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REVIEW

STYLAGE®: a range of hyaluronic acid dermal fillers containing mannitol. Physical properties and review of the literature

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Abstract: Dermatological procedures which are considered as being minimally invasive, such as those using injectable fillers based on hyaluronic acid, revolutionized aging treatment, especially of the face. By promoting the replacement of lost volume and attenuating grooves and wrinkles, they ensure a more youthful appearance and certain functional recovery of facial aesthetics. The authors review some of the main physicochemical characteristics of these dermal fillers, highlighting the product line Stylage®, the manufacture of which includes mannitol.

Keywords: fillers, hyaluronic acid, mannitol, facial aging, wrinkles, stylage®

Introduction

There are many materials successfully employed for soft tissue augmentation, such as autologous fat, collagen, and hyaluronic acid, among others. Each substance has its own characteristics that, case by case, make it the best choice, or not, indicated for the treatment of a certain individual. All need skilled physicians for their application. These techniques may be implemented for furrows, wrinkles, depressed scars, facial defects, atrophy of the lip, and skin roughness in the aging patient. Each of the materials may be highly effective when used for its correct indications and applied by skilled physicians.[1,2] Careful studies for methodical evaluation of all of these products must be performed before they reach the market.

Hyaluronic acid

Purified hyaluronic acid fillers are a very good choice for the correction of wrinkles and scars and are giving a high rate of satisfaction among patients. By the use of a well-tolerated, non-surgical method, with a low index of local inflammatory reaction, and which does not require a sensitivity test, it presents immediate and satisfactory effects and has a duration of up to one year.[3]

Reports state that a retouch after 2–4 weeks may provide better results and may make the filler last as long as 18 months;[4,5] however, there is not a consensus in the literature.

Isolated for the first time in 1934 from the vitreous humor of bovines, hyaluronic acid has been used since then in its native form, more frequently in ophthalmologic surgeries as a substitute for the vitreous humor or in retinal detachment, and in orthopedic surgeries as replacement of the synovial liquid in illnesses of the joints.[5,6]

Hyaluronic acid is a glycosaminoglycan component of the extracellular tissue of various human organs, present with the same composition in all living beings.[7] It is a polysaccharide comprising repeated units of disaccharides, D-glucuronic acid, and

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N-acetyl-D-glucosamine, with molecular weight proportional to the number of repetitions of these disaccharides.[8] The natural unmodified form of this acid is a linear molecule, biocompatible, with low potential for allergic and immunogenic reactions. Being a negatively charged polyanionic polymer at physiological pH, it has a strong affinity for water, a characteristic that explains its great hydration capacity. One gram of hyaluronic acid can bind up to 6 L of water, and this binding occurs through the formation of a hydrogen bridge with the carboxyl group of the hyaluronic acid molecule. It has a tissue half-life of 1–2 days, being easily removed through enzymatic degradation in the liver to carbon dioxide and water. Free radicals are essential cofactors in this degradation reaction.[7]

The body of an adult individual has about 15 gm of hyaluronic acid, of which approximately 50% is located in the skin.[8,9] Due to its viscoelastic properties, it is the main substance found in the dermis.[7,10]

The ideal filler must be biocompatible, nonallergenic, nonmigratory, and must provide lasting and reversible effects. Hyaluronic acid is the filler that closely meets these characteristics, and consequently, is being increasingly used in everyday practice by dermatologists and plastic surgeons.

The hyaluronic acid used in the manufacture of fillers may be of animal origin, from the rooster's crest, or nonanimal origin, obtained by bio-fermentation. The most widely used process utilizes fermentation of nonpathogenic *Streptococcus* bacterial strains that, due to not having antigenic specificity, have a low potential to cause allergic or immune reactions. Hyaluronic acid must undergo a purification process to eliminate the largest possible amount of protein derived from bacteria in order to reduce the antigenic potential and prevent hypersensitivity reactions.[7] Commercial preparations based on hyaluronic acid provide the product as sodium salt – sodium hyaluronate.[9]

Being a water-soluble polymer, hyaluronic acid is quickly eliminated when injected into normal skin. To increase its time of permanence in the tissue, a chemical process called "crosslink" is performed, whereby an artificial modification through the addition of chemicals alters its physical and mechanical properties. These modifying chemicals are called crosslinkers.[11] The most currently used crosslinker is 1,4-butanediol diglycidyl ether (BDDE), which forms irreversible carbon bridges between the hyaluronic acid molecules, causing an increase of the in vivo duration of the product.[8] The crosslink transforms the linear chains of hyaluronic acid into a three-dimensional structure that is more resistant to enzymatic degradation, while maintaining its biocompatibility. Thus, a water insoluble gel is formed and remains stable in the tissue. It is slowly resorbed over a period of months through an isovolumetric degradation.[9]

Another type of artificial connection, called dangling type link, occurs when the crosslinker molecule binds to hyaluronic acid via one of its ends, leaving the other end loose. It does not provide the hyaluronic acid with so much resiliance, but is considered when the hyaluronic acid's degree of modification is quantified. This type of connection is capable of changing the structure of hyaluronic acid, but it is not as effective in preventing its degradation. The degree of crosslinking is one of the factors responsible for the durability of the product.[8,9]

There are also natural chemical links, ie, weak chemical links formed, for instance, by hydrogen bridges or by the crosslinks between the polymers of hyaluronic acid themselves (mechanical interlocking).[9]

To the extent that the density of crosslinks increases, the distance between the segments shortens, thus thickening the gel and making it more difficult to mold. Lower density of crosslinks will form a smoother gel ("softer").[8] Thus, the firmness of the gel is directly proportional to its crosslink density.[10] A higher crosslink percentage with covalent bonds is found in firmer gels, while the high number of dangling bonds is most commonly found in thinner gels. The degree of crosslinking is defined by the ratio between the number of molecules of the crosslinking agent that form crossed links with the number of disaccharides of hyaluronic acid.[8,9] For instance, in a 10% crosslink, 10 crosslink bonds are expected for every 100 units of disaccharides that form the hyaluronic acid chain.

Concentration is another factor that influences the consistency of the final products, ie, the measured amount of hyaluronic acid contained in the gel, expressed in mg/mL. This amount comprises both soluble molecules (free particles of hyaluronic acid) and insoluble particles (related to the crosslink). Addition of free hyaluronic acid in the gel is done to facilitate passage of the filler through a needle by reducing the extrusion force.[8] With the same number of crosslinks or crosslinking percentage, higher concentrations of hyaluronic acid will result in a thicker gel. Gels with a higher rigidity have a better ability to withstand the dynamic forces that occur during movements of facial muscles; thus being more suitable for filling deeper and sharper grooves, such as nasolabial and nasogenian folds. Thinner gels are better suited for areas with static and superficial wrinkles, where resistance is lower, such as periorbital and perioral

wrinkles or areas where less volume or more smoothness is sought, such as lips.[9]

The elastic component, represented as G', is another important physical property. It reflects the ability of a gel to resist deformation when a force is applied against it.[8] In practical terms, a gel with a greater elastic component will be firmer and stronger and will undergo fewer changes in shape when pressure is applied to it. Clinically, this gel will have a greater ability to generate volume and support.[12] Additionally, it will have increased ability to withstand the daily dynamic forces, such as movements of facial muscles, therefore, it is more suitable for areas such as the nasolabial and nasogenian grooves.[8] On the other hand, gels with lower elastic modulus will be more appropriate for areas that do not suffer as much pressure, such as lachrymal fold and lips. A more fluid gel in an area that suffers high pressure would not resist deformation and would be pushed towards the area of lowest resistance, resulting in worse clinical results and lower procedure durability.[9,13]

The gel's binding capacity with water, which is the intrinsic characteristic of hyaluronic acid, is influenced by several already mentioned properties. The crosslink density directly affects this ability to absorb water. With a greater amount of crosslinks, the chains of hyaluronic acid will be closer and less flexible, making the connection with the water more difficult.[11] The presence of dangling links, which do not alter the structure of hyaluronic acid so intensely, may contribute to the gel's swelling.[8] Moreover, insofar as we have a more concentrated gel, ie, with a higher quantity of repeating disaccharide units, we expect more water molecules to bind with the polymer.[8,14] Due to its hygroscopic property, hyaluronic acid can still increase its volume by 10%–15% after application.[7] It is important to stress that the gel may or may not have reached its binding balance with water during the manufacturing process. A fully hydrated gel would have theoretically reached its maximum hydration capacity and, therefore, would not cause severe swelling after being injected into the dermis, while a gel that has not yet reached this balance would tend to swell more after the injection.[8]

The association of these physicochemical properties will provide the product's final features, including its durability; although, a reduced durability may occur in cases of uncontrolled hyperthyroidism; menopausal or postmenopausal women using oral hormone replacement and suspending the medication; heavy smokers; and patients who, soon after the procedure, undergo a dental treatment resulting in significant local inflammation and manipulation.[3]

The available commercial formulations of hyaluronic acid present great diversity as to the physicochemical properties of its products. Hyaluronic acid must pass through customized processes specific to each manufacturer, which will determine its features. The commercially available skin filling products based on hyaluronic acid, according to the manufacturing technology, can be divided into biphasic or monophasic. Biphasic gel is heterogeneous and, when applied, forms hyaluronic acid protuberances in the dermis and subcutaneous tissue. The difference between the product presentations depends on the size of the particles. Monophasic gel is homogeneous and could be further divided into monodensified and polydensified, where the latter would have a second crosslinking phase, differing from the former in the way it integrates the tissue.[10,11] The knowledge of these characteristics will help to better guide the clinical recommendation for each product.[11]

STYLAGE®: a range of hyaluronic acid dermal fillers

The Stylage® product line is manufactured by Vivacy laboratories (Paris, France), and the concentration of hyaluronic acid in the products indicated as fillers varies from 16–26 mg/dL, covering many different clinical indications. In its crosslinking process, the company uses IPN-like® technology (Manual de Stylage – IPN-Like Technology; Meizler UCB Biopharma) (interpenetrated cross-linked networks) (Figure 1).

This patented technology, as described by the manufacturer, results from the association of two or more monophasic hyaluronic acid chains previously crosslinked. These hyaluronic acid chains bind to each other through weaker links, the hydrogen bridges. In this way, an interaction between molecules occurs, promoting greater cohesion of the gel without the need to add higher amounts of chemical agents. Therefore, a more resistant gel, and at the same time, with more flexibility, will facilitate its injection.

Also in the Stylage® product line, there is a commercial presentation whose main purpose is merely hydrating the skin, without increase in volume. To that end, it resorts to hyaluronic acid in its natural, not crosslinked form, Stylage® Hydro, with a concentration of 14 mg/mL (Manual de Stylage – IPN-Like Technology; Meizler UCB Biopharma).

In Brazil, products containing lidocaine are not yet available.

Mannitol

Another distinguishing feature of this line of fillers is the presence of mannitol, a type of sugar incorporated into the gel with the purpose to act as an antioxidant.

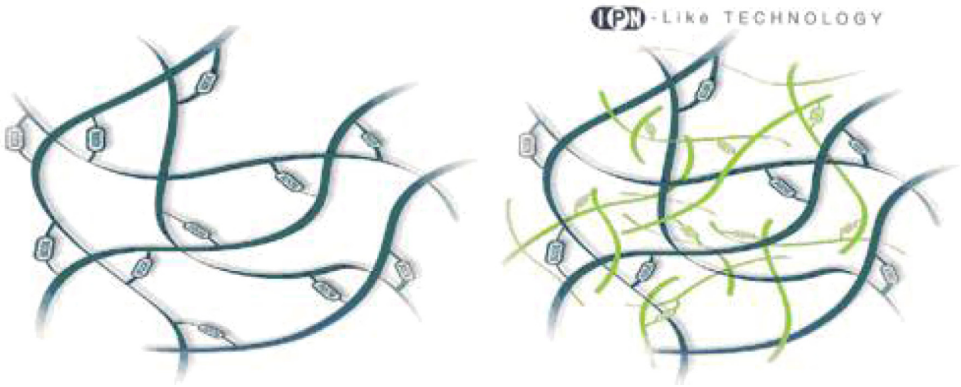

Figure 1 Schematic demonstrating the network with simple crosslinking (left) and interpenetrated crosslinking (right).

As previously stated, free radicals are largely responsible, along with hyaluronidase, for the degradation of hyaluronic acid.[8] They are chemical species with an odd number of electrons in their outer orbit, giving them high reactive power. Also called reactive oxygen species, they react with cellular structures such as DNA, proteins, and membranes, altering their chemical structure and consequently, their biological properties. Free radicals are one of the major causes of cell destruction and skin aging.[15]

To combat these effects, we naturally have enzymatic and nonenzymatic mechanisms with antioxidant properties. Superoxide dismutase, catalase, and glutathione peroxidase systems stand out as enzymatic mechanisms that fight free radicals; while nonenzymatic vitamins E and C, glutathione, and ubiquinone act by neutralizing oxygen reactive species. With aging, the fighting ability of these endogenous defense mechanisms will diminish.[15,16]

In an inflammatory state, oxidative stress generates a chain reaction that produces free radicals and chemical species such as superoxide and hydroxyl radicals, which act by damaging cells and polysaccharide components of the dermis. During the intradermal application of a filler, a phenomenon similar to the one described above occurs since the movement of the needle in the skin layers triggers an inflammatory process, eliciting the release of free radicals that promote a faster degradation of the hyaluronic acid, thus reducing its durability.

The use of mannitol as an antioxidant has been studied in vitro in other medical fields, as for example, in the treatment of secondary lung lesion to ischemia/reperfusion.[17] Mannitol, in fact, is known to exert scavenging properties against free radicals.[18]

Thus, the proposal to incorporate mannitol in the gel would aim at slowing its degradation in providing extra protection against the action of free radicals.

Authors' experience

The authors have a series of approximately 50 patients treated with this product line in private practice and at the Dermatology Sector of the University Hospital of the Federal University of Rio de Janeiro. In most cases, the primary indication was the nasolabial groove and malar and chin regions (Figures 2 and 3). There were no significant adverse or persistent effects, and slight erythema in the immediate postprocedure and minor bruising were observed in some cases, both transient. The physicians' and patients' degree

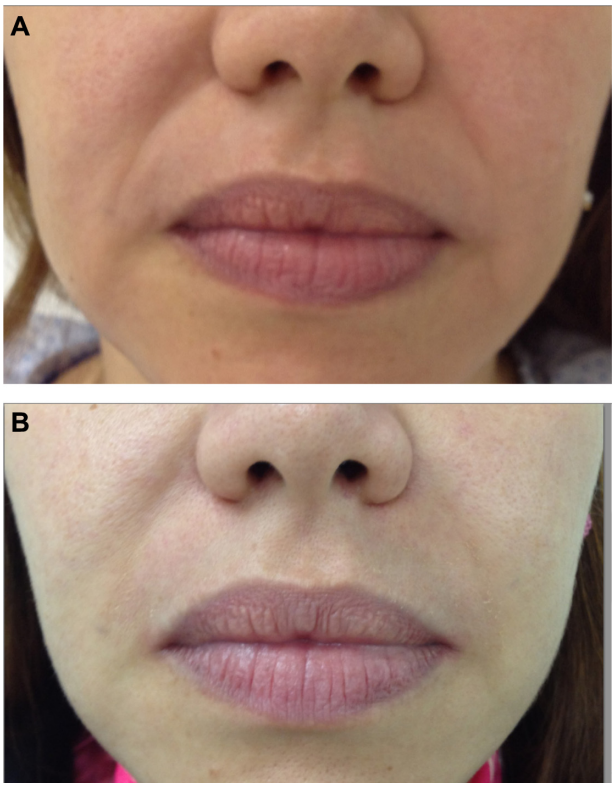

Figure 2 Patient 1 before (**A**) and after (**B**) Stylage® treatment.

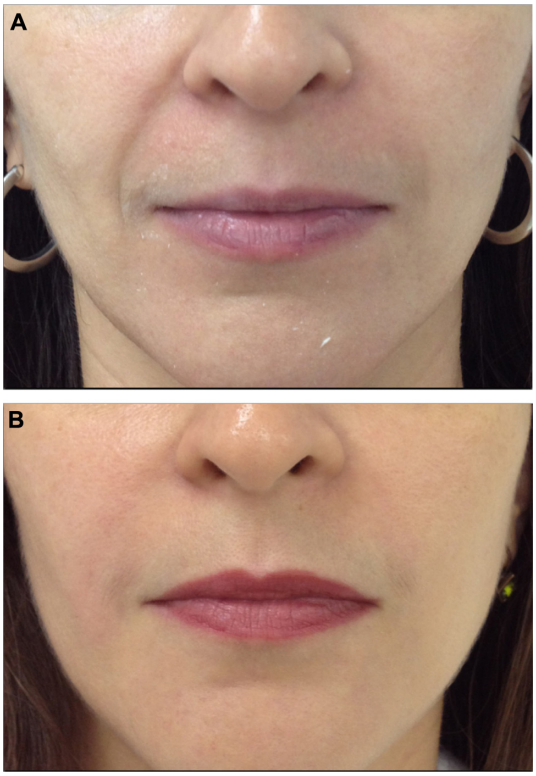

Figure 3 Patient 2 before (**A**) and after (**B**) Stylage® treatment.

of satisfaction has met expectations. The average durability of the product remained compliant with that described in literature for other products with similar characteristics.

Conclusion

Randomized and well-controlled studies, with broader case series, need to be conducted so that the assumption of beneficial effects of mannitol incorporated into hyaluronic acid gel may be further evaluated.

Disclosure

The authors report no conflicts of interest in this work.

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