



Use of hyaluronidase in the reversal of facial dermal fillers with hyaluronic acid: a literature review

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SUMMARY

This project aims to analyze the use of hyaluronidase as an effective agent in reversing failed hyaluronic acid dermal fillers, highlighting its mechanism of action, main clinical indications and contraindications, dosage, application techniques, pre- and post-procedure care, and adverse effects. The research is based on a comprehensive literature review that included original articles, theses, dissertations, clinical guidelines, and evidence-based clinical protocols addressing the role of hyaluronidase in dermal filler complications. Therefore, it is expected that the data obtained will contribute to a deeper clinical understanding of the indications and contraindications, dosage, application techniques, and adverse effects of hyaluronidase, ensuring greater safety and efficacy in the reversal of hyaluronic acid dermal fillers.

Keywords: Aesthetics, harmonization, lip, biomedical.

ABSTRACT

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The research is based on a comprehensive literature review that included original articles, theses, dissertations, clinical guidelines, and evidence-based clinical protocols addressing the role of hyaluronidase in dermal filler complications. Therefore, it is expected that the data obtained will contribute to a deeper clinical understanding of the indications and contraindications, dosage, application techniques, and adverse effects of hyaluronidase, ensuring greater safety and efficacy in the reversal of hyaluronic acid dermal fillers.

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1. INTRODUCTION

The skin is one of the largest organs in the human body. It surrounds our entire body, where it delimits the internal and external environment, performing sensory functions, regulating body temperature and blood flow and serving as an immune barrier, making it necessary for our survival (SILVA

NETO et al, 2020). With senescence, numerous changes make the skin more flaccid and wrinkled,

such as loss of water and supporting elements such as collagen (BONI; BAIDA; ROBERTO,

2022). Over the past few years, people have increasingly been searching for a standard of beauty

imposed by society; for this reason, many undergo aesthetic procedures with the aim of

aim of reducing the adverse effects that time brings (SILVA NETO et al, 2020). Despite

are subject to complications, these aesthetic procedures, especially fillers

are the ones that have been gaining the most popularity (KROUMPOUZOS; TREACY, 2023).

Of the fillers available, hyaluronic acid is undoubtedly the most widely used today.



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world (DAHER et al, 2020), since facial filling with injectable hyaluronic acid is today considered the gold standard treatment in the aesthetic approach to wrinkle reduction (DOS ANJOS; TREVISAN, 2024). Hyaluronic acid-based fillers are indeed recognized about its effectiveness and safety (SCRIMA et al, 2022), however, there is no filler that is completely devoid of risks (SILVA NETO et al, 2020), and with increased use, which includes inadvertent use of these fillers, the number of cases of complications has been increasing. To when it is necessary to reverse an unsuccessful hyaluronic acid filling, there is the enzyme hyaluronidase (SILVA; PREVITALE; GOUVEIA, 2022). First used in 1949, hyaluronidase has been widely used in aesthetic medicine for the past 15 years to dissolve hyaluronic acid (MURRAY et al, 2021). It is essential that professionals who use hyaluronidase know its mechanism of action (JUNG, 2020), its practical applications, administration instructions and the risks associated with its use (MURRAY et al, 2021).

Based on the above, it is important to know the mechanism of action, the applications practices and indications, contraindications, risks and adverse effects of the use of hyaluronidase in correction of unsuccessful hyaluronic acid fillers. Thus, this production aims, therefore, carry out a literature review to analyze benefits, risks and protocols recommended for the use of hyaluronidase and consolidate essential information for its use conscious in the context of reversal of hyaluronic acid fillers.

2. MATERIAL AND METHOD

This work consists of a bibliographic review whose analysis is of a qualitative nature, with the aim to gather, analyze and discuss the main available evidence on the use of hyaluronidase in reversal of failed hyaluronic acid dermal fillers.

The research used electronic databases such as PubMed, Scielo, CAPES Periodicals Portal, Virtual Health Library and Google Scholar. Descriptors in Portuguese and English were used, including: "hyaluronidase", "hyaluronic acid", "filler reversal", "complications in dermal filler", "hyaluronidase", "hyaluronic acid", "filler complications", "filler reversal" and aesthetic correction". 21 of the 78 publications read were selected, considering articles originals, theses, dissertations, guidelines and clinical protocols, all from the last 5 years, in order to ensure the information is up-to-date. There were no restrictions on the type of publication, as long as address the clinical application of hyaluronidase in the reversal of dermal fillers with acid hyaluronic acid.

The research, of a theoretical and exploratory nature, does not require statistical treatment, since it does not



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numerical, experimental or field data were collected. The analysis is expected to demonstrate the importance of hyaluronidase as a safe and effective tool in reversing fillers with hyaluronic acid, in addition to highlighting the need for well-established clinical protocols for its use. The analysis of theoretical data allowed us not only to understand the main clinical applications of the substance, but also recognize limitations, controversies and gaps existing in the main publications, contributing to evidence-based practice.

As this is a literature review, without direct intervention in human beings, this work did not require evaluation by the Research Ethics Committee (CEP), in accordance with CNS Resolution No. 510/2016.

3. RESULTS AND DISCUSSION

Data analysis was carried out using a qualitative approach, with an emphasis on review bibliographical review of studies published in the last 5 years on the use of hyaluronidase in the reversal of aesthetic procedures with hyaluronic acid. Data collection was carried out through searches in databases scientific databases such as PubMed, Scielo, CAPES Periodicals Portal, Virtual Library in Health and Google Scholar, using descriptors such as "hyaluronidase", "hyaluronic acid", "reversal filler", "dermal filler complications", "hyaluronidase", "hyaluronic acid", "filler complications", "filler reversal" and "aesthetic correction".

The data obtained, composed of original articles, theses, dissertations, guidelines and protocols clinical, were analyzed based on the content analysis technique, aiming to identify categories recurring themes such as: mechanism of action, practical applications and indications, contraindications, risks and adverse effects of use. This analysis allowed the interpretation of the contents critically, providing an in-depth understanding of the main evidence available in scientific literature.

3.1. ABOUT HYALURONIC ACID

In recent decades, minimally invasive aesthetic procedures have gained great popularity, with hyaluronic acid being one of the main agents used, being widely used in facial harmonization. According to the American Society of Plastic Surgery, in 2014 hyaluronic acid accounted for approximately 78% of all injectable fillers used, reinforcing its relevance in the field of aesthetic medicine (DAHER et al., 2020). The growth of The use of hyaluronic acid is evident: in 2018, more than 810 thousand procedures with acid hyaluronic acid were performed. Today, hyaluronic acid fillers are the second procedure



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most common non-surgical aesthetic, second only to botulinum toxin (OLAIYA et al., 2023).

Currently, lip filling with hyaluronic acid has stood out as one of the most sought-after aesthetic procedures, mainly due to their ability to improve contour, volume and symmetry of the lips. The arteries responsible for the arterial supply of the lips are originating from the facial artery, which in turn is a direct branch of the external carotid artery. The main artery of the upper lip is the superior labial artery, and its subalar and septal branches are sometimes facultative in this process. The lower lip is supplied by the inferior labial artery and the artery labiomentoniana (UEZU et al., 2022; YAMAMOTO, M. et al., 2022). The buccal branch of the facial nerve (VII cranial nerve) provides motor innervation to the orbicularis oris muscle, the levator labii and the angle of the lip. Most of the muscles responsible for lip depression are supplied by the marginal mandibular branch also of the facial nerve. The various branches of the trigeminal nerve (V nerve cranial) provide sensory innervation to the lips. The infraorbital branch of the maxillary division of the trigeminal (cranial nerve V2) supplies the upper lip, and the mental branch, derived from the division mandibular of the trigeminal nerve (cranial nerve V3), allows sensation of the lower lip (PICCININ; ZITO, 2025).

Hyaluronic acid is a polysaccharide naturally present in the human body (BORZABADI FARAHANI; MOSAHEBI; ZARGARAN, 2022) produced by fibroblasts, among other types of cells, a component of the extracellular matrix (WEGE et al., 2021) with a high capacity for retention of water, helping to maintain skin elasticity and hydration. Its use as an aesthetic filler due to the ease of handling and temporary results with good immunological acceptance (BORZABADI FARAHANI; MOSAHEBI; ZARGARAN, 2022).

3.2. COMPLICATIONS OF THE USE OF HYALURONIC ACID

Despite its widespread use and relative safety, hyaluronic acid is not risk-free.

Complications, although rare, can arise, such as chronic edema, granulomas, inflammation and even vascular occlusions that can lead to tissue necrosis. Hypersensitivity reactions to acid hyaluronic acid are unusual, especially since it is a bioidentical component to that present in human organism, which contributes to the safety and acceptance of the product (WEGE et al., 2021). Early complications (< 14 days after injection) after hyaluronic acid application are generally attributed to technical factors such as inadequate injection depth, speed excessive flow, large injected volumes, or lack of knowledge of the local vascular anatomy. Among these reactions include edema, formation of nodules, hematomas, and, in more severe cases, vascular occlusion and tissue necrosis (BORZABADI FARAHANI; MOSAHEBI; ZARGARAN, 2022). Vascular manifestations (ischemia and necrosis) usually appear during or shortly after



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application of hyaluronic acid. The main hypotheses that explain these conditions include arterial spasm (angiospasm) and accidental embolization of hyaluronic acid particles to within the vascular network (CUNHA; PACHECO, 2021).

Although many adverse effects are mild and self-limiting, such as edema and bruising, events serious conditions such as skin necrosis, although rare, represent aesthetic emergencies. These require immediate intervention to avoid permanent aesthetic damage. The literature highlights the importance of early diagnosis and immediate management, with hyaluronidase being the main agent used in reversal of filling with hyaluronic acid (GOMES DOS SANTOS et al., 2024).

3.3. NEEDLES VS CANNULAS

The application of fillers in the tissues varies with the use of needles or cannulas (CASTRO DE SOUSA; LIMA; ALMEIDA, 2022). A needle is a thin, sharp-pointed device, usually made of stainless steel, available in various sizes and diameters. The cannulas are similar to needles, however, are usually made of plastic and have a blunt, non-cutting tip, opening lateral close to the tip and greater flexibility. In theory, cannulas seem to lead to less trauma to the tissues (CASTRO DE SOUSA; LIMA; ALMEIDA, 2022; AL-HAGE; GALADARI, 2024). In However, despite having a blunt tip, large-caliber cannulas can dissect more tissue than a needle, which results in tissue destruction (ROSENGAUS; NIKOLIS, 2020). Cannulas are generally larger than needles, so they can deliver high viscosity materials and can be easy to inject with less. In contrast, needles have long been considered more accurate timing, as the injector can precisely direct the needle tip to the desired location (AL-HAGE; GALADARI, 2024).

3.4. ABOUT HYALURONIDASE

Hyaluronidase is a hydrolytic enzyme that cleaves the β 1,4 glycosidic bonds of hyaluronic acid, reducing its viscosity and promoting its degradation (BORZABADI FARAHANI; MOSAHEBI; ZARGARAN, 2022). Since its first use in 1949, this enzyme has gained highlighted in aesthetic medicine, especially in the last 15 years, as a method of reversing unsatisfactory or complicated fillers with hyaluronic acid (JUNG, 2020; MURRAY et al., 2021). Technical mastery over its application and dosage is essential, especially on the part of aesthetic professionals who perform the procedure. The biomedical professional, within his legal attributions and specialized training, plays an important role in the safe conduct of this treatment corrective (GOMES DOS SANTOS et al., 2024).



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In addition to its aesthetic use, hyaluronidase is compatible with lidocaine and is used in anesthesia as an adjuvant in anesthetic blocks (MURRAY et al., 2021).

3.5. HYALURONIDASE DOSAGE

Available commercial formulations include bovine derivatives (Hylase Dessau®, Amphadase®), ovine (Vitrase®) and recombinant human versions (Hylenex®, ENHANZE®), each with specific immunological and pharmacokinetic profiles. The animal origin of these preparations poses a risk allergic reaction which, although low, must be taken into account in order to use this antidote with the best benefit/risk ratio (CAVALCANTI, et al., 2024).

When stored at temperatures consistently above 25°C, the product's expiration date will be affected. Once opened, the ampoule must be used immediately, and any unused contents must be discarded.

Before injection, the area must be cleaned and thoroughly disinfected with an antibacterial solution for the skin (MURRAY et al., 2021). The action of hyaluronidase is rapid, with the onset of effect in minutes and duration ranging from 24 to 48 hours. The short half-life requires, in some cases, reapplications at hourly intervals, especially in serious situations such as vascular occlusions (GOMES DOS SANTOS et al., 2024).

There is no consensus in the literature on the dosage of hyaluronidase for complications related to fillers, and the recommended doses offered are widely divergent, with the amount of hyaluronidase used depending on the estimated volume of asymmetry and the product of filling (OLAIYA et al., 2021). In general, it is known that 30 units of hyaluronidase are necessary to dissolve 1 mL of hyaluronic acid (BORZABADI FARAHAANI; MOSAHEBI; ZARGARAN, 2022). In the case of skin necrosis resulting from the use of hyaluronic acid, the area necrotic area should be immediately flooded with a high dose of hyaluronidase at one-hour intervals. It is recommended that a minimum of 500 IU of hyaluronidase be used for every 3 cm² of the area with necrosis. In addition to the application of hyaluronidase, vigorous massage and warm compress for a period of five to ten minutes with half and one hour intervals from 3 to 5 times a day (CUNHA; PACHECO, 2021).

For inflammatory nodules, a combination of hyaluronidase, antihistamines, corticosteroids, anti-inflammatory drugs and antibiotics are often used (BORZABADI FARAHAANI; MOSAHEBI; ZARGARAN, 2022).



3.6. ADVERSE REACTIONS TO THE USE OF HYALURONIDASE

Adverse effects of hyaluronidase are rare and generally local, such as injection site reactions. (GOMES DOS SANTOS et al., 2024). In concentrations greater than 1:10 (1500 IU:10 mL) it can be irritating, with edema, erythema and itching at the injection site being the most common side effects known (MURRAY et al., 2021).

There is growing concern among physicians that an anaphylactic reaction (acute reaction) IgE-mediated type I hypersensitivity) may occur when injecting hyaluronidase. However, incidence is rare and estimated at about 0.1% unless large doses (> 200000 IU) are administered. (BORZABADI FARAHANI; MOSAHEBI; ZARGARAN, 2022). Before use, it is recommended to perform a preliminary skin test to avoid possible allergic reactions, especially in patients with a history of allergy to bee stings, since hyaluronidase is a component of the venom of this insect. (GOMES DOS SANTOS et al., 2024).

FINAL CONSIDERATIONS

Although the results of hyaluronic acid fillers are satisfactory, there is the possibility of complications and adverse effects. In such cases, it becomes essential to availability of an effective therapeutic approach to reverse or correct the effects unwanted. The use of hyaluronidase has proven to be a practical and safe solution, however, despite of its effectiveness, it still lacks greater standardization regarding dosage and application technique in order to avoid long-term adverse effects. This scenario justifies further studies in-depth information on the use of hyaluronidase for the reversal of hyaluronic acid fillers, as this can improve the safety of aesthetic procedures.

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