UNVEILING THE MULTIPLE HORIZONS OF HYALURONIDASE IN AESTHETIC PRACTICE

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Abstract

Introduction: Hyaluronidase, an enzyme that has been used for decades in medicine, plays a crucial role in the dissolution of hyaluronic acid (HA) in aesthetic procedures. Objective: This study aims to explore the various applications of hyaluronidase, both approved and off-label, highlighting its relevance in aesthetic medicine. Methodology: The study consists of a literature review, analyzing scientific studies on the functions, efficacy, and potential side effects of this enzyme. Theoretical Framework: The discussion includes the natural presence of hyaluronidase in the body, its ability to break down HA, and the different sources of the enzyme, such as bovine, ovine, and recombinant. Additionally, the use of HA as a dermal filler, the associated risks like nodules and tissue necrosis, and the role of hyaluronidase in mitigating these complications are examined. The findings indicate that hyaluronidase is effective in reversing complications associated with HA use, emphasizing the importance of a detailed knowledge of facial anatomy and injection techniques to prevent severe issues, such as blindness and necrosis. Conclusion: It underscores that, despite the safety and efficacy of hyaluronidase, it is advisable to conduct skin sensitivity tests to prevent allergic reactions. The study reinforces the need for the appropriate use of hyaluronidase in aesthetic treatments and in preventing complications related to HA.

Keywords: Hyaluronidase, hyaluronic acid, aesthetic medicine, complications, safety.

Resumo:

Introdução: a hialuronidase, uma enzima usada há décadas na medicina, desempenha um papel crucial na dissolução do ácido hialurônico (AH) em procedimentos estéticos. Objetivo: este estudo objetiva explorar as diversas aplicações da hialuronidase, tanto aprovadas quanto off-label, destacando sua relevância na medicina estética. Metodologia: consiste em uma revisão de literatura, analisando estudos científicos sobre as funções, eficácia e possíveis efeitos colaterais dessa enzima. Referencial teórico: discute-se a presença natural da hialuronidase no organismo, sua capacidade de quebrar o AH, e as diferentes origens da enzima, como bovina, ovina e recombinante. Também se examina o uso do AH como preenchedor dérmico, os riscos associados, como nódulos e necrose tecidual, e o papel da hialuronidase na mitigação dessas complicações. Resultados e Discussões: indicam que a hialuronidase é eficaz na reversão de complicações associadas ao uso de AH, destacando a importância de um conhecimento detalhado da anatomia facial e das técnicas de injeção para evitar problemas graves, como cegueira e necrose. Conclusão: ressalta que, apesar da segurança e eficácia da hialuronidase, é recomendável realizar testes de sensibilidade cutânea para prevenir reações alérgicas. O estudo reforça a necessidade do uso adequado da hialuronidase em tratamentos estéticos e na prevenção de complicações relacionadas ao AH.

Palavras-chave: Hialuronidase, ácido hialurônico, medicina estética, complicações, segurança.

I. INTRODUCTION

Hyaluronidase, an enzyme responsible for breaking down hyaluronic acid, has been used in medicine for over six decades. The U.S. Food and Drug Administration (FDA) has approved its use for various purposes, including: [1] subcutaneous fluid infusion (hypodermoclysis), [2] as an adjunct to accelerate the absorption and dispersion of drugs in subcutaneous tissue or to manage extravasation, and [3] as a complement to enhance the absorption of contrast media in urinary tract angiography (subcutaneous urography) [1,2,3]. Additionally, in Europe, it has been approved and used to increase the absorption of hematomas. Hyaluronidase has a range of uses beyond its approved indications. Its off-label uses include dissolving hyaluronic acid fillers, treating foreign body granulomatous reactions, and addressing skin necrosis associated with filler injections [4,5,6].

Cross-linked hyaluronic acid (HA) is the most popular non-surgical procedure for rejuvenation, used to restore volume and augment soft tissues. Endogenous HA is widely present throughout the body and plays a crucial role as a structural component in the extracellular matrix [7,8,9]. It is found in the skin and helps support tissue architecture while maintaining hydration due to its hygroscopic nature. Moreover, HA is extensively used in dermal fillers for its anti-aging properties, which help delay the formation of wrinkles and expression lines that develop over time. The biomolecule is applied in the dermis to reshape the face and smooth out skin folds, such as nasolabial and tear trough lines, demonstrating different stability and durability depending on the degree of cross-linking. Dense HA is indicated for deeper wrinkles, structuring tissue and adding volume. HA fillers with a lower degree of cross-linking have less molecular weight and viscosity, making them safer for filling fine and superficial wrinkles [1,10,11].

Hyaluronidase works by breaking down hyaluronan complexes, which are glycosaminoglycan polysaccharides, through a hydrolysis process. Its primary action is the cleavage of C1 and C4 bonds between glucosamine and glucuronic acid components, leading to the unraveling and fragmentation of the complex molecule [12]. Its main function in aesthetic medicine is to dissolve the cross-linked bonds in HA dermal fillers. However, it can also be used to treat resistant edema due to its ability to increase capillary and tissue permeability [12,13]. Given the growing popularity of cross-linked hyaluronic acid (HA) as a dermal filler, understanding the role of hyaluronidase in dissolving these fillers and its potential to address complications such as granulomatous reactions and skin necrosis is crucial. This literature review aims to explore the various uses of hyaluronidase in aesthetic medical practice, including its approved and off-label indications, as well as its mechanisms of action. Additionally, it investigates hyaluronidase's capacity to treat resistant edema, expanding therapeutic possibilities in aesthetic medicine.

II. METHODOLOGY

This study employs a narrative review approach to explore and synthesize existing knowledge on the use of hyaluronidase in aesthetic medical practice, with a focus on its applications in dissolving hyaluronic acid fillers and treating associated complications. Selected sources include scientific articles, reviews, clinical guidelines, case studies, and reference literature published between 2000 and 2024. Databases used include PubMed, Scopus, and Web of Science, as well as specialized sources in dermatology and aesthetic medicine. Keywords used in the search were: "hyaluronidase," "hyaluronic acid," "dermal filler," "aesthetic complications," "resistant edema," and "granulomas." Studies addressing the efficacy, safety, mechanisms of action, and off-label uses of hyaluronidase in aesthetics were included. Studies focused on other medical fields, such as ophthalmology and urology, were excluded unless relevant for understanding the enzyme's mechanisms of action. Data collected were analyzed qualitatively, highlighting FDA and EMA-approved indications, off-label uses, types of hyaluronidase available, mechanisms of action on hyaluronic acid, as well as clinical administration protocols in different aesthetic scenarios. The analysis also considered complications treated with hyaluronidase and the doses used for each application.

III. THEORETICAL FRAMEWORK

A. Hyaluronidase in the Body

Hyaluronidase is present in various organs of the human body, including the testicles, spleen, skin, eyes, liver, kidneys, uterus, and placenta. It is naturally produced in the dermis and is most active in the PH-20 form, located in the head and acrosome of the male spermatozoon. This activity aims to degrade the hyaluronic acid of the egg during fertilization [23,26]. Hyaluronidase, particularly HYAL-1, is found in the human body in low concentrations, which complicates its purification and the regulation of its activity due to its extreme instability. HYAL-1 is the primary form of hyaluronidase, present in somatic tissues of organs such as the liver, kidney, spleen, and heart, and is also found in serum and urine [7,23,26].

The enzyme's activity after exogenous injection varies depending on the site of application, dilution damage, diffusion, and deactivation over different time frames in subcutaneous tissue and plasma. Studies in rats have shown a hyaluronidase half-life of less than 30 minutes, with total activity lasting up to 1 hour [26,27]. In human studies, the half-life of intravenously administered drug was recorded with an average of 2 to 3 minutes. This short duration is attributed to the presence of inhibitors in the blood plasma and metabolism in the kidneys and liver [23].

B. Hyaluronidase: Action and Types

Hyaluronidase plays a crucial role in breaking down the disaccharides present in hyaluronic acid (HA), promoting the hydrolysis of glycosidic bonds and, consequently, inducing the depolymerization of the molecule. This process results in enhanced drug dispersion in tissues, varying its range and increasing its effectiveness. Hyaluronidase rapidly degrades, fragmenting hyaluronic acid fillers and serving as a control measure in cases of complications arising from aesthetic fillers, which may persist for 12 months or more [17]. Additionally, it acts as an adjunct in the dispersion of medications in subcutaneous tissue, including local anesthetics and immunoglobulins.

There are several types of hyaluronidase available on the market, derived from different sources, such as bovine testicle (Hylase Dessau® and Amphadase®), purified ovine testicle (Vitrase®), and recombinant human hyaluronidase (ENHANZE® and Hylenex®) [11,17,18,19].

Regarding the classification of hyaluronidases based on their action on hyaluronan, they can be divided into three distinct groups:

1. Hyaluronoglucosaminidase, also known as "testicular-type hyaluronidase," is primarily found in mammalian spermatozoa or in the venom of wasps, bees, snakes, and other animals. These enzymes degrade the β-1,4 glycosidic bonds of HA, as illustrated in Figure 1 [23,28].
2. Hyaluronate glycan-hydrolase, or "leech-type hyaluronidase," can be found in the salivary glands of leeches and hookworms. They degrade only hyaluronic acid, remaining inert to other glycosaminoglycans [18,28].
3. Hyaluronate lyase, or "bacterial-type hyaluronidase," differs from other hyaluronidases as it does not use hydrolysis but instead performs a β-elimination of β-1,4 glycosidic bonds, producing an unsaturated disaccharide [1,18,26,28]. Currently, FDA-approved products are of animal or recombinant human origin. However, the enzyme has not always been recommended due to its extraction from impure sources, which increased the risk of adverse effects, including contaminating substances such as proteases, immunoglobulins, and vasoactive factors. In Brazil, the most commonly used hyaluronidase is called Hyalozima, of bovine origin, registered with ANVISA, while Hylenex, a recombinant human enzyme, is considered safer due to its lower immunogenic response [11,18,28].

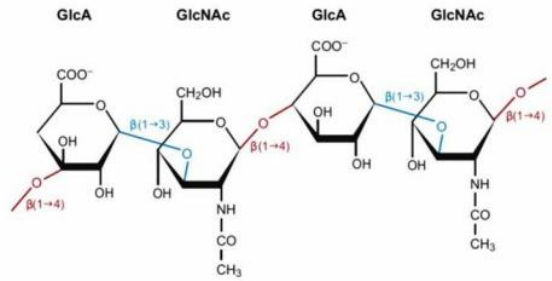

Figure 1: Structure of hyaluronic acid. D-glucuronic acid and N-acetylglucosamine are linked by β-1,3 bonds (represented in blue) to form a disaccharide. Multiple disaccharides are connected by β-1,4 bonds (represented in red) to form hyaluronic acid. Mammalian and microbial hyaluronidases cleave the β-1,4 bonds (red), while leech/hookworm hyaluronidases degrade the β-1,3 bonds (blue).

C. Hyaluronic Acid Fillers

Hyaluronic acid is widely used in facial harmonization due to its high hydration power and anti-aging properties. It is capable of reducing wrinkle formation and the depth of existing lines [1,13,17]. One of the significant advantages of hyaluronic acid fillers is that they do not require surgical procedures, allowing adjustments such as in rhinoplasty to correct nasal asymmetries, and also to restructure the middle and lower thirds of the face [17]. Some manufacturers choose to add anesthetics to the hyaluronic acid filler formulation to make the procedure more tolerable and less painful, especially in sensitive areas such as the lips, cheeks, chin, and under the eyes. Typically, lidocaine is incorporated into the gel. Alternatively, a qualified and specialized professional may administer local anesthesia before the application of the hyaluronic acid filler [17,28].

The enzyme hyaluronidase (HYA) has demonstrated effectiveness in reversing hyaluronic acid fillers. The application dose varies depending on the treatment objective, the area to be treated, and the volume of the product involved [11,19]. Treatment for complications related to the application of hyaluronic acid-based dermal fillers can vary in extent and severity. Generally, doses of 40 IU (0.1 ml) per cm² of the affected area are sufficient to disperse nodules caused by product accumulation [11].

D. Practical Application of Hyaluronidase in Aesthetic Medicine

The enzyme hyaluronidase plays a role in degrading hyaluronic acid, which is currently one of the most widely used filling molecules in aesthetic medicine. These proteins act by depolymerizing hyaluronic acid, typically enhancing tissue absorption [28]. This action is useful for preventing tissue damage that can occur due to the leakage of injected material into tissues, potentially causing arterial occlusion. Due to its diffusion capability, hyaluronidase can be effective in resolving post-filler nodules, whether inflammatory or not [13,24]. Inflammatory nodules, which are usually painful, can occur due to foreign body reactions or infection, with a risk of bacterial biofilm formation. Non-inflammatory nodules, on the other hand, result from product accumulation in a specific area, usually due to superficial injection, and are visible and palpable, particularly in the lips [13,19,24].

When hyaluronic acid is injected too superficially, without reaching the correct tissue depth, a phenomenon known as the Tyndall effect can occur, characterized by a bluish tint of the skin due to preferential scattering of blue light [13]. In addition to health risks, these effects can result in an unsatisfactory aesthetic outcome. Intravenous injection of hyaluronic acid can entail severe risks such as tissue necrosis and even blindness, due to the distribution of the ophthalmic arteries in the face [9].

Therefore, it is crucial for the professional to have extensive knowledge of the technique and facial anatomy to avoid adverse reactions.

The enzyme hyaluronidase has been approved by the U.S. Food and Drug Administration (FDA) for several specific purposes, including: [1] subcutaneous fluid infusion (hypodermoclysis), [2] as an adjunct to accelerate drug absorption and dispersion in subcutaneous tissue or to control leakage, and [3] as a complement to promote the absorption of contrast media in urinary tract angiography (subcutaneous urogram) [4,11,18]. Its off-label use includes the dissolution of hyaluronic acid fillers, treatment of foreign body granulomatous reactions, and addressing necrosis associated with hyaluronic acid filler injections. The European Union has licensed hyaluronidase for subcutaneous bruise absorption, whether post-procedure or traumatic sequelae. Hyaluronidase injections have significantly improved bruise absorption, preventing dermatological compromise and reducing fibrosis [3].

The most common and urgent application of this enzyme in dermatology is hypodermoclysis, that is, the correction of hyaluronic acid fillers, employed to eliminate visible nodules, often inflammatory and painful, or superficial infiltrations [1,4,28]. Hyaluronidase is a primary option in intra-arterial injections or AH leakage, requiring prompt treatment to reduce the risk of sequelae and permanent damage such as bone necrosis. Its administration can be performed within the first 4 hours after signs of whitening in the injected area, to enhance tissue absorption and the healing process [28].

According to the classification of hyaluronan, hyaluronidases can be defined into three groups: hyaluronoglucosaminidase, also known as "testicular-type hyaluronidase," found mainly in

mammalian sperm or the venom of wasps, bees, snakes, among other animals, which degrade the β-1,4 glycosidic bonds of HA as illustrated [18,26,28]. Hyaluronate glycan-hydrolase, or "leech-type hyaluronidase," found in the salivary glands of leeches and hookworms, degrades only HA and remains inert to other glycosaminoglycans. Hyaluronate lyase, or "bacterial-type hyaluronidase," differs from other hyaluronidases by not using hydrolysis but instead performing β-elimination of β-1,4 glycosidic bonds, producing an unsaturated disaccharide [18,26,28].

E. Intradermal Patch Test

Hyaluronidase is extensively used in ophthalmic surgeries to accelerate the diffusion of local anesthetic in periocular tissues. Approximately 0.5% of cases report immediate or delayed hypersensitivity, usually during subsequent administration [14,15]. This enzyme is derived from bovine or ovine testicles and can also be found in the venom of bees, wasps, scorpions, snakes, and other animals. Based on this, a recombinant human hyaluronidase has been developed through cDNA sequencing of the Hyal-1 protein gene, produced by chemical properties, and is believed to mitigate adverse or allergic reactions after medication administration [15,18].

Recombinant hyaluronidase, administered subcutaneously for dispersion or absorption of dermal drugs, can provoke local reactions such as erythema and warmth, particularly with larger application volumes. The intradermal test confirms the diagnosis of allergic expression, manifesting within a few days or later, within weeks [14,16]. It is an important alternative, especially after orbital infection in ophthalmic surgical cases due to infection or allergic incident, treated as acute infectious orbital cellulitis. In such cases, intravenous antibiotics are used due to the high risk of vision loss, infection migration to the face and meninges, endangering the patient's life [14]. An intradermal test can be performed to confirm the presence of hypersensitivity or allergy [16].

Typically, the test is prolonged according to the manufacturer's recommendation, applying 3 IU of hyaluronidase intradermally and observing if there is warmth and formation of an erythematous papule at the site after 5 to 20 minutes, indicating a positive result [16,17,18]. However, considering that some complications may manifest later, this skin test does not completely eliminate the risk of an allergic occurrence.

Allergic reactions to hyaluronidase are rare and are believed to be related to the route of administration and dosage. A prophylactic method would be the previously mentioned intradermal skin test, suitable due to the increased use of the enzyme in various medical fields [11,14,16,17,18]. Skin test results were positive in most hypersensitive patients. However, this is a measure to prevent anaphylactic reactions, particularly with high doses [16].

F. Allergic Risk/Side Effects Associated with Treatment

Although the use of hyaluronidase is widely considered safe, with few reports of adverse effects, the most common symptoms at the application site include pain, swelling, warmth, erythema, and itching. However, these symptoms are not indicative of an allergic reaction to the product, as they are expected reactions. The main complications reported in the literature are local swelling and burning [13,19]. Allergy to hyaluronidase is rare and generally involves isolated case reports. A case described by Bravo et al. involved lip angioedema following hyaluronidase application, which was treated with oral corticosteroids [11].

The use of hyaluronidase after dermal filler procedures is indicated for correcting asymmetries, nodules, or Tyndall effect, generally using low doses [17]. The activity is observed 24 to 48 hours after injection, safely and effectively. However, use in large volumes is more suitable for cases of vascular injury with a risk of progressing to tissue necrosis, especially when detected early [19].

Allergic manifestations with hyaluronidase occur more frequently with high doses and depend on each patient's immune response, potentially occurring minutes or months after application [16,17]. Immediate hypersensitivity reactions, occurring within 2 hours after application, are mediated by the IgE immune response, resulting in erythematous edema. In contrast, delayed hypersensitivity reactions (Type IV) are developed by T lymphocytes as part of the immune response [18].

G. Doses

Hyaluronidase is widely used in conjunction with various local anesthetics, especially in ophthalmology. Studies have evaluated the efficacy and safety of hyaluronidase combined with lidocaine through infero-nasal injection, using ultrasonography to record a higher rate of anesthetic dispersion at the site. Therefore, in local anesthesia, the addition of 50 IU/ml of hyaluronidase as an adjunct in peribulbar block primarily aims to improve the quality of anesthesia, reduce block latency, and decrease intraocular pressure (IOP) [20,26].

The literature does not present a consensus on the enzyme administration doses. Some authors recommend 150 to 200 IU of hyaluronidase per 1 ml of injected hyaluronic acid [18,19,22]. An in vitro study with different concentrations, including 24 mg/ml of fluid gel, 20 mg/ml of particulate gel, and 5.5 mg/ml of particulate gel with lidocaine, demonstrated higher resistance in the 24 mg gel, likely due to its consistency and cohesion [19]. Therefore, the study concludes that the dose of hyaluronidase depends on the cross-linking; that is, for each 0.1 ml of hyaluronic acid to be treated (in vivo), 5 IU of hyaluronidase should be used for the 20 mg/ml gel or 10 IU for the 24 mg/ml gel [29].

Immediate use of hyaluronidase is indicated in cases of necrosis, with a recommended minimum dosage of 200 IU of the enzyme to flood the area. It can be applied slowly and directly to the area with hyaluronic acid. Therefore, the dosage varies depending on the area to be treated, the volume, and the cross-linking of the injected hyaluronic acid, potentially reaching up to 1500 IU in cases of vascular occlusion [23,24,25].

H. Storage and Preparation

The procedure begins with asepsis and identification of the area to be treated. Some manufacturers offer ready-to-use products, such as Hylenex®, Amphadase®, and Vitrase®. On the other hand, Hyalozima requires preparation, consisting of mixing the lyophilized hyaluronidase powder with 5 ml of the provided diluent [21]. The reconstituted solution (400 IU/ml) should be used immediately after dilution and kept upright until application. According to the manufacturer's instructions, it is recommended to store the vial in a dry place at room temperature, between 15º and 30ºC, before opening [19,21].

Hyalase® is also available in lyophilized powder form and can be diluted in 1 ml of distilled water or saline for subcutaneous infusion (hypodermoclysis) [25]. It contains 1500 IU of hyaluronidase distributed directly into the solution to be injected, either subcutaneously, intramuscularly, or with local anesthetics, which should be mixed with the amount of local anesthetic solution to be used. In ophthalmology, a ratio of 15 IU of hyaluronidase per ml is recommended [25,30]. The enzyme's application via subcutaneous urographic contrast medium is indicated when intravenous access cannot be performed, usually for infants and children [31].

The manufacturer suggests performing a sensitivity test before use and using it immediately after reconstitution [30]. However, some authors mention that keeping the product refrigerated may increase the solution's specificity level, which could complicate its application. It is important to note that after the injection of hyaluronidase, the product maintains its immediate manipulation effect on the accumulation of hyaluronic acid following local injection [19].

I. Drug Interactions

Certain medications are incompatible with hyaluronidase, including furosemide, epinephrine, benzodiazepines, heparin, and phenytoin. In cases of diagnosed infection, the enzyme should not be used to avoid the risk of infectious transmission. It is crucial to inquire about the patient's use of medications such as salicylates, corticosteroids, estrogens, adrenocorticotropic hormones, and antihistamines, as they can make tissue more resistant to hyaluronidase, requiring higher doses of application [11,24]. During pregnancy, this medication is classified as Category C. Animal studies have shown potential teratogenic effects or embryo toxicity, but there are no controlled studies in women. Additionally, based on its formulation, it should not be used in patients allergic to bee stings, as hyaluronidase is a component of bee venom [32]. Although adverse effects and anaphylactic reactions are rare after the administration of HYA, it is

expected that the patient remains under observation for at least one hour to detect possible adverse reactions. Hyaluronidase should not be applied to areas affected by stings, as an adjunct to dopamine or α-agonist drugs, or in inflamed regions to avoid the spread of infection [30,31,32].

J. Complications

Vascular embolic complications arise due to the high pressure of fillers in the facial arterial circulation. Damage is predominantly localized near the site of application. Injections in the glabella carry an increased risk of blindness due to the carotid system, which extends from the supratrochlear arteries and dorsal nasal arteries to the ophthalmic arteries [25]. The incidence of facial embolism related to HA is extremely low, and blindness is even rarer in the literature. However, the "antidote" for managing secondary complications with fillers is based on the injection of hyaluronidase [4,25].

Most reactions with hyaluronidase applications are immediate hypersensitivity reactions, such as Type I, mediated by IgE. However, in some cases, delayed hypersensitivity reactions, Type IV, mediated by T lymphocytes, can occur even after 24 hours [11,16,18]. The most frequent manifestations include erythematous edema up to 2 hours after application. In these cases, studies suggest using systemic or topical steroids and antihistamines [23,28].

The adverse effects are not yet clearly defined, as long as the standard dosage is used for each case of recurrence in dermal filling, which can range from 5 to 75 IU, up to 150 to 200 IU per 1 ml of hyaluronic acid [29,30,31]. Although hyaluronidase has few cases of hypersensitivity and non-harmful complications, it should be administered with caution, even in patients previously exposed to the protein, as sensitization and allergic response can occur [22].

IV. RESULTS AND DISCUSSIONS

The selection of studies for this literature review on the enzyme hyaluronidase spans publications from the past twenty years. The research focused on topics such as hyaluronidase, hyaluronic acid, fillers, aesthetic medicine, and adverse effects, with an emphasis on the application of hyaluronidase in medical and aesthetic contexts. In aesthetic medicine, hyaluronidase is frequently used to reverse the effects of hyaluronic acid-based dermal fillers.

The increasing demand for facial harmonization and restructuring procedures has, consequently, led to unwanted outcomes and complications due to technical issues. The ability of hyaluronidase to dissolve hyaluronic acid fillers has increased the safety of these procedures. However, it is essential for healthcare professionals involved in the application of minimally invasive dermal fillers to discuss and share knowledge about the risks and benefits of using this enzyme, seeking safer and more effective practices in potential clinical cases.

According to the reviewed authors, although exogenous hyaluronic acid is biocompatible and safe for application, issues can arise due to specific techniques, such as administration of large doses, vascular transmission, injection into superficial planes, or allergic reactions. A significant number of publications on hyaluronidase were observed in 2021 and 2022, with a decline in the subsequent years (2023 and 2024), while the volume of records on hyaluronic acid and aesthetic medicine has remained relatively constant (Fig. 2).

Hyaluronidase works by diffusing and degrading hyaluronic acid, increasing the permeability of connective tissue and reducing its regularity (Fig. 3) through the rupture of glycosidic bonds between the C1 and C4 regions of glucuronic acid [34]. The literature reveals the role of hyaluronidase in the depolymerization of hyaluronic acid. Dayan and colleagues reported a reduction of up to 66% in infections caused by hyaluronic acid fillers when treated with hyaluronidase [34]. Although hyaluronidase is widely used to degrade hyaluronic acid dermal fillers, its use is not yet prescribed in the FDA (Food and Drug Administration) label. Cavallini et al. and Almeida et al. highlighted that the response to manipulation of hyaluronic acid varies according to the degree of cross-linking of the injected gel, the incubation time, and the volume of the treated area. Therefore, further studies and tests are needed to evaluate the biodegradability of the gel in different concentrations and formulations, to better understand the dose-response profile of the enzyme in clinical scenarios.

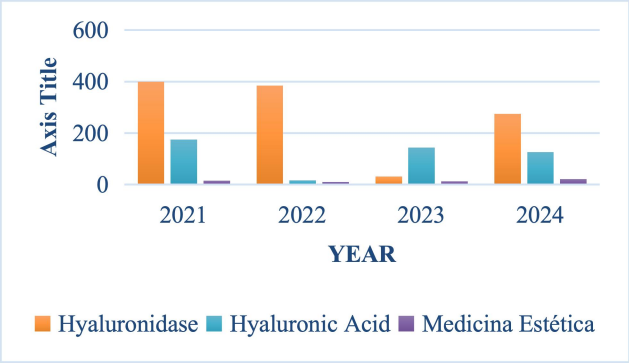

Figure 2: Graph showing search results using the keywords: hyaluronidase (green color); hyaluronic acid (purple color); aesthetic medicine (blue color). Source: PubMed.

V. CONCLUSION

The use of hyaluronidase in aesthetic and therapeutic medicine has proven to be effective and versatile, particularly in dissolving dermal fillers and treating complications. Its ability to break down hyaluronic acid and promote tissue absorption expands its applications beyond approved indications, showing potential in emergency scenarios and aesthetic procedures. Despite its overall safety, it is crucial to consider allergic risks, which, although rare, require attention and appropriate precautions. A thorough understanding of its functions and dosages remains essential to optimizing its clinical benefits.

CONFLICT OF INTEREST

The authors affirm that they have no conflicts of interest.

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