising:

supraperiostally administering into at least one treatment area of the face of the patient, an effective amount of a composition comprising BDDE-crosslinked hyaluronic acid (HA), the HA having a degree of crosslinking of about 6.5%, and having a HA concentration of greater than 20 mg/g, where the HA used for crosslinking is a mixture containing at least 50% by weight of low molecular weight HA, based on the total weight of the HA; the treatment area being selected from the group consisting of the pogonion, the mentum, the left pre-jowl sulcus, the right pre-jowl sulcus, and the sublabial crease.

21. The method of claim 20 wherein, prior to the administering, the patient has a G-Sn-Pog angle of less than about 165° based on calculations of facial angle derived from digital images of the patient.

22. The method of any one of claims 20-21 wherein the administering results in the patient having an increased G-Sn-Pog angle.

23. The method of any one of claims 20-22 wherein the patient has an increased G-Sn-Pog angle for a period of time in the range of about 9 months to about 24 months after the step of administering.

24. The method of any one of claims 20-23 wherein the patient has an increased G-Sn-Pog angle for at least about 6 months after the step of administering.

25. The method of any one of claims 20-24 wherein the patient has an increased G-Sn-Pog angle for at least about 9 months after the step of administering.

26. The method of any one of claims 20-25 wherein the patient has an increased G-Sn-Pog angle for at least about 12 months after the step of administering.

27. The method of any one of claims 20-26 wherein the patient has an increased G-Sn-Pog angle for at least about 18 months after the step of administering.

28. The method of any one of claims 20-27 wherein the patient has a G-Sn-Pog angle of about 169° or greater after the step of administering.

29. The method of any one of claims 20-28 wherein:

the HA concentration of the composition is about 25 mg/g,

wherein the HA used for crosslinking the composition is made with about 90% by weight of low molecular weight hyaluronic acid and about 10% by weight of high molecular weight hyaluronic acid, based on the total weight of the HA;

wherein the composition has an elastic modulus comprised between about 500 Pa and about 800 Pa at 5Hz

wherein the composition has a cohesivity between about 60 gmf and 100 gmf

wherein the composition has an extrusion force between about 8N and about 10N at 13 mm/min using a 1 mL COC syringe and a 27G x 13mm needle.

30. A method of creating or restoring volume to the chin or jaw of a patient, the method comprising injecting a sterile composition, subdermally or supraperiostially, into the chin area or jawline of the patient in need thereof, the composition comprising a crosslinked hyaluronic acid (HA) crosslinked with 1,4-butanediol diglycidyl ether (BDDE) and where the HA used for crosslinking is a mixture containing at least 50% by weight of low molecular weight HA, based on the total weight of the HA;

wherein the composition has an elastic modulus between about 500 Pa and about 800 Pa at 5Hz;

wherein the composition has a cohesivity between about 60 gmf and 100 gmf; and

wherein the method adds volume to the chin or jawline of the patient for a period of time in the range of about 9 months to about 24 months after injection of the composition into the chin or jawline of the patient.

31. The method of claim 30 wherein the composition has an extrusion force between about 8N and about 10N at 13 mm/min using a 1 mL COC syringe and a 27G x 13mm needle.

32. The method of claims 30 or 31 wherein the HA has a degree of crosslinking of between about 4% and about 12%.

33. The method of any one of claims 30-32 wherein the HA has a degree of crosslinking of about 6%.

34. The method of any one of claims 30-33 wherein the HA has a degree of crosslinking of about 8%.

35. The method of any one of claims 30-34 wherein the HA has a degree of crosslinking of about 10%.

36. The method of any one of claims 30-35 wherein the HA has a degree of crosslinking of about 6.5%.

37. The method of any one of claims 30-36 wherein the HA has a degree of crosslinking of about 8.5%.

38. The method of any one of claims 30-37 wherein the HA has a degree of crosslinking of about 10.5%.

39. A kit, comprising the composition according to any one of claims 1-19, prefilled in a single-use syringe such as a 1 mL COC syringe, and at least one single-use needle such as a 27G x 13mm needle.

40. A method for facial sculpturing, such as for augmenting, correcting, restoring or creating volume in the chin and and jaw area, in a patient comprising:

subcutaneously and/or supraperiosteally administering into at least one treatment area of the face of the patient, an effective amount of the composition of any one of claim 1-19 by injection of said composition; and

optionally massaging the treatment area of the patient's face, after administering is completed, to assure that the product conforms to the contour of the surrounding tissues;

wherein, prior to administering said composition, the treatment area is optionally disinfected;

the treatment area being preferably selected from the group consisting of the pogonion, the mentum, the left pre-jowl sulcus, the right pre-jowl sulcus, and the sublabial (mental) crease.

41. The method of claim 40, wherein the composition is injected using a 1 mL COC syringe and a fine gauge needle between about 18G and about 40G, more preferably about 25G to about 33G, or from about 25G to about 30G such as a 27G x 13mm needle.

42. The method of claims 40 or 41, wherein the composition is injected in an injection volume of less than 4.0 mL, such as about 2.0 mL, for a single treatment area at any treatment session.

43. The method of any one of claims 40-42, wherein the composition is injected in a maximum total volume of less than about 4.0 mL for initial and possible top-up treatments combined.

44. The method of any one of claims 40-43, wherein the pogonion is injected supraperiosteally using multiple small boluses, wherein the mentum is injected supraperiosteally using multiple small boluses, wherein the left and/or right pre-jowl sulci is injected using a deep subcutaneous fanning technique, wherein the sublabial (mental) crease is injected using linear, retrograde or anterograde superficial subcutaneous threading.

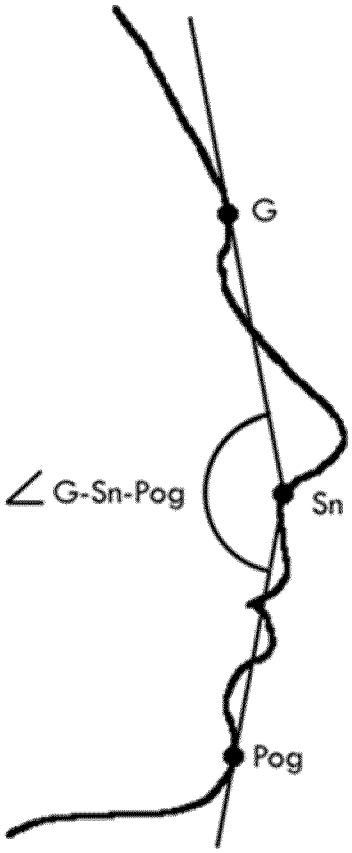
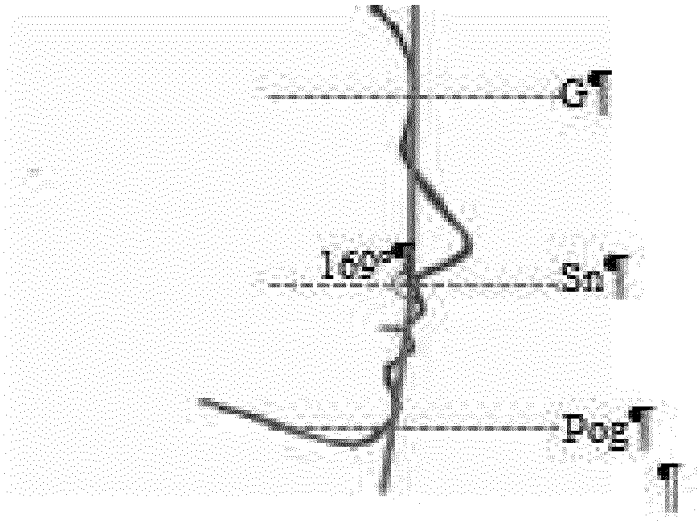


FIG. 1



G°=°glabella, Sn°=°subnasale, Pog°=°pogonion

FIG. 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/053009

A. CLASSIFICATION OF SUBJECT MATTER
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ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2010/028437 A1 (LEBRETON PIERRE F [FR]) 4 February 2010 (2010-02-04) page 1, paragraph 13 page 2, paragraph 17 page 4, right-hand column, paragraph 61 - page 5, left-hand column, paragraph 61 example 4 figure 1 ----- -/--	1-44

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Heck, Georg

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MARCOS BORRELL ET AL: "Lift capabilities of hyaluronic acid fillers", JOURNAL OF COSMETIC AND LASER THERAPY, TAYLOR & FRANCIS LTD, ABINGDON, GB, vol. 13, no. 1, 21 January 2011 (2011-01-21), pages 21-27, XP008177767, ISSN: 1476-4172, DOI: 10.3109/14764172.2011.552609 [retrieved on 2011-01-21] page 21, right-hand column, last paragraph - page 22, left-hand column, paragraph 1 -----	1-44

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/053009

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2010028437 A1	04-02-2010	AU 2009278883 A1	11-02-2010
		AU 2009278884 A1	11-02-2010
		CA 2732788 A1	11-02-2010
		CA 2732928 A1	11-02-2010
		CN 102170855 A	31-08-2011
		CN 102170856 A	31-08-2011
		CN 103285423 A	11-09-2013
		EP 2323617 A1	25-05-2011
		EP 2326302 A1	01-06-2011
		EP 2674147 A1	18-12-2013
		HK 1189518 A1	31-07-2015
		JP 5670899 B2	18-02-2015
		JP 5670900 B2	18-02-2015
		JP 5808848 B2	10-11-2015
		JP 2011529762 A	15-12-2011
		JP 2011529763 A	15-12-2011
		JP 2014237718 A	18-12-2014
		JP 2014237719 A	18-12-2014
		JP 2016000350 A	07-01-2016
		KR 20110040966 A	20-04-2011
		KR 20110043730 A	27-04-2011
		SG 10201505441T A	28-08-2015
		US 2010028437 A1	04-02-2010
		US 2010028438 A1	04-02-2010
		US 2012172328 A1	05-07-2012
		US 2013041038 A1	14-02-2013
		US 2013041039 A1	14-02-2013
		US 2013131011 A1	23-05-2013
		US 2013244970 A1	19-09-2013
		US 2014213546 A1	31-07-2014
		US 2014213547 A1	31-07-2014
		US 2015297790 A1	22-10-2015
		WO 2010015900 A1	11-02-2010
		WO 2010015901 A1	11-02-2010

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权利要求书3页 说明书13页 附图1页

(54)发明名称

用于雕塑、填充或矫正面部特征例如下巴的植入物

(57)摘要

本申请提供了一种可注射的装置，其用于长时间持续的面部雕塑和面部特征的矫正，例如用于填充和塑形轮廓，包括例如人类中的下巴、下颌外形或鼻子，所述装置包含基于透明质酸的组合物。本申请也提供了治疗方法。

CN 107223061 A

1.一种无菌组合物,其可以通过皮下或骨膜上植入到需要其的患者的下巴区域、下颌外形或鼻子中,该组合物包含与1,4-丁二醇二缩水甘油醚(BDDE)交联的交联透明质酸(HA);

其中所述组合物的HA浓度大于20mg/g;

其中用于交联的HA由低分子量透明质酸和高分子量透明质酸的混合物制成,

其中用于交联的HA为含有基于HA总重量计的至少50重量%的低分子量HA的混合物;

其中所述组合物的弹性模量在5Hz下为约500Pa至约900Pa;

其中所述组合物的粘合性大于60gmf;

其中使用1mL COC注射器和27G×13mm针头时,所述组合物的挤出力在13mm/min下为约4N至约15N。

2.根据权利要求1所述的组合物,其中所述HA的浓度为约22.5mg/g。

3.根据权利要求1或2所述的组合物,其中所述HA的浓度为约25mg/g。

4.根据权利要求1-3中任一项所述的组合物,其中所述HA的浓度为约27.5mg/g。

5.根据权利要求1-4中任一项所述的组合物,其中用于交联的HA为含有基于HA总重量计的至少70重量%的低分子量HA的混合物,优选至少90%的低分子量HA。

6.根据权利要求1-5中任一项所述的组合物,其中用于交联的HA为含有基于HA总重量计的至少90重量%的低分子量HA和约10重量%的高分子量HA的混合物。

7.根据权利要求1-6中任一项所述的组合物,其中所述粘合性为约60gmf至约200gmf。

8.根据权利要求1-7中任一项所述的组合物,其中所述粘合性为约60gmf至约100gmf。

9.根据权利要求1-8中任一项所述的组合物,其中使用1mL COC注射器和27G×13mm针头时,所述挤出力在13mm/min下为约7N至约12N。

10.根据权利要求1-9中任一项所述的组合物,其中使用1mL COC注射器和27G×13mm针头时,所述挤出力在13mm/min下为约8N至约10N。

11.根据权利要求1-10中任一项所述的组合物,其中所述组合物还包含麻醉剂。

12.根据权利要求1-11中任一项所述的组合物,其中所述组合物还包含盐酸利多卡因。

13.根据权利要求1-12中任一项所述的组合物,其中所述组合物还包含基于所述组合物总重量计的约0.3重量%的盐酸利多卡因。

14.根据权利要求1-13中任一项所述的组合物,其中所述HA的交联度为约4%至约10%。

15.根据权利要求1-14中任一项所述的组合物,其中所述HA的交联度为约4%。

16.根据权利要求1-15中任一项所述的组合物,其中所述HA的交联度为约6%。

17.根据权利要求1-16中任一项所述的组合物,其中所述HA的交联度为约8%。

18.根据权利要求1-17中任一项所述的组合物,其中所述HA的交联度为约10%或约6.5%。

19.根据权利要求1-18中任一项所述的组合物,其中所述组合物包含在补足到1mL的pH 7.2的磷酸盐缓冲液中的约25mg的交联HA和3mg的利多卡因,并且其中所述交联的HA的交联度优选地为约6.5%。

20.一种用于矫正患者的下巴后缩的方法,其包括:

通过骨膜上向患者面部的至少一个治疗区域给予有效量的一种组合物,所述组合物包

含BDDE交联的透明质酸(HA)，所述HA具有约6.5％的交联度，并且所述组合物具有大于20mg/g的HA浓度，其中用于交联的HA为含有基于HA总重量计的至少50重量％的低分子量HA的混合物；所述治疗区域选自颏前点、颏、左下颌前沟、右下颌前沟，以及唇下褶痕。

21.根据权利要求20所述的方法，其中在所述给药之前，基于对来源自所述患者的数字图像的面部角度的计算，所述患者的G-Sn-Pog角度小于约165°。

22.根据权利要求20-21中任一项所述的方法，其中所述给药使所述患者具有增加的G-Sn-Pog角度。

23.根据权利要求20-22中任一项所述的方法，其中在给药步骤后的约9个月至约24个月的时间段内，所述患者的G-Sn-Pog角度增加。

24.根据权利要求20-23中任一项所述的方法，其中在给药步骤后的至少约6个月内，所述患者的G-Sn-Pog角度增加。

25.根据权利要求20-24中任一项所述的方法，其中在给药步骤后的至少约9个月内，所述患者的G-Sn-Pog角度增加。

26.根据权利要求20-25中任一项所述的方法，其中在给药步骤后的至少约12个月内，所述患者的G-Sn-Pog角度增加。

27.根据权利要求20-26中任一项所述的方法，其中在给药步骤后的至少约18个月内，所述患者的G-Sn-Pog角度增加。

28.根据权利要求20-27中任一项所述的方法，其中在给药步骤后，所述患者的G-Sn-Pog角度为约169°。

29.根据权利要求20-28中任一项所述的方法，其中：

所述组合物的HA浓度为约25mg/g；

其中所述组合物的用于交联的HA由基于HA总重量计的约90重量％的低分子量透明质酸和约10重量％的高分子量透明质酸制成；

其中所述组合物的弹性模量在5Hz下为约500Pa至约800Pa；

其中所述组合物的粘合性为约60gmf至约100gmf；

其中使用1mL COC注射器和27G×13mm针头时，所述组合物的挤出力在13mm/min下为约8N至约10N。

30.一种产生或修复患者下巴或下颌的体积的方法，所述方法包括将一种无菌组合物通过皮下或骨膜上注入需要其的患者的下巴区域或下颌外形中，该组合物包含与1,4-丁二醇二缩水甘油醚(BDDE)交联的交联透明质酸(HA)，并且其中用于交联的HA为含有基于HA总重量计的至少50重量％的低分子量HA的混合物；

其中所述组合物的弹性模量在5Hz下为约500Pa至约800Pa；

其中所述组合物的粘合性为约60gmf至约100gmf；以及

其中在将所述组合物注入所述患者的下巴或下颌外形后的约9个月至约24个月的时间段内，所述方法增加所述患者的下巴或下颌外形的体积。

31.根据权利要求30的方法，其中使用1mL COC注射器和27G×13mm针头时，所述组合物的挤出力在13mm/min下为约8N至约10N。

32.根据权利要求30或31的方法，其中所述HA的交联度为约4％至约12％。

33.根据权利要求30-32中任一项的方法，其中所述HA的交联度为约6％。

34.根据权利要求30-33中任一项的方法，其中所述HA的交联度为约8％。

35.根据权利要求30-34中任一项的方法，其中所述HA的交联度为约10％。

36.根据权利要求30-35中任一项的方法，其中所述HA的交联度为约6.5％。

37.根据权利要求30-36中任一项的方法，其中所述HA的交联度为约8.5％。

38.根据权利要求30-37中任一项的方法，其中所述HA的交联度为约10.5％。

39.一种试剂盒，其包含根据权利要求1-19中任一项所述的组合物，所述组合物被预装在一次性注射器例如1mL COC注射器中，以及至少一支一次性针头例如27G×13mm针头。

40.一种用于患者中的面部雕塑的方法，例如用于填充、矫正、修复或产生下巴或下颌区域中的体积，所述方法包括：

向所述患者的面部的至少一个治疗区域，通过皮下或骨膜上给予有效量的权利要求1-19中任一项所述的组合物；以及

任选地在给药完成后，按摩所述患者的面部的治疗区域，以确保产品符合周围组织的轮廓；

其中在给予所述组合物之前，任选地消毒所述治疗区域；

所述治疗区域优选地选自颏前点、颏、左下颌前沟、右下颌前沟，以及唇下(颏的)褶痕。

41.根据权利要求40所述的方法，其中使用1mL COC注射器和细规格的针头注射所述组合物，所述针头规格为约18G至约40G，更优选约25G至约33G，或约25G至约30G，例如27G×13mm针头。

42.根据权利要求40或41所述的方法，其中对于在任何治疗期间的单个治疗区域，注射所述组合物，注射体积小于4.0mL，例如约2.0mL。

43.根据权利要求40-42中任一项所述的方法，其中对于组合的初始治疗和可能的补充治疗，注射所述组合物，最大总体积小于约4.0mL。

44.根据权利要求40-43中任一项所述的方法，其中使用多次小推注对颏前点进行骨膜上注射；其中使用多次小推注对颏进行骨膜上注射；其中使用深层皮下扇形技术，对左和/或右下颌前沟进行注射；其中使用直线的、逆行或顺行的表皮皮下线形法，对唇下(颏的)褶痕进行注射。

用于雕塑、填充或矫正面部特征例如下巴的植入物

[0001] 本发明概括地涉及可注射的组合物，并且更具体地涉及用于向面部的下部分增加结构和轮廓的可注射的植入物。

[0002] 皮肤填充剂是可注射的、生物相容性组合物，众所周知其可以矫正(correct)皱纹和皱褶并且增加面部体积。透明质酸(HA)仍然被许多人认为是最理想的皮肤填充剂之一，因为它没有引起过敏反应的风险，并且它是暂时和可逆的。绝大多数基于透明质酸的皮肤填充剂已被专门开发用于治疗皮肤的皱纹和皱褶。为了可用于面部轮廓化(contour)或实质上的增容(volumize)，增加组合物的膨胀(bulking)效果(也称为“提升”)将是有利的。使组合物对于在面部的软组织中所发生的剪切(shear)和正常变形的抗性最大化也是有利的。使这些抗性(例如弹性和内聚力)最大化的弊端之一，是可预期在这样做时，组合物的粘度将增加到它们难以用细针注射的程度。

[0003] 因此，亟需一种可注射的基于HA的植入物，将其特别设计为能有效地增加面部的实质性体积，例如用于轮廓化面部的下部分，例如用于填充(augment)或矫正下巴，例如用于下巴后缩的矫正，或者例如用于填充或矫正鼻子。如果这种植入物尽管具有高的粘度，但仍然易于用细针注射，则是非常有利的。

[0004] 长期以来，下巴的形状被认为是面部的一个重要特征，它引发了倾向于与个体的性格特征相关联的强的美学感知。通常将缺少凸出的有缺陷的下巴标记为“弱下巴”，而突起的下巴则标记为“强下巴”，这两者都暗示了个性的强弱。

[0005] 已有几项研究表明，具有平均比例的面部被认为是最有吸引力的，并且将包括小下巴的小特征视为女性中有吸引力的，而将由于成熟而变宽(expanded)的下巴和下颌视为男性中有吸引力的。下巴的外观是感知吸引力的决定因素，甚至可能影响个人的社会心理健康状况。

[0006] 下巴填充通常是通过手术将永久性植入物放置在下颌上方来进行。该手术是目前美国美容整形外科学会(American Society for Aesthetic Plastic Surgery)(ASAPS)所进行的顶级美容外科手术之一，并且自2010年以来已增加了71％。

[0007] 后缩的下巴可能是由于在成熟、外伤或面部衰老期间，面部下端的三分之一的生长发生了变化而造成的，其中后者(面部衰老)加剧了由于前两者(成熟和外伤)引起的变形或不对称。下颌骨的性状影响嘴部、下巴和颈部。随着个体衰老，该区域的骨架支撑的减小使软组织萎缩明显、使下脸(jowl)更大、减小下巴突出、并且使下颌外形(jawline)更弱。下巴变形是面部最常见的骨畸形中的一种，其中最常见的是以特征为存在正常垂直高度和后缩的骨下巴的水平小颏。

[0008] 由于下颌骨和下巴构成下部分面部的骨架，因此几十年来已经探索出用于治疗年龄相关的下巴后缩和下巴区域的轮廓变化或者治疗小颏的填充方法。当矫正下巴后缩的方法为增加体积时，治疗方法包括下巴植入物、颏成形术以及注射硅氧烷和半永久性填充剂，如聚甲基丙烯酸甲酯微球和羟磷灰石钙(calcium hydroxyapatite)。然而，所有这些治疗方法都有弊端。例如，下巴植入物和颏成形术包括疼痛的外科手术，该手术可能不会矫正该区域的下巴后缩和美学混合。这种方法可能加剧骨质吸收和感染，导致需要移除植入物。注

射半永久性填充剂是在与半永久填充剂相关的增容能力和不良事件之间的折衷。

发明内容

[0009] 因此，本发明提供了一种可注射的植入物用于面部雕塑(sculpting)，例如，用于在人的下巴和其他面部特征中填充、矫正、修复或产生体积。

[0010] 本发明提供了暂时的、可逆的、基于HA的结构凝胶，其被专门制造来提供产生面部体积或面部轮廓的安全的微创方法。相对于其它基于HA的注射剂，本发明的植入物提供了改善的增容和提升性能，原因是在仍然易于用细针注射的同时，包括高弹性和高粘合性在内的机械性能的组合。本发明植入物可用于注射到皮下和/或骨膜上空间(space)。在许多实施方案中，所述植入物在注射后是可模塑(moldable)的，因此允许对整个注射区域(例如下巴和下颌(jaw)区域)进行雕塑、轮廓化和塑形。

[0011] 所述植入物通常包含含有与选自下述交联剂交联的透明质酸(HA)的组合物，所述交联剂选自1,4-丁二醇二缩水甘油醚(BDDE)、1,4-双(2,3-环氧丙氧基)丁烷、1,4-双缩水甘油氧基丁烷、1,2-双(2,3-环氧丙氧基)乙烯和1-(2,3-环氧丙基)-2,3-环氧环己烷。在一些实施方案中，所述植入物通常包含含有与BDDE交联的透明质酸(HA)的组合物。所述组合物适合于例如通过细规格的针头注射，并且能够在面部填充、矫正或产生体积或提升，例如在面部的下部分，如下巴或下颌，或者用于面部中部，例如鼻子。

[0012] 在一些实施方案中，HA浓度大于20mg/g。在一些实施方案中，HA浓度为约21mg/g，或约22mg/g，或约23mg/g，或约24mg/g，或约25mg/g，或约26mg/g，或约27mg/g，或约28mg/g，或约29mg/g，或约30mg/g或更大。在其它实施方案中，所述组合物具有的HA浓度为22.5mg/g至27.5mg/g，例如25.0mg/g。

[0013] 在一些实施方案中，在给药或注射到患者的下巴或下颌外形之后的约9个月至约24个月的时间段内，该方法增加了患者的下巴或下颌外形或鼻子的体积和提升(lift)。所述组合物可以是可模塑的，例如通过在注射后一段时间内对植入物附近的组织进行物理操作。所述组合物的凝固时间可为植入或注射后约24至约48小时内，此时所述组合物不再是可模塑的并且在植入时间内基本保持其形状。

[0014] 在一些实施方案中，所述组合物还包括麻醉剂，例如利多卡因HCl。例如，组合物可以包括约0.3％w/w利多卡因HCl。

[0015] 在优选的实施方案中，所述组合物包含在磷酸盐缓冲液(pH7.2)中的透明质酸凝胶，优选地量为约25mg；和盐酸利多卡因，优选地量为约3mg，优选地体积补足到1mL。

[0016] 在一些实施方案中，组合物是由低分子量透明质酸和高分子量透明质酸的混合物制成。例如，在用交联剂交联之前，交联的透明质酸可以是由约50％至约100％的低分子量透明质酸制成。在一些实施方案中，在用交联剂交联之前，交联的透明质酸是由约70％至约90％的低分子量透明质酸制成。在一些实施方案中，在用交联剂交联之前，交联的透明质酸是由约90％的低分子量透明质酸制成。

[0017] 在交联前主要使用低分子量HA(例如约50％或更大，如约70％或约90％的低分子量HA)，而不是主要使用高分子量HA，来产生更坚固、持续时间更长、可模塑的水凝胶，其具有更高的粘合性和弹性，尤其是适用于通过皮下或骨膜上注射进行的面部雕塑和填充。

[0018] 在一些实施方案中，HA的交联度为约4％至约12％。例如，HA的交联度为约4％、或

约6％、或约8％、或约10％。在一些实施方案中，HA的交联度为约6.5％。在其它实施方案中，HA的交联度为约7.5％、或约8.5％、或约9.5％、或约10.5％。

[0019] 在本发明的另一方面，提供了用于矫正患者下巴后缩的方法。所述方法通常包括在患者的下巴中，通过骨膜上给予有效量的包含BDDE交联的透明质酸(HA)的组合物，HA的交联度为约10％，具有的HA浓度大于20mg/g。例如，在优选的实施方案中，HA的浓度为约25mg/g。

[0020] 在具体实施方案中，组合物包含与约10％BDDE(w/w)交联的低分子量透明质酸(NaHA)，并且在pH 7.2的磷酸盐缓冲液中，将其配制成浓度为约25mg/g(其中含0.3％盐酸利多卡因(w/w))，而且在1mL COC(环烯烃共聚物)注射器中供应。

[0021] 所述组合物可通过细规格的针头挤出，例如针头的规格为25G、26G、27G、28G、29G或30G。在具体实施例中，所述针为27G×13mm/27G1/2×26mm。

[0022] 挤出力为以一定速率将所述组合物从其注射器中挤出所需的力(以牛顿N计)。例如，使用所提供的1mL COC注射器和TSK 27G×13mm针头，将本发明的一些组合物以约13mm/min挤出时，挤出力可为约4N至约15N，这被认为是非常低的。例如，挤出力可为约7N至约12N，优选地约8N至约10N。

[0023] 在本发明的另一方面，本发明提供了用于轮廓化或矫正个体的面部特征(例如，后缩的下巴)的方法。所述方法包括，例如，将有效量的本发明组合物皮下给药至患者的治疗区域的步骤，所述有效量为例如约1.0ml或更多，例如约2.0ml或更多，例如约3.0ml或更多，例如4.0mL。待改善或轮廓化的面部特征可为下巴，例如患者的后缩下巴。治疗区域可以包括选自颏前点、颏(mentum)、左下颌前沟、右下颌前沟以及唇下褶痕(sublabial crease)的区域。所述治疗可包括将所述组合物给予两个或更多个治疗区域。

[0024] 本文描述的每个特征，以及两个或更多这样的特征的每一种组合都将包括在本发明范围内，条件是包括在这种组合中的特征相互之间没有不一致。

附图说明

[0025] 图 1示出用于计算患者G-Sn-Pog角度的面部轮廓和特征点(landmark)。

[0026] 图2示出平均下巴的Burstone角度。

具体实施方式

[0027] 在本说明书中使用的某些术语旨在表示如下文详细描述的以下定义。在术语的定义偏离该术语的常用含义的情况下，除非特别指出，否则申请人意欲使用下文所提供的定义。

[0028] 数值范围中的术语“约”容易为本领域技术人员所理解，其优选地表示特定值可以+/-10％改变。关于范围的终点，修饰词“约”优选地表示下端点(lower endpoint)可以减少10％，上端点(upper endpoint)增加10％。还想到的是，本申请中公开的每个数值或范围可以是绝对的，即可删除修饰词“约”。

[0029] 在本文中，表示HA的“分子量”的所有数字应理解为表示以道尔顿(Daltons)为单位的重均分子量(Mw)。

[0030] HA的分子量是由固有粘度测量，使用以下Mark Houwink关系式计算的：

[0031] 固有粘度(L/g)＝9.78×10-5×Mw0.690

[0032] 根据欧洲药典(HA专论号1472,01/2009)中规定的方法,测量固有粘度。

[0033] 除非另有说明,分子量指的是重均分子量(Mw)。用于制备本发明组合物的HA可包含高分子量HA、低分子量HA和/或中等分子量HA的混合物,其中高分子量HA的分子量大于约2,000,000Da(或固有粘度大于2.2L/g),其中低分子量HA的分子量小于约1,000,000Da(或固有粘度小于1.4L/g)。例如,本发明组合物中的高分子量HA的平均分子量可为约2MDa至约4.0MDa,例如约3.0MDa(2.9L/g)。在另一个实例中,高分子量HA的平均分子量可为约2.4MDa至约3.6MDa,例如约3.0MDa。高分子量HA的固有粘度可为大于约2.2L/g,例如约2.5L/g至约3.3L/g。

[0034] 低分子量HA的分子量可为约200,000Da(0.2MDa)至小于1.0MDa,例如约300,000Da(0.3Ma)至约750,000Da(1.1L/g),最高可以达到但不超过0.99MDa(1.4L/g)。低分子量HA的固有粘度可为小于约1.40L/g,例如约0.6L/g至约1.2L/g。

[0035] 优选地,低分子量HA材料和高分子量HA材料的分子量分布之间不存在重叠。

[0036] 优选地,低分子量HA和高分子量HA的混合物具有双峰分子量分布。所述混合物也可具有多峰分布。

[0037] 在本发明的一个方面,所述组合物包含具有高分子量组分和低分子量组分的HA,并且高分子量组分的重均分子量是低分子量组分的重均分子量的至少两倍。

[0038] 本文所用的“交联度”指的是将单个HA聚合物分子或单体链连接成永久性结构,或如本文所公开的软组织填充剂组合物的分子间连接。此外,对于本公开内容而言,将交联度进一步定义为在基于HA组合物的交联部分内,交联剂与HA-单体单元的重量百分比。其是通过交联剂与HA单体的重量比进行测量。

[0039] 如本文所用的“未交联的HA”指的是未交联的单个HA聚合物分子。未交联的HA通常保持水溶性。在所述组合物中也可任选地包括未交联的HA组分,例如用作润滑剂以及有利于注入面部组织。这种组合物可包含未交联的HA级分,其中所添加的未交联的HA以约0.1mg/g至约3mg/g的浓度存在。优选地,未交联的HA可以约0.2mg/g至约1.5mg/g的浓度存在。

[0040] 在其它实施方案中,所述凝胶中不存在未交联的HA,或者至少未向凝胶中加入未交联的HA以用作润滑剂。

[0041] 本文所述的组合物显示出高水平的弹性,其表示为弹性模量(G')值,该数值是通过使用锥板系统的应变为0.8%的振荡流变学,以及在一定频率范围下测量的。在一些实施方案中,在5Hz频率下测量的组合物的弹性模量为约500Pa至约900Pa。在基于HA的皮肤填充剂的情况下,这被认为是高弹性的,并且通过使植入物对于剪切变形更具有抗性而有助于提升效果。

[0042] 粘合性指的是凝胶保持附着于其自身的能力,例如,意指对切割的抗性,以及在不将其分离成片状的情况下伸长或压缩凝胶的能力。根据本发明,所述凝胶的粘合性可以如下量化(参见Derek Jones“Injectable Filers:Principles and Practice”,Wiley,2011,第3章)。将小的凝胶样品(例如1mL)放置在流变仪的平面上。放置所述样品以使得其形成一个小堆(heap)。将可移动的上板放置在样品上,使得样品被完全覆盖,例如,当以垂直于流变仪表面的方向观察所述板时,不能看到样品。为了确保这一点,必须选择比样品尺寸大的

板尺寸。理想地，将板的中心放置在样品上。通常，对于1mL凝胶材料，使用25mm直径的上板。

[0043] 在所述测量的下一步骤中，将可移动板和表面之间的间隙调整到2.5mm。在2分钟内，将所述板从该初始位置缓慢地且稳定地移动到间隙宽度为0.9mm时，记录样品在法向方向(normal direction)上施加的力(Fn)。

[0044] 一旦间隙宽度达到0.9mm，该系统可以松弛12分钟。在此期间，测量继续。进行五次测量。为了使测得的力归一化，将测试开始时测量的所有5个初始Fn值取平均值(算术平均值)，并从所有其他数据点中减去所得到的平均值。将在该测试的压缩部分结束时(当达到上板和平面之间的最小0.9mm间隙宽度时)的最大力称为压缩力，并且该压缩力为用于确定凝胶粘度的特征值。

[0045] 具体地，20gmf(0.1962N)或更大的力表示本发明意义上的粘合性材料。在本发明的上下文中，认为具有较低的压缩力值的凝胶通常不具有粘合性。测量的准确度的量级为约5gmf。在本发明的上下文中，可注射制剂具有至少约60gmf，例如约60至约200gmf的高粘合性。例如，在优选的实施方案中，粘合性为约60至约100gmf，其将赋予植入物对于面部软组织中压力和法向力(normal force)的高的抗性。

[0046] 在皮肤填充剂的内容中，如上定义的粘合性将有助于临床上由凝胶提供的提升能力(临床称为增容/膨胀效果)及其弹性模量G'。虽然粘合性凝胶可以显示出良好的增容效果，但具有相似弹性模量的非粘合性或弱粘合性材料则表现出较低的提升能力，这是因为在进行垂直压缩时，非粘合性凝胶材料与具有更大粘合性的材料相比扩散得更多。在本发明的上下文中，所述组合物表现出高水平的弹性模量和高水平的粘合性，以使植入时的提升效果最大化。

[0047] 在某些有利的、示例性实施方案中，本发明的植入物或填充剂通常包含粘合性的无菌组合物，其可以通过皮下或骨膜上植入到需要其的患者的下巴区域、鼻子或下颌外形中，例如需要改善的面部轮廓或更强的下巴的患者。所述组合物通常包含与1,4-丁二醇二缩水甘油醚(BDDE)交联的交联透明质酸(HA)；并且所述组合物的HA浓度大于20mg/g。例如，在一些实施方案中，HA浓度为约22.5mg/g，或约25mg/g，或约27.5mg/g。用于交联的HA可以由低分子量透明质酸和高分子量透明质酸的混合物制成。在一些实施方案中，所述组合物在5Hz下的弹性模量为约500Pa至约900Pa，并且粘合性大于约60gmf。有利地，在一些实施方案中，使用1mL COC注射器和27G×13mm针头时，所述组合物的挤出力在13mm/min下为约4N至约15N。

[0048] 在本发明的一个方面，相对于市售的基于HA的皮肤填充剂而言，提供了具有改善的提升能力的可注射的基于HA的植入物。在本公开内容的某些实例下，本发明的植入物也可称作皮肤填充剂和皮下填充剂。本发明的植入物和填充剂是基于透明质酸(HA)和HA的药学上可接受的盐(例如透明质酸钠(NaHA))。也提供了制备这些组合物的方法以及这些组合物的使用方法。

[0049] 如在本文中使用的，透明质酸(HA)可以指其任意的透明质酸盐，并且包括但不限于透明质酸钠(NaHA)、透明质酸钾、透明质酸镁、透明质酸钙及其组合。HA及其药学上可接受的盐均可用于本发明。

[0050] 此外，在具有麻醉剂的实施方案中，一种或多种麻醉剂的浓度为在注射所述组合物时有效缓解所经历的疼痛的量。至少一种局部麻醉剂可选自氨部卡因(ambucaine)、阿莫

拉酮(amolanone)、阿米卡因(amylocaine)、丁氧普鲁卡因(benoxinate)、苯佐卡因(benzocaine)、贝托卡因(betoxycaine)、苯柳胺酯(biphenamine)、布比卡因(bupivacaine)、布他卡因(butacaine)、氨苯丁酯(butamben)、布坦卡因(butanilicaine)、丁胺卡因(butethamine)、丁托西卡因(butoxycaine)、卡替卡因(carticaine)、氯普鲁卡因(chloroprocaine)、己基苯酰爱康因(cocaethylene)、可卡因(cocaine)、环美卡因(cyclomethycaine)、地布卡因(dibucaine)、奎尼卡因(dimethisoquin)、二甲卡因(dimethocaine)、地哌冬(diperodon)、双环维林(dicyclomine)、去水芽子碱(ecgonidine)、芽子碱(ecgonine)、氯乙烷、依替卡因(etidocaine)、β-优卡因(beta-eucaine)、尤普罗辛(euprocin)、非那可明(fenalcomine)、formocaine、海克卡因(hexylcaine)、羟丁卡因(hydroxytetracaine)、对氨基苯甲酸异丁酯、亮氨卡因甲磺酸酯、左沙屈尔(levoxadrol)、利多卡因(lidocaine)、甲哌卡因(mepivacaine)、美普卡因(meprylcaine)、美布卡因(metabutoxycaine)、氯甲烷、麦替卡因(myrtecaine)、纳依卡因(naepaine)、利多卡因(octocaine)、奥索卡因(orthocaine)、奥昔卡因(oxethazaine)、对乙氧卡因(parethoxycaine)、非那卡因(phenacaine)、苯酚、哌罗卡因(piperocaine)、匹多卡因(piridocaine)、聚乙二醇单十二醚(polidocanol)、普拉卡因(pramoxine)、丙胺卡因(prilocaine)、普鲁卡因(procaine)、丙泮卡因(propanocaine)、丙对卡因(proparacaine)、丙哌卡因(propipocaine)、丙氧卡因(propoxycaine)、假可卡因(pseudococaine)、吡咯卡因(pyrrocaine)、罗哌卡因(ropivacaine)、水杨醇、丁卡因(tetracaine)、托利卡因(tolycaine)、三甲卡因(trimecaine)、佐拉敏(zolamine)及它们的盐。在一个实施方案中,所述至少一种麻醉剂为例如以利多卡因HCl形式的利多卡因。本文所述的组合物可具有的利多卡因浓度为所述组合物的约0.1重量%至约5重量%,例如所述组合物的约0.2重量%至约1.0重量%。在一个实施方案中,所述组合物具有的利多卡因浓度为所述组合物的约0.3重量%(w/w%)。本文所述组合物中利多卡因的浓度可以是治疗有效的,这意指浓度足以提供治疗益处而不对患者造成伤害。

[0051] 本发明组合物可通过以下步骤制备:提供例如NaHA纤维形式的纯化的HA材料;使HA材料水合,所述HA材料具有所需的分子量,例如所需比例的低分子量和高分子量HA的混合物;并使所需比例的水合的HA材料与合适的交联剂交联,以形成交联的基于HA的凝胶。然后可以将凝胶中和并且溶胀。如果需要,可以加入含有利多卡因(优选利多卡因盐酸盐的酸性盐)的溶液,以形成HA/利多卡因凝胶。可以例如通过用剪切力打浆或混合使凝胶匀化。然后将匀化的组合物装入注射器中。然后在有效温度和压力下,将注射器通过高压灭菌消毒。例如,通过高压灭菌对组合物进行灭菌,例如在至少约120℃至约130℃的温度和/或至少约12磅/平方英寸(PSI)至约20PSI的压力下,暴露至少约1分钟至约15分钟的时间段。将灭菌的注射器与细针头一起包装,以供医生使用。

[0052] 更具体地,最初的HA原材料可以包含NaHA的纤维或粉末,例如细菌来源的NaHA纤维。或者,HA材料可以为动物来源,例如来自公鸡冠。应到想到的是,HA材料可为包括HA的原材料和至少一种其它多糖(例如另一种糖胺聚糖(GAG))的组合。

[0053] 在一种制造所述组合物的方法中,将纯的干燥的NaHA纤维在碱性溶液中水合以产生未交联的NaHA凝胶。在该步骤中,任何合适的碱性溶液均可用于水合NaHA,例如但不限于含有氢氧化钠(NaOH)、氢氧化钾(KOH)、碳酸氢钠($NaHCO_3$)、氢氧化锂(LiOH)等的水性溶液。

所得的碱性凝胶的pH将大于7.5。所得的碱性凝胶的pH可以具有大于9的pH,或大于10的pH,大于12的pH或大于13的pH。

[0054] 所述制造过程中的下一步骤可包括用合适的交联剂来交联水合的碱性NaHA凝胶的步骤。交联剂可以是已知的适用于使多糖及其衍生物通过其羟基进行交联的任何试剂。一种特别合适的交联剂为1,4-丁二醇二缩水甘油醚(BDDE)。

[0055] 在另一个实施方案中,在HA纤维水合期间,通过在含有交联剂(例如BDDE)的碱性溶液中使组合的高分子量和低分子量纤维发生水合,来完成HA的交联。

[0056] 在本发明组合物的HA组分中,交联度为至少约4%,并且最高达约12%BDDE/HA,w/w,例如约10%,例如约8%,例如约6%,例如约4%。在一个具体实施方案中,交联度为约6.5%。在一些实施方案中,HA的交联度为约6.5%。在其它实施方案中,HA的交联度为约7.5%、或约8.5%、或约9.5%、或约10.5%。

[0057] 可将水合的交联的HA凝胶溶胀以获得所需的HA浓度。该步骤可通过中和交联的水合HA凝胶来实现,例如通过加入含有酸如HCl的水溶液。然后将凝胶在磷酸盐缓冲盐水(PBS)溶液中于低温下溶胀足够的时间。

[0058] 目前可以通过常规方法来纯化凝胶,例如用磷酸盐缓冲液透析或醇沉淀来以回收交联的材料,以稳定材料的pH并移除任何未反应的交联剂。可以加入额外的水或微碱性水溶液以使所述组合物中HA的浓度达到所需浓度。在一些实施方案中,将所述组合物的HA浓度调节至大于20mg/g,例如至约25mg/g。在其它实施方案中,对HA进行浓度调整以得到约21mg/g,约22mg/g,约23mg/g,约24mg/g,约26mg/g,约27mg/g,约28mg/g,约29mg/g或约30mg/g的HA浓度。

[0059] 在其中最终组合物中包括有麻醉剂(例如利多卡因)的实施方案中,可以调节纯化的交联HA凝胶的pH以使所述凝胶成为微碱性,以使得所述凝胶的pH值为大于约7.2,例如约7.5至约8.0。该步骤可以通过任何合适的方法实现,例如通过向凝胶加入适量的稀NaOH、KOH、$NaHCO_3$或LiOH,或任何其它碱性分子、溶液和/或缓冲组合物。

[0060] 然后将有效量的麻醉剂(例如利多卡因,如利多卡因HCl)加入到纯化的交联NaHA凝胶中。例如,在一些实施方案中,将利多卡因HCl以可使用注射用水(WFI)而溶解的粉末形式提供。为了最终的HA/利多卡因组合物具有所需的、基本上中性的pH,采用缓冲液或通过采用稀释的NaOH进行调节,使所述凝胶保持中性。包含利多卡因的最终组合物可具有的利多卡因浓度为所述组合物的至少约0.1重量%至约5重量%,例如约2重量%,或在另一实例中约0.3重量%。

[0061] 在加入利多卡因HCl后,或者在加入利多卡因HCl期间,使HA/利多卡因凝胶或组合物匀化,以产生具有所需一致性(consistency)和稳定性的高度均匀的HA/利多卡因凝胶。优选地,匀化步骤包括用受控的剪切力混合、搅拌或打浆凝胶,以获得基本均匀的混合物。

[0062] 在使HA组合物匀化之后,可将一定量的未交联的HA溶液或凝胶加入到所述组合物中以增加润滑性。

[0063] 在一些实施方案中,在匀化后,不将未交联HA的溶液加入到所述组合物中。

[0064] 然后将所述组合物引入注射器并灭菌。根据本说明书,可使用的注射器包括本领域中已知的能够递送粘性皮肤填充剂组合物的任何注射器。注射器的内部体积通常为约0.4mL至约3mL,更优选地约0.5mL至约1.5mL或约0.8mL至约2.5mL。该内部体积与注射器的

内径相关联，所述内径在注射高粘性皮肤填充剂组合物所需的挤出力中发挥关键性作用。所述内径通常为约4mm至约9mm，更优选地为约4.5mm至约6.5mm，或约4.5mm至约8.8mm。此外，从注射器递送HA组合物所需的挤出力还取决于针头规格。所使用的针头规格通常包括约18G至约40G，更优选地约25G至约33G或约25G至约30G的规格。例如，在一些实施方案中，将所述组合物装入1mL注射器中并使用27G针头注射。

[0065] 一种优选的预装注射器(filled syringe)的灭菌方法是通过高压灭菌器。高压灭菌可通过将热量、压力和湿气(moisture)的混合施加到需要灭菌的样品上来实现。许多不同的灭菌温度、压力和循环时间可用于此步骤中。例如，预装注射器可以在至少约120℃至约130℃或更高的温度下灭菌。可能利用或可能不利用湿气。在一些实施方案中，所施加的压力取决于灭菌过程中所用的温度。灭菌周期可为至少约1分钟至约20分钟或更长。

[0066] 灭菌的另一种方法包括使用已知的可杀死或消除可传染源的气态物质。优选地，将环氧乙烷用作灭菌气体，并且本领域中已知其可用于消毒医疗器械和产品。

[0067] 灭菌的另一种方法包括使用本领域中已知的用于杀死或消除可传染源的辐射源。辐照束以含有HA组合物的注射器为目标，并且能量波长杀死或消除不需要的可传染源。优选地，可使用的能量包括但不限于紫外线(UV)光、γ照射、可见光、微波或任何其它波长或波段(其杀死或消除不想要的可传染源)，优选地基本上不改变或降解HA组合物。

[0068] 优选地，在将本发明组合物长时间储存时，其也保持稳定。例如，在在约2至25摄氏度的温度下储存时，许多本发明组合物的贮存期限为约6个月、约12个月、约18个月或约24个月或更长。在一个具体实施方案中，在2至25摄氏度的温度下，所述组合物在至少18个月的时间段内是稳定的。在另一个具体实施方案中，在2至25摄氏度的温度下，所述组合物在至少24个月的时间段内是稳定的。

[0069] 用于注射本发明组合物的技术可以根据倾斜的角度和取向以及给药量而变化。通常，将本发明的组合物以皮下注射和/或骨膜上注射以增加下巴凸出，同时限制对颏前点、颏(下巴的下面)、下颌前沟(左和右)、以及唇下(颏的)褶痕的治疗以达到最佳的矫正和美观的下巴轮廓。合适的注射体积将由研究者确定，但对于初始和补充治疗的组合，一般不超过约4.0mL的最大总体积。对于反复治疗，允许总计约4.0mL。在任何治疗期间(treatment session)，允许将不超过约2.0mL注射到单个治疗区域，其中治疗区域被定义为颏前点、颏、下颌前沟(左和右)、以及唇下(颏的)褶痕。

[0070] 在注射本发明组合物之前，治疗区域必须彻底消毒，以确保可注射填充剂不会被细菌或异物(例如化妆品、手套的滑石粉)污染。

[0071] 然后，应该将所提供的27G 1/2”/27G×13mm的针头连接到注射器(根据使用指南)。在注射本发明的组合物之前，必须将柱塞杆(plunger rod)压下直到可以看见产品流出针头并且在无菌纱布上擦拭任何过量的产品。

[0072] 本发明的组合物按如下方式注射：缓慢注射本发明的组合物，并观察皮肤的颜色变化或变色的迹象。观察受试者的疼痛或不适。以平稳和测量的方式注射本发明的组合物。插入针头时应留意注射部位的局部血管解剖结构。抽吸(aspirate)以确保没有血液回流，其表明针的尖端在血管内的位置。

[0073] 可以使用多次小推注，对颏前点进行骨膜上注射。可以使用多次小推注，对颏进行骨膜上注射。可以使用深层皮下扇形(deep subcutaneous fanning)技术，对下颌前沟(左

和右)进行注射。可以使用直线的、逆行或顺行的浅表性皮下线形(superficial subcutaneous threading)法,对唇下(颏的)褶痕进行注射。

[0074] 在治疗完成时,可轻轻按摩治疗部位,以确保产品均匀分布,并适合周围组织的轮廓。如果发生过度矫正,请轻轻按摩手指之间或骨骼上方的区域,以获得最佳效果。

[0075] 不要将本发明的组合物注入血管中(血管内)。将透明质酸引入血管可能堵塞血管,并可能导致梗死或栓塞。血管闭塞和栓塞的症状包括,与操作不成比例的或远离注射部位的疼痛,延伸超出注射区域且可呈现出血管分支分布的立即性发白(blanching),以及反映缺血性组织(例如暗灰的外观或网状外观)的颜色变化。

[0076] 在小面积上过于浅表地或大量地注射所述产品都可导致可见的且持久的结块(lump)和/或变色。

[0077] 当使用逆行性技术时,注射本发明的组合物时,将压力均匀地施加在柱塞杆上,同时缓慢地将针头向后拉。重要的是,正好在针头穿过皮下/皮肤界面之前停止注射,以防止物质渗出或在皮肤的过于浅表处结束。当使用顺行性技术时,在注射开始之前,确保针头位于皮下组织中。

[0078] 如果针头被堵塞,不要增加柱塞杆上的压力,而是停止注射并更换针头。

[0079] 如果在注射后治疗区域立即肿胀,则可将冰袋短时间地施用于该部位。如果受试者报告持续1周以上的炎症反应,或发生了任何其他的副作用,医生应采取适当的治疗。

[0080] 在优选的实施方案中,本发明的组合物包含在磷酸盐缓冲液(pH7.2)中的透明质酸凝胶,优选地其量为约25mg;和盐酸利多卡因,优选地其量约为3mg,优选地体积补足到1mL,将其预装于例如1mL一次性注射器中,其中透明质酸凝胶与BDDE交联。可将这种预装的例如1mL一次性注射器以及两支一次性针头(例如27G 1/2”/27G×13mm针头)容纳于一个试剂盒(泡罩包装)中。注射器的内容物可通过湿热法(moist heat)进行灭菌。一次性针头可通过辐射灭菌。

[0081] 本发明的组合物为旨在用于修复和产生面部体积(例如在下巴和下颌区域中)的可注射植入物。利多卡因的存在是为了在治疗期间减轻受试者的疼痛。

[0082] 实施例1

[0083] 根据本发明实施例的可注射植入物的制备

[0084] 称取预先干燥的分子量为约0.9MDa的透明质酸钠(NaHA)纤维(0.9g)到第一容器中。

[0085] 称取预先干燥的分子量为约3.0MDa的NaHA纤维(0.1g)到第二容器中。

[0086] 在20℃至50℃下,将两种不同等级的NaHA合并,并且在1%氢氧化钠溶液中进行稀释,混合1至2小时,以获得基本均匀的碱性HA凝胶。

[0087] 在单独的容器中,将所选择的交联剂1,4-丁二醇二缩水甘油醚(BDDE)在1%氢氧化钠溶液中稀释至终浓度为10%BDDE(wt/wt)。

[0088] 向碱性HA凝胶中加入10%(wt/wt)BDDE(1g预先制备的BDDE溶液)。将所得混合物进行机械匀化。

[0089] 然后所述混合物在50℃下保持3至4.5小时。

[0090] 随后将所得的交联的HA聚合物浸入含有盐酸的磷酸盐缓冲液(PB)中以稳定pH。

[0091] 之后将如此获得的交联的HA聚合物浸入磷酸盐缓冲液的浴液中,以除去未反应的

交联剂和HA，从而提供纯的水凝胶，其中交联度为约6.5％。

[0092] 任选地，在1升磷酸盐缓冲液中，将具有高分子量的干HA材料水合以获得未交联的HA凝胶。这种未交联的HA凝胶可被加入到交联的HA组合物中，以占总HA浓度的最高达5％(w/w)。

[0093] 然后将所得的水凝胶进行机械匀化以确保最终的均匀性，并将其装入已经在高压灭菌器中灭菌过的注射器中。

[0094] 所得的凝胶为可以通过细规格针头(例如27规格)进行皮下或骨膜上给药的可注射组合物。该组合物可用于修复、轮廓化(contour)或产生面部体积(例如在人的下巴、下颌区域或鼻子中)，如本文别处所记载的。

[0095] 在本发明的一个方面，提供了用于改善患者面部轮廓的方法。例如，在一些实施方案中，提供了用于改变人的G-Sn-Pog面部角度的方法，例如用于增加人的G-Sn-Pog面部角度。例如，在一些实施方案中，提供了用于矫正患者的下巴后缩的治疗方法。在本发明的一些实施方案中，所治疗的患者的初始的治疗前G-Sn-Pog面部角度为小于约165°。治疗后，所述患者的G-Sn-Pog面部角度增加，即面部角度大于初始的治疗前的面部角度。在一个实施方案中，在给药步骤后，所述患者的G-Sn-Pog面部角度为约169°或更大。G-Sn-Pog角度可使用常规设备和计算进行测量，例如，可使用Canfield科学面部成像设备，基于由患者的数字图像得到的面部角度的计算。图1示出了用于计算患者的G-Sn-Pog角度的面部轮廓和特征点，使用已知方法可将其用于来诊断或确定下巴后缩的存在和/或程度。

[0096] 所述方法通常包括向患者面部的至少一个治疗区域，给予有效量的这样一种组合物，所述组合物包含BDDE交联的透明质酸(HA)，HA的交联度为约6.5％或约10％，并且所述组合物具有大于20mg/g的HA浓度。

[0097] 在一些实施方案中，提供了治疗方法，所述方法包括将组合物(例如本文所述)通过骨膜上给予至患者面部的至少一个治疗区域中，其中患者的G-Sn-Pog面部角度为145°至165°。面部角度值可基于对由患者的数字图像得到的面部角度的计算或者使用其他技术得到的面部角度的计算。根据一些实施方案，相对于治疗前(例如在临给药步骤之前)患者的G-Sn-Pog面部角度，给药的步骤会使所述患者的G-Sn-Pog面部角度增加。在一些实施方案中，在给药步骤后的一段时间，至少约3个月，或更优选至少约6个月，例如约9个月至约24个月，所述患者具有增加的G-Sn-Pog角度。例如，在给药步骤后的至少约6个月，或至少约9个月，或至少约12个月或至少约18个月或至少约24个月，所述患者具有增加的G-Sn-Pog角度。

[0098] 在一些实施方案中，治疗区域是选自以下的区域：颏前点、颏、左下颌前沟、右下颌前沟，以及唇下褶痕。治疗可以包括将组合物给予两个或更多治疗区域。所述给药包括将组合物按每个治疗区域约0.5mL至约3.0mL的量进行骨膜上或皮下注射。在一些实施方案中，注入给定治疗区域的量不超过2.0mL。在一些实施方案中，在单个治疗期间——所有治疗区域中——注射的总量为2.0mL至约6.0mL，例如约2.5mL，约3.0mL，约3.5mL，约4.0mL，约4.5mL，约5.0mL，约5.5mL或约6.0mL。在一些实施方案中，在单个治疗期间的给药量为约4.0mL或更少。

[0099] 下巴和下颌中体积的修复或产生

[0100] 在一个方面，本发明提供了在下巴和下颌中修复或产生体积的方法，例如对整个面部特定治疗区域的雕塑、塑形和轮廓化。治疗区域可以包括一个或多个颏前点(下巴前表

面上最突出的点)、颏(下巴的最低点)、左下颌前沟和右下颌前沟(左侧靠近下颌角点的凹槽(left antigonion notch)和右侧靠近下颌角点的凹槽(right antigonion notch))、以及唇下(颏的)褶痕(下唇和颏之间的褶痕)。

[0101] 下巴的形状和凸出有助于作为吸引力基础的面部的成比例平衡。通常将缺少凸出的下巴标记为“弱下巴”,而凸出的下巴则标记为“强下巴”并且暗示了个性的强弱。已有几项研究表明,具有平均比例的面部被认为是最有吸引力的,并且将包括小下巴的少年特征视为女性中有吸引力的,而将强的下巴和下颌视为男性中有吸引力的。下巴的外观是感知吸引力的决定因素,并且可能影响个人的社会心理健康状况。

[0102] 平均比例是通过对群体中的面部轮廓的示意图分析来规定的,并且包括鼻子、唇部和颏之间的距离和角度。在头部测量分析中已经使用了几个软组织特征点以测量和诊断与平均面部参数相比的下巴前突(protrusion)和后缩偏离。对于面部上部分和面部前下部分的交点和由眉间点、鼻中隔下点和颏前点(G-Sn-Pog)上的点而形成的角度进行广泛的分析,以了解人群中常见的平均下巴凸出。已将平均下巴的Burstone角度(图2)定义为大约169°,并且近似角度(168°至169°)已在几项研究中得到确认。

[0103] 与平均下巴的偏差增加将产生面部不具有吸引力的感知。分析面部轮廓与吸引力感知之间的关系表明,下巴突起在这种感知中发挥着重要的作用。为了理解下巴突起程度和吸引力之间的关系,将一系列与理想轮廓图像相比改变为2毫米以内的增加的轮廓图像,呈现给一组预治疗的正畸患者、临床医生和非专业人士。要求受试者按照7分Likert量表给每张图像评分,从极其不具有吸引力到极其具有吸引力。对于每2毫米的下巴后缩,在Likert量表上感知吸引力的评分会平均下降0.15,并且在4毫米变化后,感知吸引力的评分则是显而易见的。对于患者和临床医生而言,需要进行外科手术的下巴后缩程度为11mm,而对于非专业人员为10mm。最有吸引力的图像为能够显示出理想的正颌轮廓的图像,其具有落在(resting on)真正的垂直线上的软组织颏前点。

[0104] 实施例2

[0105] 用于在具有下巴后缩或弱下巴的受试者中增加S GN POG面部角度的方法

[0106] 通过在32岁男性受试者的下巴和/或下颌区域中进行皮下或骨膜上注射,将本发明的组合物作为可注射植入物给予。所述受试者抱怨他有一个“弱下巴”。医生测量了受试者的面部角度,并确定G-Sn-Pog角度约为150°,这大大地低于平均下巴的经典Burstone角度(约169°)。该测量是基于从使用Canfield成像设备和软件获得的数字图像而得出的面部角度的计算。

[0107] 医生认为受试者的下巴/下颌后缩适于这样的矫正,即其治疗目标为水平地增加下巴突出(在剖面图中),而不是下巴拉长或变宽。

[0108] 医生认为通过使用本文所述的可植入组合物,他可以为受试者提供更具吸引力的面部轮廓和更强的下颌外形。

[0109] 如下所述,受试者经历三次治疗阶段,包括初始治疗、补充(top-up)治疗和重复治疗。

[0110] 对于每次治疗,治疗区域包括至少一个或多个以下的治疗区域:颏前点(下巴前表面上最突出的点)、颏(下巴的最低点)、左下颌前沟(左侧靠近下颌角点的凹槽)、右下颌前沟(右侧靠近下颌角点的凹槽)、和/或唇下褶痕(下唇和颏之间的褶痕)。

[0111] 在任何治疗期间,医生在单个治疗区域内植入不超过2.0mL。

[0112] 对受试者进行的初始治疗如下。医生使用无菌皮肤处理(preparation),并按照他的标准操作进行麻醉。施用冰和局部麻醉可减轻注射不适。注射麻醉仅限于治疗区域,并且确定注射麻醉的给药不会使所规划的治疗区域变形。

[0113] 使用由试剂盒提供的针(27规格×13mm/27G1/2"),医生通过皮下和/或骨膜上注射本文所述的组合物以增加下巴凸出(在剖面视图中为水平地),以及进行美学上的雕塑、轮廓化和塑形,同时限制了对颏前点、颏、下颌前沟及唇下(颏的)褶痕的治疗。合适的注射技术已记载在上文中。治疗目标为增加下巴凸出(在剖面视图中为水平地)并实现符合美学的下巴轮廓。医生确定用于组合的初始治疗和可能的补充治疗的合适注射体积为最高达约4.0mL。

[0114] 医生使用对覆盖组织的人工操作来温柔地塑造(mold)治疗区域,以实现所需的面部轮廓。

[0115] 如果受试者需要,或者如果按照医生的观点,通过初始治疗未能达到下巴凸出和/或美学轮廓的最佳(完全)增加,则在初始治疗后约30天进行补充治疗。如果进行补充治疗,所给予的组合物的体积以组合总量(初始治疗和补充治疗)计为约2.0mL至约4.0mL之间。在该探视期间,医生评估治疗区域的任何局部反应,并讨论任何报告的症状。捕获3D面部数字图像(正面和轮廓图像),用于下巴后缩角度的客观计算。如果医生在补充的随访中确定初始治疗后未能达到下巴凸出或美学轮廓的最佳(完全)增加,则应建议受试者可以接受补充治疗。

[0116] 如果如果按照医生的观点认为需要和/或受试者希望进行重复治疗,则在18至24个月期间的预定访视中给予单次重复治疗。对于重复治疗,下巴的注射体积不超过4.0mL的总体积。

[0117] 尽管已经在一定程度上详细描述和说明了本发明,但是应当理解,本公开内容仅用于举例说明,并且本领域技术人员在不偏离后文中权利要求所限定的本发明范围的情况下,能够获得对各个部分的组合和布置的许多变化。

[0118] 除非另有说明,否则应理解在说明书和权利要求书中使用的所有表示成分的量、性质(例如分子量、反应条件等)的数值在所有情况下都被术语"约"修饰。因此除非有相反指示,否则说明书和所附权利要求中提出的数值参数为近似值,该近似值可根据待通过本发明获得的期望性质而改变。最低限度,但不是试图限制对权利要求范围的等同原则的应用,每个数值参数至少应该根据所报告的有效数字的数值和通过应用普通舍入技术来解释。

[0119] 尽管阐明本发明的较宽范围的数值范围和参数是近似值,但是具体实施例中列出的数值是尽可能精确报道的。然而,任何数值都固有地包含在其各自的试验测定中存在的必然由标准偏差产生的某些误差。尽管阐明本发明的较宽范围的数值范围和参数是近似值,但是具体实施例中列出的数值是尽可能精确报道的。然而,任何数值都固有地包含在其各自的试验测定中存在的必然由标准偏差产生的某些误差。

[0120] 在权利要求中可以使用表述由……组成或基本上由……组成来进一步限制本文公开的具体实施方案。当在权利要求中使用时,无论是原始提交的还是根据修改添加的,过渡术语"由……组成"均不包括权利要求中未指定的任何要素、步骤或成分。过渡术语"基本

上由...组成”将权利要求的范围限定至指定的材料或步骤,以及不会实质上会影响基本和新的特征的那些材料和步骤。本文所要求保护的本发明的实施方案在本文中被固有地或明确地描述和实现。

[0121] 总之,应当理解,本文公开的本发明的实施方案是对本发明的原理的举例说明。在本发明范围内可以采用其它修改。因此,通过示例而非限制的方式,可根据本文的教导利用本发明的备选形式(configuration)。因此,本发明并不限于所准确示出和描述的那些。

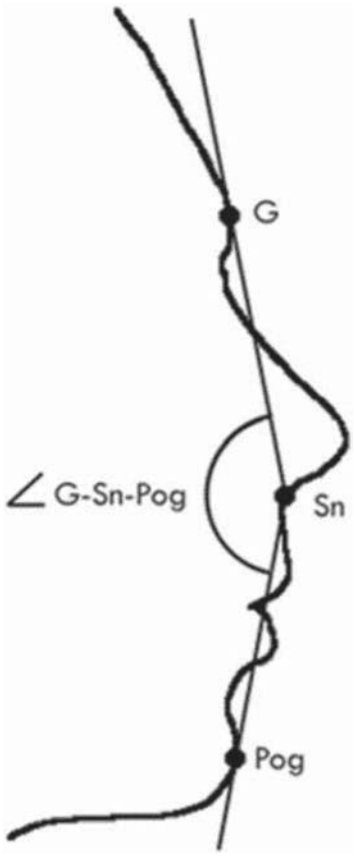

图1

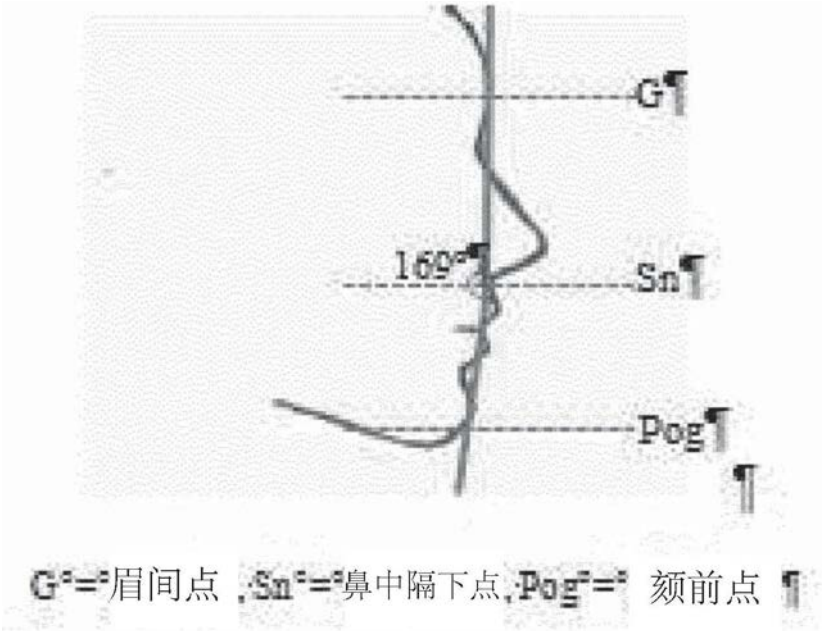

图2