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Hyaluronidase: Understanding Its Properties and Clinical Application for Cosmetic Injection Adverse Events

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The recent global consensus on the management of cosmetic aesthetic injectable complications from hyaluronic acid (HA) has increased the focus on the use of hyaluronidase more than ever before (M. Signorini et al., 2016). A comprehensive knowledge of facial anatomy, including structural positioning of facial arteries and veins, and an extensive knowledge of HA products available for injection procedures, combined with best practice protocols, will assist to prevent adverse events. Despite the growing number of patients using cosmetic fillers for facial restoration, the incidents incidence of adverse events remains low. Indeed, the avoidance of complications through safe and effective injection practice remains the key to preventing the need to use hyaluronidase.

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To understand why hyaluronidase is the recommended treatment for HA complications, it is important to understand the nature of this compound and the potential access limitations, its effect on various HAs, and the anticipated physiologic outcomes for the patient.

BACKGROUND

Hyaluronidase is found in human and multiple sources of animals including various venoms, ovine or bovine testes, as well as human serum (Ranzy, Becker-Wegerich, Bachmann, Erdmann, & Wollina, 2009).

The substance has been widely utilized throughout medicine because of its ability to increase the degradation extracellular matrix of HA and increase permeability of tissue (Burhren et al., 2016). Interestingly, the physiologic theory is also seen in some gram-positive bacteria, whereby the bacteria possess HA lyases, which they use to assist in their penetration into the tissues (Makris, Wright, Ingham, & Holland, 2004).

PREPARATION AND DISTRIBUTION

The most common source of hyaluronidase remains to be ovine and bovine, and it is produced by a recombinant DNA methodology (Ranzy et al., 2009). The recombinant DNA is purified glycoproteins formed by using amino acids that are then placed in a sterile, nonpreserved, solution. As with any industry, variances are common in the production of compounded hyaluronidase. It may be processed differently on the basis of its various indications, such as cosmetic, nutraceutical, pharmaceutical, or injectable grade hyaluronidase. The process may also differ on the basis of the required testing process for impurities. The lower the molecular weight

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of the hyaluronidase, the more significant the penetration and diffusion in the tissues.

The recommended compound hyaluronidase salt 150 U/ml is the standard prescription in Canada for the indication of HA filler adverse events. The average current cost is $150.00 for a 10-ml vial (Smith's Pharmacy Toronto, 2017). The product is to be used within 30 days and should be kept refrigerated (Hylenex Drug Monograph, 2006).

Hyaluronidase preparations are generally made available in the commercial market; however, in some countries, health regulations prevent the commercial distribution and, thus, clinicians in Canada must utilize compounding pharmacy preparations. Unfortunately, when the product is a compounded substance, it will not be accompanied by a drug monograph to provide the clinician with a full drug review and specific direction for use. It is essential that the practitioner choose the compounding pharmacy with experience in compounding hyaluronidase for the use in HA adverse events to ensure the appropriate preparation is created.

MECHANISM OF ACTION

Hyaluronic acid responds to hyaluronidase through a mechanism of breaking the glucosaminidic bond of the HA product and stimulating tissue absorption in the area. The destruction of this bond changes the molecular structure, or the moiety, of the product's cohesiveness and thus allows the product to be infiltrated by the body's own process for absorption of the residual by-products as a result of the dispersion (Kassir, Kolluru, & Kassir, 2011). The amount of product hydrolysis is directly related to the quantity of hyaluronidase that is injected, and the full resolution of the impact of hyaluronidase occurs relatively quickly and should be fully resolved by 48 hours posttreatment. It is possible that, with repeated exposure, individuals could develop a resistance (antibodies) to hyaluronidase because it is a recombinant DNA source (Hylenex Drug Monograph, 2006).

CONTRAINDICATIONS

The only true contraindication for use of hyaluronidase is in patients with known sensitivity to the medication, or any of its stabilizing components, which may be present as a result of the compounding of the product. An allergic reaction to hyaluronidase is uncommon and, currently, prior skin testing is considered unnecessary because of the low incidence rate of adverse reactions (0.1% urticarial or angioedema) (Lee, Grummer, Kriegel, & Marmur, 2010). However, if the recipient has a history of significant allergies, it may be warranted to perform a skin test, given the severity of potential HA adverse events. The skin test would involve placing a small skin bleb injection of 0.02 ml (three units of 150 unit/ml) under the skin surface, which would be monitored. It would be considered positive, should a reactive wheal form after 5 minutes of observation and the wheal could last to a maximum of 30 minutes. Occasionally, this would have associated pruritus (Hylenex Drug Monograph, 2006).

PRACTICE IMPLICATIONS

It is essential for clinicians to be aware that when using hyaluronidase in the clinical setting there is potential for varying responses, which may occur on the basis of the type of HA filler being targeted with the treatment. The clinician should provide a full assessment and collect all relevant patient health data as well as their HA injection health history. This would also include the types of HA injectable they have received and any history of reactions or responses. The practitioner should attempt to acquire the exact HA type, which will be treated with the hyaluronidase, and thoroughly document all information in the patient chart. Results are somewhat dependent upon the viscosity and cross-linking preparation of the HA product. In a recent study by Alam et al. (2015), an analysis of dose response and interval testing showed that the 24-mg/ml HA filler exhibited more resistance to enzymatic impact than the 20- and 5.5-mg/ml HA products. It was concluded the increased HA content and cross-linking impacted the ability for the hyaluronidase to degrade the product.

A full review of the risks associated with the use of hyaluronidase and the potential for variable results should occur with the patient prior to the initiation of the treatment to ensure the patient has realistic understanding and expectation of the treatment process.

An evidence-based clinical treatment protocol should be developed and readily available in all clinics. The protocol should be followed by each injector in the clinic to ensure consistency in practice. This protocol should include not only the practical use of hyaluronidase but also the recommended follow-up appointments, as appropriate.

Hyaluronidase is the substance recommended for the treatment of adverse events with HA fillers. Understanding the mechanisms of action assists the clinician in the comprehension of treatment delivery. From the compounding of the product, to the biophysical results, the integration of knowledge improves the clinician's skill and judgment, which thus will improve the outcome results of this treatment in patients.

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