



**ORIGINAL RESEARCH PAPER**

**General Medicine**

**BIBLIOGRAPHICAL REVIEW OF TREATMENT OF THE MALAR AREA WITH HYALURONIC ACID**

**KEY WORDS:** Hyaluronic Acid, Filling Materials, Facial Reshaping, Malar Region, Rejuvenate, Beautify, Prevent

<b>Pablo Llerena Jara*</b>	MD General Practitioner *Corresponding Author
<b>Melissa Jara Sagñay</b>	MD General Practitioner
<b>Gabriela Valarezo Regalado</b>	MD General Practitioner
<b>Susana Simbaña Suntaxi</b>	MD General Practitioner
<b>Ana Gabriela Corella Cazares</b>	MD General Practitioner
<b>Patricia Corella Sanguil</b>	MD General Practitioner
<b>Lorena Alomoto Quimbita</b>	MD General Practitioner
<b>Adriana Sandoval Granizo</b>	MD General Practitioner
<b>Marianella Pareja Merchan</b>	MD General Practitioner
<b>Carlos Andrade Villalba</b>	MD General Practitioner

**ABSTRACT**

Stabilized hyaluronic acid of non-animal origin has lately been used in different regions of the human body; Since its approval by COFEPRIS in 2000, for the treatment of wrinkles, folds and since 2006 its use has been indicated for different areas of soft tissue atrophy at the facial level, with the main regions of the malar, chin or depressions in the mandibular border, etc. The production of hyaluronic acid has been boosted worldwide and we have different physical characteristics, in addition to the amount of crosslinks and the concentration per ml. All these characteristics mean that hyaluronic acid can form several subtypes, which makes it very versatile, allowing it to help refinement in facial volumetric rejuvenation. In this study, the mechanism of action, the indications, precautions and recommendations that should be taken to have an adequate and safe treatment will be presented.

**HISTORY AND MAIN FUNCTIONS OF HYALURONIC ACID**

Hyaluronic acid was discovered in 1934 by the German pharmacist Karl Meyer and John Palmer who managed to isolate it from the vitreous body of the eyes of cows. In 1942, the scientist Endre Balazs was able to synthesize the acid from the combs of roosters, which to this day continues to be one of the sources of hyaluronic acid. Later the parts of the body that contain large amounts of hyaluronic acid were discovered, this substance is mainly found in tissues and organs of our body such as: connective tissue in the spine, cartilage, synovial fluid of the joints and epidermis (table I); Among its main properties we have that it allows the hydration of the skin by the physiological action of water retention; (10,3) in addition, it also helps to provide firmness and softness in the skin by lubricating the collagen fibers; (3) it serves as a defensive barrier since it prevents the movement of certain pathogens. (table II). The metabolism of Hyaluronic Acid (HA) is very dynamic, it is degraded by several types of enzymes: Hyaluronidase, beta-D glucuronidase, betaD-N-acetylhexosaminidase; the first being the most important. (4, 10).

**Clinical uses:** It is currently used in many areas of health, due to the functions and properties it possesses:

In orthopedics, it is used for joint problems; In the study conducted on "Acute local reaction after intra-articular infiltration with Synvisc," new findings are discussed that highlight the benefits of the use of hyaluronate in patients with osteoarthritis, effectively reducing inflammation.

In plastic surgery it turns out to be a non-invasive alternative that helps to rejuvenate the skin.

**MATERIALS AND METHODS:**

A bibliographic review was carried out, using databases such as Google scholar, Scielo, Science Direct; Keywords were used such as hyaluronic acid, malar zone; making combinations with the conjunction Y (AND) and the disjunction O (OR), terms such as: Filling materials, Facial remodeling, Malar region, Rejuvenate, Beautify, Prevent were also included

For the selection of studies, observational publications, bibliographic reviews, and systematic reviews were included. The quality of the articles was assessed by STROBE for observational studies; Based on the selected articles, the generalities about hyaluronic acid, the objectives, are initially described, to conclude with the results, discussion and conclusions.

**CONCEPT AND CHARACTERISTICS**

HA (hyaluronate at physiological Ph), is a glycosaminoglycan, a polysaccharide of high molecular weight (between 100,000 and 8,000,000), with a structure of repeating disaccharide units, made up of 200-10,000 linear polyanionic polymers of N-acetylglucosamine linked to acid D-glucuronic (Fig. 1) [D-glucuronic acid (1-B-3) N-acetyl-D-glucosamine (1-b-4)] n. Each of the HA molecules is 2.5 µm in length, but can be as long as 20 µm. The total concentration in humans is about 15 g, renewing a third every day. Its plasma half-life is 2.5 to 5.5 minutes (2).

One of the main functions of hyaluronic acid HA is hydration, lubrication and cellular stabilization, it represents an alternative in the treatment of facial aging and has been used for more than a decade in the filling of soft tissues to correct depressions in the skin, wrinkles and skin folds and lasts for 4-12 months. (3,28)

The suitable filler material should have the following characteristics:

- It should be biocompatible with the implantation area,
- Induce minimal reaction to foreign body,
- Remain stable in the implanted place,
- Maintain its volume and not make prominence on the skin,
- Do not migrate at a distance and do not be phagocytosed [2,3].

Among the adverse effects these can appear many years after treatment and, sometimes, the removal of the injected material is the only therapeutic possibility.

**ADVERSE REACTIONS**

HA does not have specificity for any organ or species, so no skin tests are needed prior to HA injection because it is biodegradable (5). The few reported cases of hypersensitivity reactions due to this filler material could be due to impurities from bacterial fermentation, such as the presence of DNA, rather than the HA itself.

Adverse reactions from cosmetic fillers can be divided into:

- Immediate (0-2 days), they are frequent, but for the most part transitory and banal, and include pain, itching, bruising and inflammation, among others.
- Early (less than 14 days), more frequent are infections and eczema
- Late (after 14 days). they can appear months or years after infiltration, and include infections, granulomatous reactions, and migration. Among others.

Intralesional injections with hyaluronidase are the treatment of choice to reverse these local hypersensitivity reactions. Systemic hypersensitivity reactions secondary to HA injections are even rarer than local side effects

HA is probably the most widely used absorbable filler today. Its advantages with respect to collagen are that it does not require storage in a refrigerator, it does not require overcorrection, it is not mandatory to do a prior allergy test and its duration in the tissues practically doubles that of collagen, since it persists an average of 6 months.

**Indications:**

- Injection into lips,
- Nasolabial folds,
- Glabella,
- Cheeks,
- Lacrimalnasal sulcus,
- Front,
- Mandible,
- Hands,
- Breasts or buttocks

**LOCATION OF HYALURONIC ACID**

The skin, given its great extension, constitutes the first reservoir of the whole body, accounting for 50% of the total (6). In the epidermis it is found in higher density in the stratum spinosum, in lower density in the basal layer and it is not found

in the stratum granulosum and corneum (7). In the dermis it is found between collagen and elastic fibers, spatially related to collagen microfibrils (8). HA patterns in the skin change according to the age of the subject, tending to decrease in its free form.

**HA AS A TREATMENT OF SKIN AGING**

HA for the treatment of skin aging can be obtained from natural substances, such as cockscomb, shark fin and umbilical cord, or through bioengineering techniques, thanks to a bacterial fermentation process.

One of the newest cosmetic techniques in the treatment of skin aging is the one that attempts to correct wrinkles by infiltrating certain substances, among which is HA. However, the short duration of the beneficial effects requires frequent applications, partially limiting the good results obtained.

**HYALURONIC ACID + DEXTRANOMER MICROPARTICLES**

It is a fairly recent filler material, used since 2004 for cosmetic purposes. It is a suspension of a resorbable gel composed of a mixture of non-animal HA and dextranomer microspheres (Matridex®, Revidermintra®). Its duration is estimated at one or two years, which is the time it takes for the dextranomer spheres to degrade into sugars.

**Indications**

It is used for the cosmetic treatment of facial lines, wrinkles and for lip augmentation.

**Adverse effects**

There is only one published case of granulomatous reaction to Matridex®, on the cheek of a woman 4 weeks after injection. The biopsy showed a suppurative granuloma around a foreign material represented by HA.

**PRODUCTS USED IN FILLINGS FROM THE MALAR REGION**

Currently one of the most widely used fillers and undoubtedly the best studied is a "non animal stabilized hyaluronic acid" (NASHA) produced from Streptococcus equi cultures through a crosslinking process with 1,4-butanediol diglycidyl ether (BDDE) giving a concentration of 20 mg / ml. and 100,000 gel particles.

In areas where greater volume is required, such as deep nasolabial and melolabial folds, cheekbones and in bioplasty or volumizing techniques, the use of Perlane®, Juvederm Ultra Plus®, or sub Q is more appropriate.

The products come pre-filled in a syringe with its corresponding 1 mL needle or cannula, or 0.5 mL in the case of Restylane® and Perlane®. In the case of sub Q®, the syringe is 2 mL.

The periocular region and cheekbones is confirmed as the anatomical region with the greatest number of manifested adverse effects and of greater severity, so it is necessary in this area to always recommend resorbable materials. The use of a cannula can avoid the risk of bruising and damage to anatomical structures.

**Filler material application area**

In 29.3% of the cases the area of application of the filler material was the lips and in 27.3% in cheekbones, 7.3% in the orbital-malar. (table IV)

Immediate reactions (within 72 hours after injection)

- Transient erythema
- Transient induration
- Transient itching
- Infections
- Color changes (whitening, bluish color)
- Hyperpigmentation
- Local necrosis
- Herpes reactivation
- Granulomatous formations
- Ulcerations
- Abscesses

Hyaluronic acid granulomas (Figure 1) are treated with corticosteroids, although it should be noted that many patients improve without treatment

There is no rule for hyaluronidase treatment. It is very important to know the clinical and histological differences between nodules and granulomas, because corticosteroids are effective in cell proliferation, but not in the nodules of clustered particles or microspheres.

**CONCLUSIONS**

The use of stabilized hyaluronic acid of non-animal origin has proven to be a safe filler of reasonable duration, and the placement in different planes of the different subtypes has allowed to prolong the effect of the filler, in addition to having satisfactory results for the patients. If we consider an effective treatment from all possible points of view, until now there is no optimal filler material that meets all the properties and characteristics necessary to be so. What exists are specific parameters that must be respected when using a product, in addition to verifying the absolute and relative contraindications for the application of fillers. In case of doubt due to previous fillings, it is essential to request imaging studies, ultrasounds or resonance to rule out which previous product we find and with it possible complications and if necessary histopathological study. In areas where greater volume is required such as cheekbones and in bioplasty or volumizing techniques, it is more appropriate to use Perlane®, Juvederm Ultra Plus®, or sub Q, taking into account a correct application to avoid exaggerated (superficial) corrections or that the product is moved (applied by deep subcutaneous or supraperiosteal injection). The use of a cannula can avoid the risk of bruising and damage to anatomical structures. In the case of intravascular injection, it is necessary to apply hyaluronidase, so when using this product it is always necessary to have it in our office.

**FIGURE 1: GRANULOMA DUE TO HYALURONIC ACID**

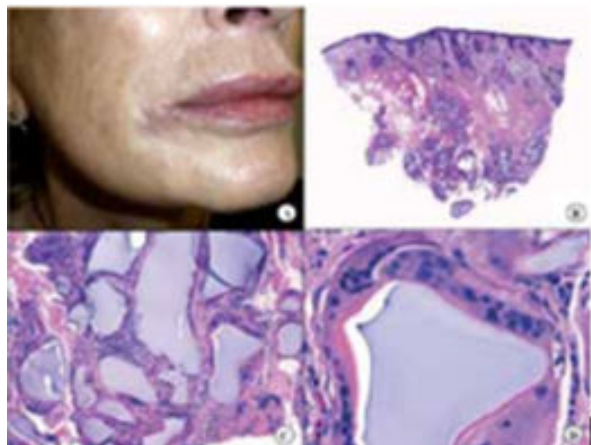


Figure 1: Hyaluronic acid granuloma. A) Granulomatous reaction after injection of hyaluronic acid in the right corner of the mouth. B) Panoramic image in which a basophilic material is observed at different levels of the dermis. C) At higher magnification, basophilic material surrounded by histiocytes and multinucleated giant cells is observed. D) Detail of hyaluronic acid (H-E, B x 10, C x 200, D x 400).

**FIGURE 2: PERIOCULAR EDEMA**



Figure 2: Periocular edema. It can be caused by improper placement or crosslinking of Hyaluronic Acid. Evolution of abscess in cheekbone after Restylane implant

**FIGURE 3: ABSCESS IN PUMULUS**



Figure 3: Evolution of abscess in cheekbone after Restylane implant

**REFERENCES**

- Negrin-Diaz ML, Vásquez L, Sardi J, Camejo O. Reacciones adversas a materiales de relleno. Presentación de una serie de casos y revisión de la literatura. *Dermatol Venez* 2009; 47: 14-29.
- Lemperle G, Morhenn V, Charrier U. Human histology and persistence of various injectable filler substances for soft tissue augmentation. *Aesthetic Plast Surg* 2003; 27: 354-66.
- Laeschke K. Biocompatibility of microparticles into soft tissue fillers. *Semin Cutan Med Surg* 2004; 23: 214-7.
- Pimentel VN, Capote A, Santos E, Sánchez M. Efectos indeseables de los materiales de relleno. *Monogr Dermatol* 2011; 24: 244-8.
- Requena L, Requena C, Christensen L, Zimmermann US, Kutzner H, Cerroni L. Adverse reactions to injectable soft tissue fillers. *J Am Acad Dermatol* 2011; 64: 1-34.
- Alfageme-Roldán F. Aplicaciones prácticas de la ecografía cutánea. *Piel* 2012; 27: 204-9.
- Wortsman X, Wortsman J, Orlandi C, Cardenas G, Szazinc I, Jemec GB. Ultrasound detection and identification of cosmetic fillers in the skin. *J Eur Acad Dermatol Venereol* 2012; 26: 292-301.
- Robinson JK, Hanke CW. Injectable collagen implant: Histopathologic identification and longevity of correction. *J Dermatol Surg Oncol* 1985; 11: 124-30.
- Knapp TR, Kaplan EN, Daniels JR. Injectable collagen for soft tissue augmentation. *Plast Reconstr Surg* 1977; 60: 389-405.
- Wallace DG, McPherson JJ, Ellingsworth LE. Injectable collagen for tissue augmentation. En: Nimmi ME (ed) : Collagen, Vol III, Biotechnology. Boca Raton, FL, CRC Press, 1988, pp 117-44.
- Castrow II FF, Krull EA. Injectable collagen implant -updated. *J Am Acad Dermatol* 1983; 9: 889-93. DeLustro F, Smith ST, Sundsmo J, Salem G, Kincaid S, Ellingsworth L. Reaction to injectable collagen: results in animal models and clinical use. *Plast Reconstr Surg* 1987; 79: 581-94.
- Baumann L, Kaufman J, Saghari S. Collagen fillers. *Dermatol Ther* 2006; 19: 134-40.
- Baumann L. CosmoDerm/CosmoPlast (human bioengineered collagen) for the aging face. *Facial Plast Surg* 2004; 20: 125-8.
- Sclafani A, Romo T, Jacono AA, McCormick SA, Cocker R, Parker A. Evaluation of acellular dermal graft in sheet (Alloderm) and injectable (micronized Alloderm) forms for soft tissue augmentation: clinical observations and histologic findings. *Arch Facial Plast Surg* 2000; 2: 130-6.
- Fagien S. Facial soft-tissue augmentation with injectable autologous and allogenic human tissue collagen matrix (autologen and dermalogen). *Plast Reconstr Surg* 2000; 105: 362-73.
- Ackerman AB, Cuo Y, Vitale P. Clues to Diagnosis in Dermatopathology II. Chicago, ASCP Press, 1992, p. 385-8.
- Kligman AM, Armstrong RC. Histologic response to intradermal Zyderm and Zyplast (glutaraldehyde cross-linked) collagen in humans. *J Dermatol Surg Oncol* 1986; 12: 351-7.
- Burke KE, Naughton G, Cassai NA. Histological, immunological and electron microscopic study of bovine collagen implants in the human. *Ann Plast Surg* 1985; 14: 515-22.
- Stegman S, Chu S, Armstrong R. Adverse reactions to bovine collagen implant: clinical and histologic features. *J Dermatol Surg Oncol* 1988; 14: 39-48.
- Elson ML. The role of skin testing in the use of collagen injectable materials. *J Dermatol Surg Oncol* 1989; 15: 301-3.
- Rapaport MJ. Granuloma annulare caused by injectable collagen. *Arch Dermatol* 1984; 120: 837-8. García-Domingo MI, Alijotas Rey J, CisteroBahima A, Treserra F, Enrique E. Disseminated and recurrent sarcoid-like granulomatous panniculitis due to bovine collagen injection. *J Invest Allergol Clin Immunol* 2000; 10: 107-9.
- McGrew RN, Wilson RS, Havener WH. Sudden blindness secondary to injection of common drugs in the head and neck. Part 1: Clinical experiences. *Otolaryngology* 1978; 86: 147-51.
- Douglas RS, Donsoff I, Cook T, Shorr N. Collagen fillers in facial aesthetic surgery. *Facial Plast Surg* 2004; 20: 117-23.
- Sclafani A, Romo T, Jacono AA, McCormick SA, Cocker R, Parker A. Evaluation of acellular dermal graft in sheet (Alloderm) and injectable (micronized Alloderm) forms for soft tissue augmentation: clinical observations and histologic findings. *Arch Facial Plast Surg* 2000; 2: 130-6.
- Baumann LS, Kerdel F. The treatment of bovine collagen allergy with cyclosporine. *Dermatol Surg* 1999; 25: 247-9.
- Moody BR, Sengelmann RD. Topical tacrolimus in the treatment of bovine collagen hypersensitivity. *Dermatol Surg* 2001; 27: 789-91.
- Wang F, Garza LA, Kang S, Varani J, Orringer JS, Fisher GJ, Voorhees JJ. In vivo

- stimulation of de novo collagen production caused by cross-linked hyaluronic acid dermal filler injections in photo damaged human skin. *Arch Dermatol* 2007; 143: 155-63.
28. Asin-Llorca M, Elipe-Rives I. Selección de materiales. Tendencias actuales y futuras. *Monogr Dermatol* 2010;24: 188-95.
  29. Dachie OE, Mahalingam M, Parada M, El Helou T, Philips T, Bhawan J. Adverse reactions to soft tissue fillers – a review of the histological features. *J Cutan Pathol* 2008;35:536-48.
  30. Parada MB, Michalany NS, Hassun KM, Bagatin E, Talarico S. A histologic study of adverse effects of different cosmetic skin fillers. *Skinmed* 2005; 4:345-9.
  31. Micheels P. Human anti-hyaluronic acid antibodies: is it possible? *Dermatol Surg* 2001; 27: 185-91. Hamilton RG, Strobos J, Adkinson NF Jr. Immunogenicity studies of cosmetically administered nonanimal-stabilized hya - luronic acid particles. *Dermatol Surg* 2007; 33 Suppl 2: S176-85.
  32. Pinheiro MV, Bagatin E, Hassun KM, Talarico S. Adverse affect of soft tissue augmentation with hyaluronic acid. *J Cosmet Dermatol* 2005; 4: 184-6.
  33. Brody HJ. Use of hyaluronidase in the treatment of granulomatous hyaluronic acid reactions or unwanted hyaluronic acid misplacement. *Dermatol Surg* 2005;31:893-7.
  34. Grossman KL. Hyaluronic acid gel fillers: hypersensitivity reactions. *Aesthet Surg J* 2005; 25: 403-5. Barbucci R, Lamponi S, Magnani A, Renier D. The influence of molecular weight on the biological activity of heparin like sulphated hyaluronic acids. *Biomaterials* 1998; 19: 801-6.
  35. Pacini S, Ruggiero M, Cammarota N, Protopapa C, Gulisano M. BioAlcamid, a novel prosthetic polymer, does not interfere with morphological and functional characteristics of human skin fibroblasts. *Plast Reconstr Surg.* 2003; 111(1):489-491.
  36. Casavantes L, Izábal J. Estabilidad, tolerancia y seguridad de polialquilimida gel (Biocalmid), endoprótesis inyectables para la corrección de defectos mayores en tejidos blandos. *Dermatología Cosmética Médica y Quirúrgica.* 2004;2(2):98-103
  37. Treacy PJ, Goldberg DJ. Use of a biopolymer polyalkylimide filler for facial lipodystrophy in HIV-positive patients undergoing treatment with antiretroviral drugs. *Dermatol Surg.* 2006 Jun;32(6):804-8.
  38. Schelke LW, van den Elzen HJ, Canninga M, Neumann MH. Complications after treatment with polyalkylimide. *Dermatol Surg.* 2009 Oct;35 Suppl 2:1625-8.
  39. Nelson L, Stewart KJ. Early and late complications of polyalkylimide gel (Bio-Alcamid)®. *Plast Reconstr Aesthet Surg.* 2011 Mar;64(3):401-4.
  40. Ross AH, Malhotra R. Long-term orbitofacial complications of polyalkylimide 4% (bio-alcamid). *Ophthal Plast Reconstr Surg.* 2009 Sep-Oct; 25(5):394-7.
  41. Hevia O. Six-year experience using 1,000-centistoke silicone oil in 916 patients for soft-tissue augmentation in a private practice setting. *Dermatol Surg.* 2009 Oct;35 Suppl 2:1646-52.
  42. Anastassov GE, Schulhof S, Lumerman H. Complications after facial contour augmentation with injectable silicone. Diagnosis and treatment. Report of a severe case. *Int J Oral Maxillofac Surg.* 2008 Oct;37(10):955-60. Epub 2008 Jun 12.
  43. Homicz MR, Watson D. Review of injectable materials for soft tissue augmentation. *Dermatol Surg.* 28 (6):491-494.
  44. Bjarnsholt T, Tolker-Nielsen T, Givskov M, Janssen M, Christensen LH. Detection of bacteria by fluorescence in situ hybridization in culture negative soft tissue filler lesions. *Dermatol Surg.* 2009;35(suppl 2):1620-1624.
  45. Requena L, Requena C, Christensen L, Zimmerman U. Adverse reactions to injectable soft tissue fillers. *JAAD.* 2011;64(1):1-34.