

Possible Risks of Using Hyaluronidase in Complications Caused by Hyaluronic Acid in Dentistry

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Abstract

Currently, the orofacial harmonization performed by the dentist has been growing exponentially. Several techniques contemplate this list of procedures, among them the application of botulinum toxin; facial fillers; facial lifting (polydioxanone thread); autologous blood derivatives; percutaneous collagen inducers; hormonal regulation; biophotonic procedures and therapeutic laser; facial lipoplasty; bichectomy; and liplifting. In the facial and peribuccal filling technique, the main material currently used is hyaluronic acid. Naturally, hyaluronic acid is an endogenous intercellular component of our tissues. Synthetically, it is used in rehabilitation and aesthetic medicine, gaining, in this last indication, greater property. However, due to aesthetic applications, several complications have been reported, including the formation of granulation tissue (foreign body) and possible risk of tissue necrosis. In this perspective, the application of hyaluronidase has been carried out indiscriminately. However, hyaluronidase can also present possible complications. The purpose of this article is to present the possible complications resulting from the application of hyaluronidase, and to discuss the importance of rational use in Dentistry.

Keywords: Hyaluronidase; Hyaluronic Acid; Dentistry

Introduction

Currently, facial aesthetics have been growing exponentially due to the performance of the dental surgeon. This new approach was initiated by the use of botulinum toxin in stomatological indications, particularly in cases of gummy smile; parafunctional habits (bruxism, bruxism and masseteric hypertrophy); temporomandibular disorders; orofacial pain and headache associated; adjuvant applications in Implantology and Oral Surgery; facial palsy; orofacial or oromandibular dystonia; and sialorrhea [1,2]. Subsequently, the botulinum toxin applications has achieved facial cosmetic applications.

At the same time, other materials and procedures were included in Orofacial Harmonization, such as the application of facial fillers; autologous blood derivatives; percutaneous collagen inducers (micro needling); facial lifting (polydioxanone thread); and liplifting (surgical techniques for lip correction). Recently, in Brazil, Orofacial Harmonization was regulated as a dental specialty by the Federal Council of Dentistry [3].

Regarding oral and facial filling techniques, the most used material today is hyaluronic acid [4-7]. Naturally, hyaluronic acid is an endogenous substance, synthesized by the body itself. Aesthetically, hyaluronic acid is defined as a temporary filling material, which can last up to 12 months [6].

With the increased incidence of hyaluronic acid application, complications resulting from its application have been reported, such as temporary post-injection pruritus, edema, allergic and anaphylactic reactions, formation of nodules by granulation tissue (foreign bodies), vascular occlusions, necrosis and blindness [3-9]. Several procedures and techniques can be conducted to interrupt the filling plunger formation, such as massage, hot compression, nitroglycerin paste and hyperbaric oxygen [7]. However, one of the first treatment options for complications resulting from the use of hyaluronic acid is the application of hyaluronidase, a degrading enzyme responsible for lysing hyaluronic acid. Unfortunately, there is little information regarding its use, indications and possible complications resulting from the use of hyaluronidase.

Purpose of the Study

The purpose of this article is to present the possible complications due to application of hyaluronidase, and discuss the importance of its rationale use in Dentistry.

Discussion

Hyaluronidase is an enzyme that breaks down hyaluronic acid by cleaving glycosidic bonds and other mucopolysaccharides from connective tissue. Additionally, hyaluronidase stimulates angiogenesis by defragmenting hyaluronic acid. Hyaluronidase does not cross the blood-brain barrier [6,9-11]. Traditionally it has been used in Ophthalmology, Dentistry, Plastic Surgery and particularly in Anesthesia, to improve the permeation of local anesthetics [5,6,10-14,16].

Hyaluronidase has an off label use for correction of adverse reactions induced by hyaluronic acid. The pharmacological compounds of hyaluronidase can contain various contaminating substances such as proteases, immunoglobulins and vasoactive factors, thus becoming more immunogenic. Allergic reactions to hyaluronidase [5,6,9-16] have been reported, usually characterized by erythematous edema [9,10,12,14-16].

Hyaluronidase is an enzyme preparation extracted from bovine or sheep testicles, or from hamster ovary cells [6,9,16]. Commercially, extraction from recognized sources has been reported, completely free of Bovine Spongiform Encephalopathy [6]. However, considering the prion as an undetectable protein particle, including by diagnostic methods of molecular biology, one must consider the prion disease in humans - Creutzfeldt-Jakob disease [16,17].

In order to reduce the risk of allergic reactions to hyaluronidase, skin tests can be performed. Three units of hyaluronidase are injected intradermally. The presence of local reddish nodules, occurring within 5 minutes and persisting for 20 to 30 minutes, is considered a positive reaction. Erythema alone is not a positive reaction. However, the skin test can be suppressed in cases of urgency, such as in cases of vascular occlusions. In these situations, the availability of adrenaline is advisable. Cross hypersensitivity to hyaluronidase has been reported in some patients allergic to bee and wasp stings, as the poisons also contain hyaluronidase [5,6,9,14].

Hyaluronidase is sold in the form of lyophilized powder, and must be reconstituted in 0.9% saline solution, mixed and injected in the region containing the changes in hyaluronic acid. There is no

evidence of the utility of diluting hyaluronidase with lidocaine or epinephrine solution [6].

The onset of the allergic response can be classified as immediate (within a few minutes), early (within a few hours), intermediate (within a few days) or late (within a few weeks) [9-11,15,16]. Immediate hypersensitivity is more frequent, while late hypersensitivity is more rare [11]. Hyaluronidase applications can be performed for a variable period. If an active infectious process is suspected, hyaluronidase should be injected after the start of appropriate antibiotic treatment. On the contrary, the enzyme can facilitate the spread of infection to the surrounding areas [5,6]. It has been reported that the application of hyaluronidase 4 hours after the injection of hyaluronic acid (up to 24 hours) can reduce the size of the necrotic areas. In cases of blindness caused by the intravascular injection of hyaluronic acid, it is treatable by the immediate injection of hyaluronidase, being promising [5].

Hyaluronidase applications for complications resulting from the application of hyaluronic acid must be subcutaneous, by direct infiltration of the visible alteration or lesion, or of the palpable mass of hyaluronic acid. Massage is recommended to promote the degradation of hyaluronic acid. In case of vascular obstruction, whether local or remote, the enzyme should, theoretically, be delivered directly to the occluded vessel. However, the chances of injecting the same artery again are very low [5,7]. Another difficulty observed is that, in case of the need for intra-arterial injection of hyaluronidase, hyaluronic acid causes resistance, spreading to peripheral areas and not to the area of obstruction [7]. Higher doses of hyaluronidase are probably necessary and able to compensate for the relative resistance of the hyaluronic acid gel to degradation [5].

Areas with white or violet spots, or reticulate discoloration that indicate imminent local necrosis, should receive an injection every 3 to 4 cm in the ischemic area, followed by massage [5]. Post-injection edema can be controlled by steroid administration [6].

Hyaluronic acid-based products are completely degraded 24 hours after subcutaneous injections of hyaluronidase. However, in the treatment of vascular complications caused by the application of hyaluronic acid, complete degradation requires more time and depends on the type of material, the anatomical site, the patient's metabolism and the type of hyaluronidase. Additionally, in these cases, repeated treatments with hyaluronidase applications may be necessary, since it favors blood perfusion and recovery of collateral vessels, managing blood supply if hyaluronic acid dissolves in

sufficiently small particles [7]. Due to the possibility of a potential increase in spread, hyaluronidase should not be injected in an area that has been treated with botulinum toxin type A in the last 48 hours [6].

Among the therapeutic modalities used in the complications of hyaluronidase, treatment with corticosteroids (local and systemic) [9,13-15], antibiotics and antihistamines [9,15,16] has been reported. Signs and symptoms resolve within a few weeks [9].

Conclusion

Hyaluronidase is a therapeutic modality for the treatment of complications resulting from the injection of hyaluronic acid in Orofacial Harmonization and in Dentistry. However, dental surgeons should be aware of the immunogenic potential of hyaluronidase. When possible, skin tests can be performed before using hyaluronidase, in order to minimize risks. When referring, patients should be informed of possible complications. Among the possible therapeutic approaches for the complications of hyaluronidase injection, we highlight the corticosteroid drugs, antibiotics and antihistamines.

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