Hyaluronidase: a necessity for any dermatologist applying injectable hyaluronic acid

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.

Original Articles

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

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, consequentemente, adversos – às vezes severos – reações vão surgir concomitantemente ao aumento do uso de preenchimentos 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 na correção de complicações ou efeitos inestéticos após preenchimentos à base de ácido hialurônico.

Resultados: 23 pacientes apresentaram algum tipo de efeito adverso, restrito ao local de injeção, variando de eritema, ardência, e 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 uma ferramenta extremamente eficaz tanto para a reversão dos resultados insatisfatórios e diluição de biofilme, e sua aplicação deve ser de domínio técnico de todas aqueles que aplicam o ácido hialurônico em seus pacientes.

Palavras-chave: ácido hialurônico; enzimas; acidentes.
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 cosmetic procedures were the most commonly performed during the study period. 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. 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. 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® 2,000 UTR - Aspen) 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 anatomical 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 2,000 UTR hyaluronidase lyophilisate powder vial (Hyalozima®) was dissolved in 5.0 ml of the diluent supplied with the product, generating a 400 U/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 400 U/ml Hyalozima® solution per cm² area to be corrected. The total doses applied ranged from 0.05 to 0.4 ml (20-160 UTR) 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-
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

---

**Graph 1:** Frequency of adverse events after intradermal injection of hyaluronidase for correcting HA-based filler complications.
respond to the use of oral corticosteroids and antihistamines. 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. These occur mainly due to immediate hypersensitivity, with some reports of patients with delayed reactions, starting within minutes, hours, or even days after exposure.

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. 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 Szczepaniak et al. for the use in CNS tumors chemotherapy. Support with intravenous or intramuscular epinephrine, intravenous or intramuscular corticosteroids. There were no reports of anaphylaxis after subepidermal intravenous corticosteroids and follow-up with oral corticosteroids. There were no reports of anaphylaxis after subepidermal applications for the correction of HA-based filling. 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. Recent articles have demonstrated that hyaluronidase injections in the treatment of biofilms with HA favor the degradation of the substrate matrix, facilitating the

<table>
<thead>
<tr>
<th>Trade mark</th>
<th>Source</th>
<th>Preservative Other ingredients</th>
<th>Available formulation</th>
<th>Available source countries</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphadase</td>
<td>Bovine</td>
<td>Thimerosal</td>
<td>Solution</td>
<td>EUA</td>
<td>150/ml</td>
</tr>
<tr>
<td>Vitrase</td>
<td>Ovine</td>
<td>Lactose</td>
<td>Solution</td>
<td>EUA</td>
<td>200/ml</td>
</tr>
<tr>
<td>Hylase Dessau</td>
<td>Bovine</td>
<td>-</td>
<td>Pó</td>
<td>Germany</td>
<td>150,300,1500/frasco</td>
</tr>
<tr>
<td>Desinfiltral</td>
<td>Ovine</td>
<td>-</td>
<td>Solução</td>
<td>England</td>
<td>1500/frasco</td>
</tr>
<tr>
<td>Hyalozima</td>
<td>Bovine</td>
<td>-</td>
<td>Pó</td>
<td>Brazil</td>
<td>2000/frasco (400/ml)</td>
</tr>
</tbody>
</table>

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. 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. There were no reports of anaphylaxis after subepidermal applications for the correction of HA-based filling. The authors believe that this is due to the use of much lower doses of the product when compared to other indications.
migration of macrophages and the penetration of antibiotics. Some authors have reported a favorable response to the use of hyaluronidase in resistant inflammatory reactions after dermal filling, regardless of the material used. 

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 2,000 UTR Hyalozima® vial is carried out in 5.0 ml of solvent that comes with the product, generating a 400 UTR/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 – in addition to lowering the probability of allergic reaction. Nonetheless, amounts equivalent to 40 U (0.1 ml) per cm² 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.

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.

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.
REFERENCES

1. American Society of Plastic Surgeons [Internet]. 2012 plastic surgery pro-
cedural statistics. [Cited 2014 Jul 20]. Available from: http://www.plastic-
text.html.

2. Tiemeyer EP, Hanke CW. Recent trends in cosmetic and surgical procedure

3. Ozuruk CN, Lu Y, Tung R, Parker L, Pilkang MP, Zins JE. Complications fol-

4. Crocco EL, Alves RG, Alessi C. Eventos adversos do ácido hialurônico inje-

5. Park TH, Seo SW, Kim JK, Chang CH. Clinical experience with hyaluronic

2010;36(7):1071-77.


8. Neri SRN, Ador FASA, Parada MB, Schalka S. Uso de hialuronidase em
complicações causadas por ácido hialurônico para volumização da face:

9. Pirello RD, Ting Chen C, Thomas SH. Initial experiences with subcutaneous


et al. Hyaluronidase toxicity: a possible cause of postoperative periorbital

12. Kim TW, Lee JH, Yoon KB, Yoon DM. Allergic reactions to hyaluronidase in
pain management -A report of three cases-. Korean J Anesthesiol.

13. Feighery C, McCoy EP, Johnston PB, Armstrong DK. Delayed hypersensi-
tivity to hyaluronidase (Hyalase) used during cataract surgery. Contact

14. Feighery C, McCoy EP, Johnston PB, Armstrong DK. Delayed hypersensi-
tivity to hyaluronidase (Hyalase) used during cataract surgery. Contact

15. Dielamn M, Bettink-Remeijer MW, Jansen J, Hoppenreijs VP, van der Pol
R, Baarnsma S, et al. High incidence of adverse reactions to localregional
anesthesia containing hyaluronidase after uneventful ophthalmic sur-

16. Agrawal A, McLure HA, Dabbis TR. Allergic reaction to hyaluronidase after

17. Akliluxalis H, Lukaris A, Lane CM. Delayed allergic reaction to hyaluronid-

for every dermatosurgeon that injects hyaluronic acid. J Cosmet Laser Ther.

19. Kim JH, Choi GS, Ye YM, Nahm DH, Park HS. Acute urticaria caused by the
injection of goat-derived hyaluronidase. Allergy Asthma Immunol Res.

20. Ebo DG, Goossens S, Opsomer F, Britts CH, Stevens WJ. Flow-assisted

21. Lee HK, Choi EJ, Lee PB, Nahm FS. Anaphylactic shock caused by the epi-

22. Lyall DA, McQueen M, Ramasah K, Weir C. A sting in the tale: cross reac-

allergic reaction to hyaluronidase in paediatric oncological patients. Eur

24. Vartanian AJ, Frankel AS, Rubin MG. Injected hyaluronidase reduces res-

25. Hilton S, Schrumpf F, Buhren BA, Böcke E, Gerber PA. Hyaluronidase injec-
tion for the treatment of eyelid edema: a retrospective analysis of 20

26. Scalfani AP, Fagen S. Treatment of injectable soft tissue filler complica-


28. Andre F, Flechet ML. Angioedema after ovine hyaluronidase injection for

29. Kim DW, Yoon ES, Ji YH, Park SH, Lee BI, Dhong ES. Vascular complications
of hyaluronic acid fillers and the role of hyaluronidase in management. J

30. Hirsch RJ, Cohen JL, Carruthers JDA. Successful Management of an
Unusual Presentation of Impending Necrosis Following a Hyaluronic
Acid Injection Embolus and a Proposed Algorithm for Management with


32. Dayan SH, Arkins JP, Brindise R. Soft tissue fillers and biofilms. Facial Plast

33. Brody HJ. Use of hyaluronidase in the treatment of granulomatous hyla-
uronic acid reactions or unwanted hyaluronic acid misplacement.

34. Pierre A, Leys PM. Hyaluronidase offers an efficacious treatment for
2007;6(3):159-62.