Original Articles

Hyaluronidase: a necessity for any dermatologist applying injectable hyaluronic acid

Hialuronidase: uma necessidade de todo dermatologista que aplica ácido hialurônico injetável

Authors:
Laila Klotz Almeida Balassiano[1]
Bruna Souza Felix Bravo[2]

[1] Graduate Student, Dermatology Department, Policlínica Geral do Rio de Janeiro – Rio de Janeiro (RJ), Brazil

[2] Head of the Cosmetic Dermatology Clinic, Instituto de Dermatologia Professor Rubem David Azulay of the Santa Casa de Misericórdia do Rio de Janeiro and Hospital Federal da Lagoa Rio de Janeiro – Rio de Janeiro (RJ), Brazil

ABSTRACT

Introduction: Injectable hyaluronic acid is regarded as the gold standard treatment in the aesthetic correction of wrinkles, loss of contour, and restoration of facial volume. However, it is expected that consequentially adverse – sometimes severe – reactions will arise concomitant with the growth in use of hyaluronic acid-based cutaneous fillers.

Objective: To evaluate the application of hyaluronidase in the treatment of adverse effects of injectable hyaluronic acid, as well as possible reactions to the intradermal injection of that enzyme.

Methods: A retrospective study was carried out with 50 patients who underwent the application of hyaluronidase aimed at correcting complications or unaesthetic effects following hyaluronic acid-based filling procedures in the face.

Results: Twenty-three patients had some type of adverse effect (restricted to the injection site) ranging from erythema, burning sensations, and mild edema, during or after the application, with spontaneous improvement. There were no cases of moderate to severe edema. Most patients reported regression of excess hyaluronic acid a few hours after the injection.

Conclusions: Hyaluronidase is an extremely effective tool both in acute adverse events and in the reversal of unsatisfactory results, and in the dilution of biofilm. All those who use hyaluronic acid when treating their patients should have technical mastery of hyaluronidase application.

Keywords: hyaluronic acid; enzymes; accidents.

RESUMO

Introdução: *O ácido hialurônico injetável é considerado o padrão ouro na abordagem estética para correção de rugas, perda de contorno e reposição de volume facial. No entanto, é de esperar que, concomitante ao aumento do uso de preenchedores à base de ácido hialurônico, estes sejam implicados com efeitos indesejáveis, às vezes graves.*

Objetivo: *avaliar a aplicação da hialuronidase no tratamento de efeitos adversos do ácido hialurônico injetável, assim como possíveis reações à injeção intradérmica dessa enzima.*

Métodos: *foi realizado estudo retrospectivo de 50 pacientes submetidos à aplicação de hialuronidase para correção de complicações ou efeitos inestéticos após preenchimentos à base de ácido hialurônico na face.*

Resultados: *23 pacientes apresentaram algum tipo de efeito adverso, restrito ao local de injeção, variando de eritema, ardência a edema leve, durante ou após a aplicação, com melhora espontânea. Não houve nenhum caso de edema moderado a grave. A maioria dos pacientes relatou regressão do excesso de ácido hialurônico após poucas horas da injeção de hialuronidase.*

Conclusões: *a hialuronidase é ferramenta extremamente eficaz, tanto nos episódios adversos agudos como na reversão dos resultados insatisfatórios e diluição de biofilme, e sua aplicação deveria ser de domínio técnico de todos aqueles que aplicam o ácido hialurônico em seus pacientes.*

Palavras-chave: *Ácido hialurônico; enzimas; acidentes.*

Correspondence:
Dr. Bruna Souza Felix Bravo
Rua Dona Mariana 143 – Botafogo
cep: 22280-000 - Rio de Janeiro (RJ), Brazil
E-mail: brunabravo@globo.com

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INTRODUCTION

Injectable hyaluronic acid (HA) is currently considered the gold standard treatment for the aesthetic correction of wrinkles, loss of facial contour, and for volume replacement. According to the American Society of Plastic Surgeons some two million procedures using dermal fillers were carried out in 2012, 5% more than in 2011 and 205% more than in 2000. Second only to botulinum toxin type A, these two minimally invasive and non-surgical cosmiatric procedures were the most commonly performed during the study period.[1] Data from the American Society of Dermatologic Surgeons shows a similar trend, and a study carried out from 2001 to 2007 showed that the procedure that has had the greatest increase (of those performed by dermatologists) was dermal filling, with an impressive growth of 405% (70% of which were HA-based filling products). HA's popularity is attributed to its accessibility, quality, and relative safety, and to its rapid and significant clinical results.[2-4] However, as the use of HA-based fillers grows, it is expected that they will become the most commonly implicated source for undesirable – and sometimes severe – side effects.[5] Despite it being a substance that can be broken down by the human body, and that the majority of adverse effects are only unaesthetic, some complications require fast and aggressive treatment in order to reduce the risk of sequelae or morbidity. Therefore, dermatologists should be able to control these events by applying an enzyme that specifically degrades HA: hyaluronidase.

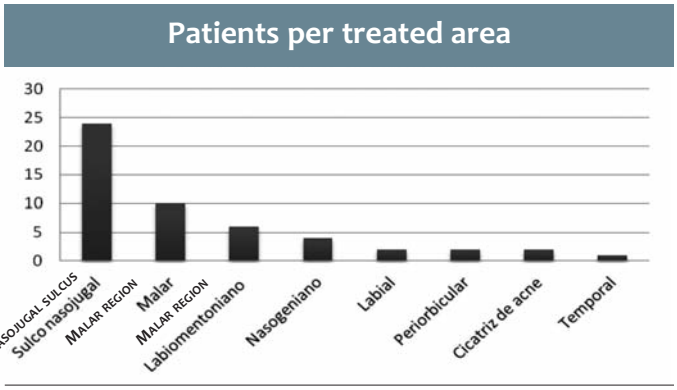
MATERIALS AND METHODS

A retrospective study was carried out with 51 patients who underwent an application of hyaluronidase (Hyalozima® 2,000UTR - Apsen) to correct complications or unaesthetic effects after injectable HA-based dermal filling in the face. The cases were selected from those treated at a private practice from January 2012 to August 2014, and included all patients who underwent dermal filling at the practice and those referred by other physicians, regardless of the brand of HA that was used. Based on the analysis of medical and photographic records, the following data were evaluated: age, gender, anatomical subunits involved, number of sessions, volume of hyaluronidase used, and adverse effects after the application of the enzyme. These reactions were rated by the study team according to the presence or absence of a burning sensation and/or erythema, mild edema (only in the application site), moderate edema (in the treated anatomic subunit), severe edema (across the face or angioedema), and anaphylaxis. All patients were photographed before and after the application and informed about the procedure, including about the possible adverse effects of hyaluronidase. During the interview, patients were questioned about their knowledge of any allergic reaction to bee and/or wasp stings in their medical history. Intradermal testing was not carried out due to the fact that it was not part of the practice's clinical protocol. In the four cases where there was a clinical suspicion of local infection by biofilm, antibiotic therapy was started with macrolide and quinolone for seven days, with hyaluronidase only then being applied. After the procedure, the antibiotic therapy was continued for one week. The routine established for each application was: skin asepsis with cleansing lotion followed by 0.5% alcoholic chlorhexidine solution. The total content of a 2,000UTR hyaluronidase lyophilisate powder vial (Hyalozima®) was dissolved in 5.0 ml of the diluent supplied with the product, generating a 400UTR/ml solution. The application was carried out using a BD Ultra-fine 30U or 50U syringe, and 6.00 mm x 0.25 mm needles (31G).

RESULTS

The study evaluated 51 patients (2 men and 49 women), aged between 27 and 61 years. The standard dose used was 0.1 ml of 400UTR/ml Hyalozima® solution per cm^2 area to be corrected. The total doses applied ranged from 0.05 to 0.4 ml (20-160UTR) per treated anatomical subunit per session. The regions treated, in order of frequency were: nasojugal, malar, mentolabial sulcus, nasolabial, lips, acne scars, periorbicular and temporal (Graph 1). The maximum and minimum doses applied per anatomical subunit are in Table 1.

Regarding the enzyme's possible adverse effects, 28 patients had not had any type of effect with hyaluronidase, while 23 reported some type of symptom or local sign: erythema, burning sensation, or mild edema, during or after the application. Symptoms typically decreased spontaneously within min-



Graph 1: Number of patients treated with hyaluronidase per treated subunit

Table 1: Dose used per area as a fraction of 400 U/ml hyaluronidase solution.

Treated areas	Doses used (ml)
Nasojugal sulcus	0,05-0,4
Malar region	0,03-0,2
Mentolabial sulcus	0,05-0,1
Nasogenian sulcus	0,05-0,2
Lips	0,05-0,1
Periorbicular region	0,2
Acne scars	0,15 - 0,3
Temporal region	0,1

utes or a few hours, and lasted no more than 24 hours, without the need for any additional medication (Graph 2). There were no cases of moderate to severe edema or anaphylaxis. Most patients reported that the regression of excess HA began a few hours after the injection of hyaluronidase. Cases with complete resolution after a single session also reported complete dilution of the HA within 24-48 hours (Figures 1 to 3). Five patients required two sessions, and in only one case did a patient require three sessions to be carried out. In these cases the 15-day interval between applications was observed.

DISCUSSION

Hyaluronidase is an enzyme that occurs naturally in the dermis and acts by depolymerization of HA, which is a viscous mucopolysaccharide, an essential component of the extracellular matrix that is responsible for maintaining cell adhesion by acting as a cement. In this manner, hyaluronidase decreases the intercellular viscosity and temporarily increases the tissue's permeability and absorption. The US Food and Drug Administration (FDA) endorses three indications for the medical use of hyaluronidase: (1) as an adjuvant to increase the absorption and diffusion of other injected drugs, in the clinical practice it is commonly used in retrobulbar anesthesia block in ophthalmic surgery; (2) in hypodermoclysis, consisting of the administration of fluids and/or drugs subcutaneously, an alternative route in cases of mild to moderate dehydration mainly in elderly patients receiving care in the home; (3) to enhance the resorption of radiopaque agents in subcutaneous urography, especially in children and young adults, when intravenous administration can not be performed. Its use in dermatology to dissolve HA is off-label and, although growing, still little discussed.[6]

The hyaluronidase fillings are extracted from cattle and sheep testicles, and a new formulation from a human recombinant enzyme has already been commercially distributed in the US. Table 2 presents the characteristics of the enzymes currently marketed in the US and Europe. Some formulations may contain preservatives and other substances, such as thimerosal (present in Amphadase®), lactose (present in Hylenex®), and albumin (in the most recently preparation, purified from recombinant human DNA, in the Vitrase®). In Brazil, bovine hyaluronidase (Hyalozima®) is available. The different sources, formulations, and concentrations generate great controversy regarding the possibility of side effects and allergic events resulting from the use of hyaluronidase.[6-9]

In practice, however, adverse effects after the use of hyaluronidase are rare, transient, and most frequently reported in the body site where it was applied. The symptoms are mainly local, with edema, heat, erythema, pruritus, and pain, which

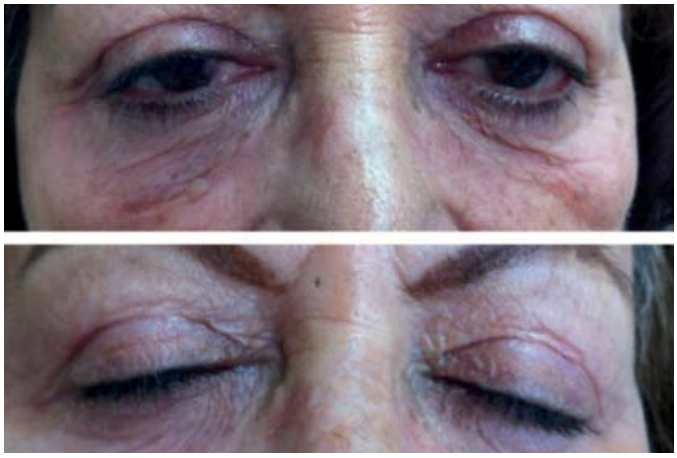
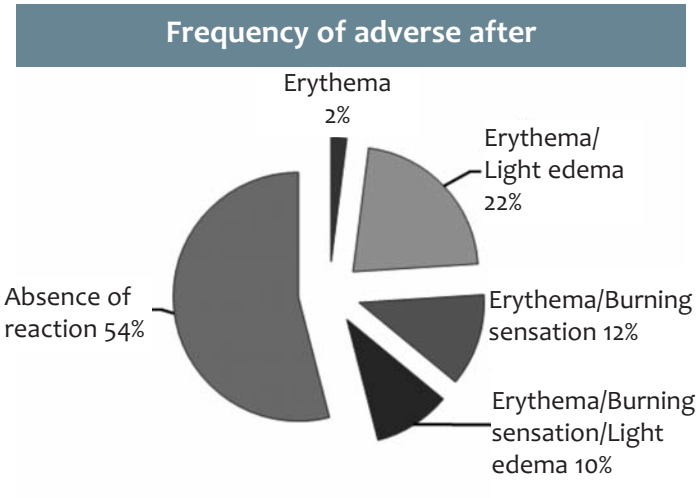


Figure 1: Patient with tyndalization in the right nasojugal groove after injectable HA-based filling and complete regression after application of hyaluronidase.

Figure 2: Patient with nodules in the right nasojugal groove after injectable HA-based filling and complete regression after application of hyaluronidase.



Graph 2: Frequency of adverse events after intradermal injection of hyaluronidase for correcting HA-based filler complications.

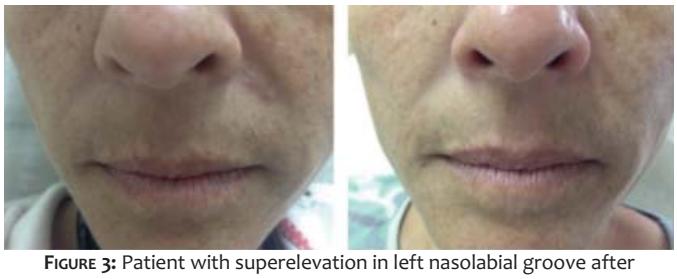


Figure 3: Patient with superelevation in left nasolabial groove after injectable HA-based filling and complete regression after the application of hyaluronidase

respond to the use of oral corticosteroids and antihistamines.[10-17] Less than 0.1% of the treated patients have urticaria or angioedema, and most cases found in the literature are related to the combined use of anesthetics, ophthalmic surgery, analgesia, and chemotherapy.[6,18] These occur mainly due to immediate hypersensitivity, with some reports of patients with delayed reactions, starting within minutes, hours, or even days after exposure.[12-14, 19] This wide range in the onset of symptoms suggests that type I reactions (IgE mediated) and IV (cellular – T lymphocytes) can contribute to the immune response.[10, 11, 19]

It is worth noting that in many of the reports of adverse effects, the patients already had a history of prior exposure to the enzyme in ophthalmic surgery, using hyaluronidase in retrobulbar anesthesia, analgesia and/or old chemotherapy sessions or had an allergy to bees or wasps. Cases of anaphylaxis have been reported after retrobulbar anesthesia block, analgesia for the control of chronic pain, and when combined with chemotherapy for the treatment of CNS tumors in children. In these cases, the doses of hyaluronidase are much higher than those used in the correction of cutaneous fillers and are usually administered intravenously or intrathecally, ranging from 1,500IU and up to 200,000IU, as reported by Szeâpfalusi et al. for the use in CNS tumors chemotherapy. Support with intravenous or intramuscular epinephrine, intravenous or oral corticosteroids, antihistamines and volemic replacement have reversed the reaction picture.[20-23] Thus, several authors have questioned the importance of sensitization as a risk factor for developing hypersensitivity, as well as the route of administration and the dose injected. In this manner, performing an intradermal test prior to the use of the medication, in order to assess the presence of hypersensitivity to hyaluronidase or to one of the solution's components is still a controversial issue for the authors, and was not considered in this study protocol. The discussion regarding the test is centered on the fact that it does not exclude either the presence of allergic hypersensitivity in patients with no previous exposure nor a possible dose-dependent toxicity, yet it is still able to function as sensitizer. The test consists of an intradermal injection of 0.02 ml (3U) of 150U/ml solution. A positive result leads to the appearance of linear erythematous-edematous plaques arising five minutes after the application and persisting for 20-30 minutes, associated with pruritus. Only local erythema or transient vasodilation do not indicate a positive test result. A positive test as well as a history of hypersensitivity to bee and wasp stings contraindicate the use of hyaluronidase, since the enzyme is active in the venom. In addition, enzymes of animal origin should not be used if there is a known allergy to ovine or bovine derived products, or even to excipients present in the solution.[6, 7, 18, 24]

The use of hyaluronidase to dissolve HA-based fillers is relatively recent. Few cases of hypersensitivity were found in the dermatological literature – most of which were restricted to the studied location, ranging from pruritus at the injection time to edema, erythema, and warmth, as observed in the present study.[24-27] A single case of facial angioedema was described by Pierre et al. without mucosal or upper airway involvement, arising minutes after the completion of ovine hyaluronidase injection. The patient had a history of asthma and atopic dermatitis, however denied a hypersensitivity to bee or wasp stings and previous use of the enzyme. The picture was reversed with immediate intravenous corticosteroids and follow-up with oral corticosteroids.[28] There were no reports of anaphylaxis after subepidermal applications for the correction of HA-based filling.[6,19] The authors believe that this is due to the use of much lower doses of the product when compared to other indications.

In addition to being used to treat unaesthetic complications, when used early on in cases of intra-arterial injection of HA, hyaluronidase has been demonstrated to be capable of reducing this complication, with greater benefits when performed in the first 24 hours after the ischemic event. The intra-arterial injection of fillers causes pain, color change, and tissue necrosis.[25,26,29,30] Recent articles have demonstrated that hyaluronidase injections in the treatment of biofilms with HA favor the degradation of the substrate matrix, facilitating the

Table 2: Hyaluronidase trade marks currently marketed in the United States, Europe and Brazil

Trade mark ®	Source	Preservative	Other ingredients	Available formulation	Available source countries	Units
Amphadase®	Bovine	Thimerosal	-	Solution	EUA	150/ml
Vitrase®	Ovine	-	Lactose	Solution	EUA	200/ml
Hylenex®	Recombinante humana	-	Albumina	Solution	EUA	150/ml
Hylase Dessau®	Bovine	-	-	Pó	Germany	150,300,1500/frasco
Desinfiltral®	Ovina	-	-	Solução	England	1500/frasco
Hyalozima®	Bovine	-	Mannitol benzalkonium chloride	Pó	Brazil	2000/frasco (400/ml) 20000/frasco (4000/ml)

migration of macrophages and the penetration of antibiotics.[3,31] Some authors have reported a favorable response to the use of hyaluronidase in resistant inflammatory reactions after dermal filling, regardless of the material used.[32]

The authors based the guidance for the application based on the review of recent literature on the role of hyaluronidase in HA depolymerization and on the authors' own experience. The dilution of the lyophilic powder contained in a 2,000UTR Hyalozima® vial is carried out in 5.0 ml of solvent that comes with the product, generating a 400UTR/ml solution (Video 1). The volume to be injected depends on the amount of HA to be corrected. This avoids high doses in a single application, which could lead to atrophic and unaesthetic results – due to suspicions about the possibility of hydrolysis of the native HA[5,8] – in addition to lowering the probability of allergic reaction. Nonetheless, amounts equivalent to 40 U (0.1 ml) per cm^2 of the area to be corrected are usually sufficient and should be injected only in the nodules of the product to be diluted (Video 2). In case there is an unsatisfactory result, further doses may be offered within 10 to 15 days. There is no evidence that the addition of lidocaine or epinephrine is useful, and they have not been used by the authors. Patients should be informed that erythema, edema, and warmth are possible and expected reactions after the injection, and do not indicate an allergic reaction to the medicament. Cases of hypersensitivity to hyaluronidase should be dealt with according to their severity.

Furosemide, epinephrine, benzodiazepines, heparin, and phenytoin are incompatible with hyaluronidase. Patients using salicylates, corticosteroids, estrogens, adrenocorticotropic hormones, and antihistamines may require higher doses, as these medications seem to increase the tissues' resistance to the effect of hyaluronidase. The enzyme should not be used to increase the absorption of dopamine or alpha-agonists and should not be injected into the infected areas or in the presence of inflammation due to the risk of dissemination of the infection. Local malignancy is also considered as a contraindication. Hyaluronidase is classified as a category C drug during pregnancy.[6,33]

In most of the reported cases, patients had already begun to notice that the HA nodules started to decrease a few minutes after the injection of hyaluronidase, with approximately 50% of the mass regressing after 1 hour and complete resolution in 24 hours, without inflammation.[33,34]

CONCLUSION

The authors of the present study had as their aim to share their experience with the use of hyaluronidase for correcting the unaesthetic effects of HA, which, according to their findings, is consistent with the medical literature. Given that hyaluronidase is an extremely effective tool both in acute adverse events and in the reversion of unsatisfactory results, as well as in the dilution of biofilm, the application of the enzyme and its side effects should be technically mastered by all those who apply HA in their patients.

Video 1: http://www.sgponline.com.br/scd/sgp/downloadvideo.asp?cod_video=21&cod_fluxo=557
Video showing the dilution of the lyophilic powder in a 2,000UTR Hyalozima® vial in 5.0 ml of the solvent supplied with the product, generating a 400UTR/ml solution.

Video 2: http://www.sgponline.com.br/scd/sgp/downloadvideo.asp?cod_video=22&cod_fluxo=557
Video demonstrating the application of hyaluronidase to dissolve nodules that formed in the nasojugal region of a patient after a filling procedure with injectable HA.

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