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Considerations for Proper Use of Hyaluronidase in the Management of Hyaluronic Acid Fillers

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Summary: Effective management of complications from hyaluronic acid (HA) fillers is crucial in aesthetic medicine. This article examined the role of hyaluronidase in addressing adverse effects associated with HA fillers, such as nodules, vascular occlusions, and excessive volume. It highlights the enzyme's ability to degrade HA, thereby resolving issues that may arise from filler treatments. The discussion includes practical aspects of using hyaluronidase, such as recommended dosing, injection techniques, and potential risks. The benefits of hyaluronidase, including its rapid action in dissolving problematic fillers and its role in improving patient outcomes, are explored. The article also addresses limitations and safety considerations to provide a comprehensive understanding of hyaluronidase in the context of filler complications. By offering insights into the application and effectiveness of hyaluronidase, this article aimed to enhance practitioners' ability to manage HA filler–related issues effectively and ensure optimal results in aesthetic procedures.
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INTRODUCTION

Hyaluronic acid (HA) fillers have become a cornerstone in aesthetic medicine due to their ability to provide volume and contour with minimal invasiveness.[1] These fillers are chemically cross-linked to enhance their stability and longevity within the body, significantly extending their duration compared with natural HA, which typically has a short half-life of 24–48 hours. The persistence of HA fillers varies according to their injection depth and the specific facial area.[2–5] The longevity of HA fillers is influenced by their injection depth and the local concentration of hyaluronidase. Although it is commonly believed that fillers last longer when injected into deeper layers, such as near the periosteum, where hyaluronidase levels are lower, this is not always the case. Fillers in areas with significant movement or pressure, such as the glabella region, may not benefit from extended duration due to the dynamic nature of these regions.[6] The impact of injection sites and depths on the longevity of HA fillers remains an area of ongoing research.

Hyaluronidase is a crucial enzyme involved in the degradation of HA, playing a significant role in the management of unwanted HA deposits. This enzyme is typically derived from recombinant human technologies or extracted from animal tissues.[6,7] Among the 6 identified isoforms of hyaluronidase, HYAL1 and HYAL2 are particularly relevant in human physiology, functioning sequentially to hydrolyze HA into smaller fragments that are subsequently cleared from the body. The degradation of cross-linked HA fillers can occur over several months, and current research is exploring potential associations between delayed immune responses and the persistence of residual filler fragments.[8,9] The pharmacokinetics of hyaluronidase, including its duration of action and its effects on HA fillers, are not yet fully understood. However, existing evidence suggests that the enzymatic activity of hyaluronidase can persist for several hours after injection. To use hyaluronidase effectively, it is essential to consider various factors, beginning with a comprehensive understanding of the enzyme's properties and its intended applications.

HYPERSENSITIVITY TO HYALURONIDASE

The administration of hyaluronidase can occasionally trigger hypersensitivity reactions, resulting in a range of allergy-related symptoms. Given this potential risk, it is critical to be prepared for such reactions when using hyaluronidase.[10,11] Although pretreatment skin testing

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is recommended to identify potential sensitivities, conducting these tests routinely in clinical settings is often impractical.

As a precautionary measure, it is advisable to have antihistamines and intramuscular hydrocortisone injections readily available to manage any hypersensitivity reactions that may arise during or after treatment.[12] For mild-to-moderate allergic reactions, a dose of 25–100 mg of hydrocortisone can be administered intramuscularly. In cases of more severe reactions, such as anaphylaxis or significant allergic responses, a higher dose of 100–250 mg may be warranted. For patients with a history of allergic reactions to hyaluronidase, the preventive use of antihistamines and corticosteroids during the injection is recommended to mitigate adverse effects.[10]

REQUIRED DOSE OF HYALURONIDASE

The pharmacokinetics of hyaluronidase are not fully established, and the precise mechanism by which it interacts with HA fillers remains under investigation. HA fillers are composed of cross-linked HA molecules that aggregate into a cohesive filler mass. The current understanding suggests that although penetration of hyaluronidase into the filler might be beneficial, the dissolution process may primarily occur via a surface reaction rather than deep penetration. This implies that hyaluronidase acts on the surface of the filler particles, gradually dissolving them over time.[11]

The degree of cross-linking in HA fillers influences their dissolution rate. Highly cross-linked fillers, which have denser particle spacing due to strong hydrogen bonding, typically require higher doses of hyaluronidase for effective dissolution. However, given the challenges associated with these dense structures, using multiple doses of hyaluronidase over a short period may be more effective than administering a single large dose. This approach ensures a more consistent interaction between the enzyme and the filler material.[7,13]

For dissolution purposes, especially when dealing with highly cross-linked monophasic HA fillers, a dose of 600–750 units of hyaluronidase per milliliter of filler is generally recommended. This dosage is based on clinical experience and practical application, as specific evidence for this exact range is limited. The aim is to maximize the enzyme's interaction with the filler, promoting efficient breakdown and facilitating complete dissolution.

In cases of suspected vascular obstruction, a high-dose pulsed protocol should be adopted. A total dose of 450–1500 units should be infiltrated over the affected area, including the vessel course.[11,14–16] This approach allows perivascular hyaluronidase to penetrate vascular walls. To enhance diffusion and mechanical breakdown, the area should be massaged. Importantly, if vascular compromise persists after the initial treatment, administering lower doses of hyaluronidase more frequently—approximately every 30–60 minutes—is recommended, rather than relying on a single high dose.[16,17] This strategy may reduce the risk of adverse effects while ensuring adequate enzymatic action.

Takeaways

Question: What factors ensure the effective use of hyaluronidase in managing complications from hyaluronic acid dermal fillers?

Findings: Effective management of hyaluronic acid fillers, particularly highly cross-linked ones, depends on precise hyaluronidase dosing, timing, and techniques. Higher doses and methods such as massage may be required for dense fillers. Hypersensitivity risks also need careful handling, especially for hard nodules or granulomas.

Meaning: Customizing hyaluronidase use based on filler type and patient specifics optimizes outcomes, enabling safe complication resolution and reducing the risks of incomplete filler breakdown and adverse effects.

In cases of intravascular injections with potential or actual tissue necrosis, the use of anticoagulants may be beneficial. Patients should be observed for adverse reactions, and appropriate aftercare advice should be provided. In emergencies such as blindness due to periocular embolism, immediate transfer to a hospital eye department is critical. In these situations, a retrobulbar injection of 150–200 units in 2–4 mL of diluent may be considered for practitioners with appropriate experience while awaiting emergency services.[16,18–20]

REACTION TIME OF HA FILLERS TO HYALURONIDASE

The results of the hyaluronidase dissolution experiments conducted on HA fillers demonstrate distinct reactions between biphasic and monophasic fillers to diluted hyaluronidase. Biphasic HA fillers, which have looser spaces between particles, allow the diluted hyaluronidase solution to integrate uniformly with the filler almost immediately, often within approximately 5 minutes. This rapid hydration of the filler facilitates the exposure of HA molecules within the particles to the enzyme. Moreover, the smaller number of chemically cross-linked HA units in biphasic fillers permits the HA molecule structures to break down quickly after injection, resulting in the filler mass dissolving almost completely within 1–2 hours.

Conversely, monophasic HA fillers, which feature extensive cross-linking, present tighter particle spaces that delay the infiltration of the hyaluronidase solution. It typically takes approximately an hour after injection for the solution to begin permeating the spaces between the particles. The breakdown of HA molecules is further prolonged due to the higher number of cross-linked units, and the dissolution process can extend up to 24 hours, depending on the specific type of filler used. Under normal circumstances, rapid dissolution of the filler mass may not be critical. However, in emergencies related to vascular complications, it is imperative to dissolve the filler particles as quickly as possible.[12,20–23] Therefore, for highly cross-linked monophasic HA fillers, injecting a larger quantity of hyaluronidase at once is recommended to reduce the dissolution time compared with when

Table 1. HA Filler Brands, Manufacturers, Cross-linking Technologies, and Classification as Monophasic or Biphasic[13,24–26]

Type	Brand of HA Filler	Company	Cross-linking Technology
Monophasic	Restylane Vital, Vital Light, Restylane, Restylane Lyft	Galderma	Nonanimal stabilized HA technology
Monophasic	Restylane Fynesse, Refyne, Kysse, Volyme, Defyne	Galderma	Optimal balance technology
Monophasic	Belotero Soft, Balance, Intense, Volume, Lips-Shape, Lips-Contour	Merz	Cohesive polydensified matrix
Monophasic	Teosyal RHA 1, 2, 3, 4, Kiss	Teoxane	Resilient hyaluronic acid
Biphasic	Juvederm Ultra 2,3,4	Allergan	Hylacross technology
Biphasic	Juvederm Volux, Voluma, Volift, Volbella, Volite	Allergan	Vycross technology

dissolving for aesthetic corrections. For an overview of commonly utilized clinical products in either monophasic or biphasic HA formulations, refer to Table 1.

CONSIDERING THE ACTIVE DURATION OF HYALURONIDASE FOR INJECTION INTERVALS

When hyaluronidase is used to dissolve HA fillers, a single injection may sometimes be insufficient to achieve the desired results. In these scenarios, multiple injections may be necessary, typically administered at intervals of 30–60 minutes, particularly in severe cases such as intravascular filler injections. The frequency of these injections is crucial to ensure effective dissolution and management of the filler. Observing the patient for signs of vascular compromise and reassessing the treatment response after each injection is essential to determine the need for additional doses. This strategy helps to maximize the enzymatic action of hyaluronidase and mitigate potential complications associated with HA fillers.[17,27]

USING SUFFICIENT AMOUNTS OF NORMAL SALINE FOR DILUTION AND MASSAGE

Hyaluronidase consists of 4 units, each with approximately 14,000 subunits, resulting in a total molecular weight of approximately 55,000–61,000 Da. Due to its large molecular size, hyaluronidase cannot immediately penetrate the HA molecules that make up HA filler particles. Initially, it diffuses into the areas where it contacts the filler particles. Therefore, maximizing the contact area between the surface of the filler particles and hyaluronidase is essential for effective enzymatic degradation.

In the case of biphasic fillers, the hyaluronidase solution penetrates the spaces between the filler particles effectively, allowing for homogeneous mixing with the filler mass. Conversely, with monophasic fillers, the hyaluronidase solution initially remains separate from the filler. As it begins to dissolve and interact with the filler, the contact area gradually increases, leading to improved mixing. Thus, increasing the contact area through techniques such as massaging the injection site is beneficial for achieving efficient enzymatic degradation. Particularly when dissolving tightly bound monophasic HA fillers, expanding the contact area by massaging the injection site immediately after injection is advisable to enhance the dissolution process.

The use of normal saline in combination with hyaluronidase has been observed to enhance the effectiveness of the dissolution process. Saline facilitates the even distribution of hyaluronidase throughout the filler and may contribute to improved resorption by creating a more fluid environment. Although scientific evidence on saline's specific role in resorption is limited, clinical experience suggests that saline, along with immediate postinjection massage, helps optimize the breakdown of tightly bound monophasic HA fillers. This approach leverages practical insights to support more effective filler dissolution.

INJECTION OF HYALURONIDASE FOR HARD HA FILLER NODULES

Fillers can occasionally induce abnormal immune reactions, leading to the formation of thick fibrous capsules around the filler material.[28–32] If these lumps or nodules are not excessively hard, they can often be relatively easily removed using hyaluronidase. The fibrous capsule is not typically very thick, so injecting a sufficient amount of diluted hyaluronidase solution around the mass, combined with active massaging, can help dissolve the hard mass.[33,34] However, if calcification progresses and the capsule thickens, simply injecting and massaging around the mass may not completely resolve the hardened material.[35,36] Generally, only the HA fillers in the surrounding connective tissue dissolve, leaving the hard lumps or nodules intact (Fig. 1). Figure 1 illustrates a biofilm, a microbial community encapsulated in an extracellular matrix. Although hyaluronidase can weaken biofilms by degrading the HA component, it may not completely eliminate the biofilm due to the presence of other substances, such as proteins and polysaccharides.[37,38] To effectively address biofilm-related complications, additional methods are often needed. These may include antibiotic therapy to target microbial elements, mechanical disruption through needle aspiration or surgical removal, topical treatments to enhance antimicrobial agent penetration, and heat or laser therapy to further disrupt the biofilm matrix.[39,40] Combining hyaluronidase with these complementary approaches can provide a more comprehensive strategy for managing biofilm-associated issues.

In particular, if recurring inflammation surrounds a lump or nodule with a biofilm, leading to the formation of a biofilm and progression to infection, the filler mass can become a very hard granuloma.[41–43] At this stage, thick and tough fibrosis forms around the capsule, necessitating direct injection of hyaluronidase into the center of the granuloma for effective treatment (Fig. 2). Diluting a sufficient amount of hyaluronidase in saline

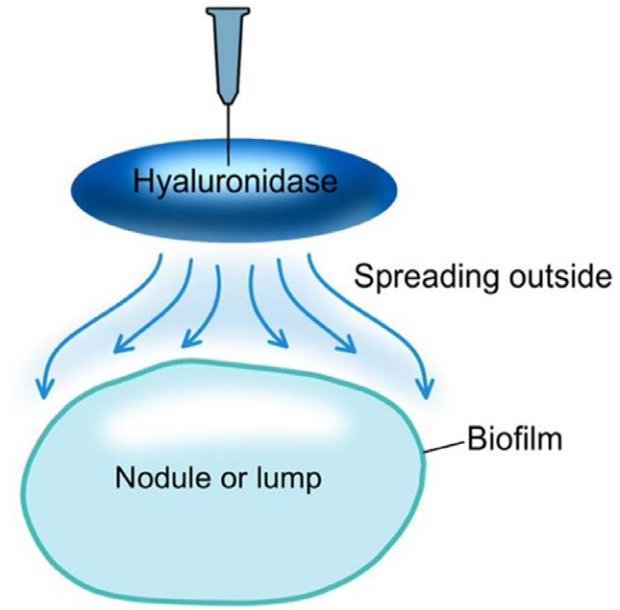

Fig. 1. An illustration of the expected spreading of hyaluronidase solution along the biofilm surrounding the nodule.

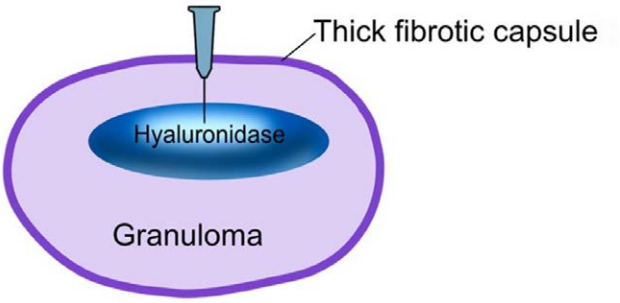

Fig. 2. An illustration of an injection of hyaluronidase solution at the center of a granuloma. Note the needle must penetrate the thick fibrotic capsule to reach the filler mass for dissolution.

and injecting it precisely into the lesion, followed by vigorous pressing and massaging of the injected area, can help break down the nodule into smaller pieces. These smaller pieces can then be further degraded by the hyaluronidase. In cases where the capsule is particularly thick and the nodule is too firm to dissolve with hyaluronidase alone, combining the enzyme with a small amount of intralesional corticosteroid, specifically, triamcinolone, can enhance the degradation of the mass. A typical dose of 10–40 mg of triamcinolone may be injected alongside the hyaluronidase. This combination, followed by vigorous massage, can improve the treatment outcome.[44,45]

Ensuring accurate injection of hyaluronidase into the center of the nodule is crucial to prevent incomplete dissolution and avoid unwanted side effects. Key indicators of correct injection include feeling increased resistance during injection if the needle tip is in the center of the nodule and observing the nodule swelling if the solution is injected correctly. If the injection is effective and the nodule is massaged vigorously, the mass should break down and decrease in size, provided the capsule is not excessively tough.[34,46]

DISCUSSION

The effective use of hyaluronidase in managing HA filler complications demands a comprehensive understanding of both the chemical properties of HA fillers and the biological activity of hyaluronidase (Table 2).[7] One significant challenge is the variability in degradation rates depending on the type and cross-linking density of HA fillers. Monophasic fillers, characterized by their high cross-linking and dense molecular structure, often require higher doses of hyaluronidase and more intensive techniques, such as massage, to ensure effective breakdown. This is detailed in Table 3, which outlines the specific dose and frequency of hyaluronidase needed to address naturally dispersed HA fillers and HA granulomas, as well as adjustments required in cases of severe complications such as impending tissue necrosis or vision compromise.

In emergency situations involving vascular complications—whether due to direct intravascular injections, compression of the vasculature by the injected material, or swelling from allergic reactions or bleeding—rapid dissolution of the filler is essential to prevent tissue damage and effectively address the underlying vascular issue. The variability in response necessitates a tailored approach, as outlined in Table 3, where the dosage and frequency of hyaluronidase are adjusted based on the severity of the complication and the type of HA filler involved. This approach ensures that the treatment is both effective and safe, addressing the diverse challenges presented by different filler types and clinical scenarios.

The interaction between hyaluronidase's enzymatic activity and the filler's molecular structure is complex, necessitating careful consideration of injection techniques, dilution, and the timing of repeated injections. For instance, the activity of hyaluronidase diminishes over time, making timely postinjection massages crucial to maximize contact between the enzyme and the filler, thereby enhancing enzymatic degradation.

In challenging cases, such as hardened nodules or granulomas, precise injection of hyaluronidase is vital. Ultrasound guidance can be beneficial in these scenarios to ensure accurate injection into the fibrous capsule surrounding the filler. In the absence of ultrasound, practitioners must rely on palpation to locate and confirm the presence of the mass, necessitating a precise injection technique to ensure effective dissolution.

Often, a combination of hyaluronidase and intralesional corticosteroids, such as triamcinolone, is used to facilitate the breakdown of the granuloma. For intralesional administration, a low-to-moderate dose of triamcinolone, typically ranging from 10 to 40 mg, is recommended. This approach aims to achieve an effective balance between therapeutic efficacy and the minimization of potential side effects.

Table 2. The Key Considerations for the Proper Use of Hyaluronidase in Dermal Filler Management

Consideration	Key Points
Hypersensitivity to hyaluronidase	Hyaluronidase can cause hypersensitivity reactions; skin testing is recommended but not always practical. Antihistamines and steroids should be available
Required dose of hyaluronidase	Higher doses of hyaluronidase are required for more cross-linked monophasic HA fillers due to difficulty in penetration
Reaction time of HA fillers to hyaluronidase	Biphasic fillers react quickly to hyaluronidase, whereas monophasic fillers take longer and may require more aggressive treatment
Active duration of hyaluronidase for injection intervals	Multiple injections (2–3) may be necessary, particularly in severe cases such as intravascular filler injections, with intervals of 1–2 wk
Sufficient amounts of normal saline for dilution and massage	Dilution (5–10 mL) and massage increase the contact area (defined as 2–3 cm^2), enhancing enzymatic degradation of the filler
Injection of hyaluronidase for hard HA filler nodules	For hard nodules or granulomas, hyaluronidase may need to be injected directly into the lesion center, sometimes with steroids, with 1–2 injections at 1–2-wk intervals

Table 3. Properties of Fillers and Hyaluronidase Treatment Guidelines

Scenario	Properties/Considerations	Dose and Frequency of Hyaluronidase	Treatment Considerations
Monophasic fillers	High cross-linking, dense molecular structure	General dissolution: 100–300 units per area, may need repeated doses based on response Granulomas: higher doses may be required, often with massage	• Requires more intensive treatment due to high cross-linking • Often needs repeated applications and manual massage for effective dissolution
Biphasic fillers	Less cross-linking, often with larger gel particles	General dissolution: 100–200 units per area, typically fewer repeated doses Granulomas: moderate doses, combined with massage	• Dissolves more readily compared with monophasic fillers • Typically requires fewer doses and less intensive massage
Impending tissue necrosis or vision compromise	—	Immediate action: higher doses (up to 100–200 units), often administered rapidly Frequency: may require multiple doses in quick succession	• Immediate and aggressive treatment required • May need additional emergency interventions, including surgical options
Naturally dispersed filler	—	Standard dissolution: 100–200 units per area, adjusted based on dispersion Granulomas: adjust doses based on nodule size and location	• Standard treatment usually effective • Regular monitoring to ensure complete dissolution without overuse

Local complications from hyaluronidase, such as transient erythema, swelling, or discomfort, are relatively common but generally resolve within a few days. These effects are typically related to the injection process rather than the enzyme itself. However, in some instances, patients may experience more prolonged or severe reactions. Such reactions can include significant and persistent swelling, prolonged erythema, severe pain or discomfort, or, very rarely, tissue necrosis and severe allergic reactions. Such complications require close monitoring and appropriate management to address underlying issues effectively.[6,16]

Regarding the overinjection of hyaluronidase, careful dosing is crucial. Excessive application can lead to overdissolution of the filler and potential complications. Reinjection, if needed, should be based on the clinical response and extent of dissolution required. It is generally advisable to wait at least a few days to a week before considering additional administration to allow for evaluation of the initial treatment and to minimize the risk of adverse reactions. Each case should be assessed individually to determine the appropriate timing and dosage for reinjection.

In the context of facelift surgery, careful planning for the dissolution of HA fillers is critical. The timing of hyaluronidase administration should allow for a complete breakdown of the filler well before the surgical procedure. It is generally advisable to dissolve the filler at least 2–4 weeks before surgery to ensure that the filler is fully cleared from the treatment area, thereby reducing the risk of interference with the surgical technique and optimizing the accuracy of the facelift. The dosage and frequency of hyaluronidase administration should be tailored to the specific type and volume of HA filler used, as well as to the patient's individual characteristics. For instance, monophasic fillers with high cross-linking may require higher doses and more frequent administrations compared with biphasic fillers, which tend to dissolve more readily. This personalized approach ensures effective filler dissolution and minimizes potential complications, contributing to better outcomes for both filler management and subsequent surgical interventions.

In summary, the management of HA filler complications and presurgical dissolution involves a nuanced understanding of filler properties, careful application of hyaluronidase, and individualized treatment strategies. These considerations are essential for optimizing patient outcomes and minimizing risks associated with dermal fillers and surgical procedures.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

DECLARATION OF HELSINKI

This study was conducted in compliance with the principles set forth in the Declaration of Helsinki.

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