



Five Factors to Consider before Treatment of a Hyaluronic Acid Filler-Induced Vascular Complications

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Soft tissue fillers are common aesthetic procedures for facial rejuvenation.¹ Among the fillers in the market, hyaluronic acid filler has been the most popular because it is degraded by hyaluronidase. The most serious complications of filler injections are vascular complications, such as skin necrosis and ocular sequelae. Various treatment modalities, including hyaluronidase injection, have been proposed. Hyaluronidase, which normally exists in human tissues, dissolves hyaluronic acid. It degrades the β 1,4 chain of the disaccharide hyaluronic acid. The hyaluronic acid filler can be degraded by hyaluronidase when vascular complications develop. However, multiple factors must be considered before injecting hyaluronidase. This report proposed five important considerations for hyaluronidase injection.

Modification Degree of Injected Filler

Hyaluronic acid filler is composed of hyaluronic acid and a crosslinker, such as 1, 4 Butanediol diglycidyl ether. Hyaluronic acid exhibits various degrees of modification (MOD) depending on the manufacturing process. This indicates how the filler was modified by a crosslinker and its susceptibility to degradation by hyaluronidase. Typically, the MOD is estimated by using rheological results (**►Table 1**). However, nuclear magnetic resonance accurately determines the MOD. In addition, a degradation test can be performed to estimate the response of the filler to hyaluronidase (**►Fig. 1**).

There are numerous hyaluronic acid fillers available in the market. The manufacturing process is different, so their MOD

varies. Therefore, the rate of filler degradation by hyaluronidase also differs.

Dose and Efficiency of Different Hyaluronidase

There are various types of hyaluronidase in the market (**►Fig. 2**).

It can be made from ovine and bovine testicular, or human recombinant products. Each product possesses a different potency. In addition, each product has different units. Hylenex is 150 USP, while Vitrase is 200 USP. Hyalose is 1,500 IU. A previous study suggested the application of hyaluronidase in the treatment of skin necrosis.² However, the potency and dosage of hyaluronidase should be considered. Five bottles of Vitrase (200 USP) were administered at a lesser dosage than one bottle of Hyalose (1,500 IU).

Affected Vessels

Knowledge of vascular anatomy is essential to prevent vascular complications. The affected vessel should be identified and verified before subcutaneously injecting hyaluronidase. Facial arteries are connected with each other, and the filler can compromise adjacent territories. For example, after filler injection at the nasolabial fold area, skin necrosis can develop in the nasolabial fold and forehead areas because the facial artery is connected to the angular artery, dorsal nasal artery, and supratrochlear artery. Therefore, hyaluronidase should be injected into the nasolabial fold, lateral nasal, and

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Table 1 Various hyaluronic acid fillers tested by the author ([frequency 0.02 Hz] MCR 301 rheometer [Anton Paar Co. Austria]) G': elastic modulus, measure of the capacity of a gel to resist an applied stress, G'': loss modulus, high G' filler needs relatively high amount of hyaluronidase to be degraded

Product	G' (Pa)	G'' (Pa)	Complex viscosity (μ)	Tan delta	Cohesiveness (N)
Restylane	349	145	3,011,188	0.42	0.3509
Perlane	411	199	3,637,022	0.49	0.2869
Juvederm Voluma	284	58	2,309,805	0.21	0.4043
Lorient No. 2	203	41	1,673,007	0.20	0.4401
Lorient No. 4	338	95	2,795,776	0.28	0.4237
Lorient No. 6	413	121	3,423,232	0.29	0.4454

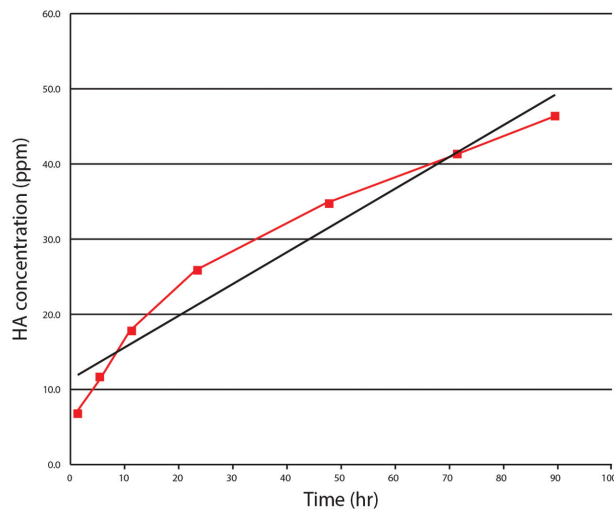


Fig. 1 Degradation test (Lorient). Trend line ($y = 0.8546x + 21.81$, black line), degradation result line (red line), hyaluronic acid concentration means free HA concentration after degraded by hyaluronidase (red dot).

forehead areas. Thus, understanding arterial anatomy is important for treatment and prevention.

Subcutaneous Hyaluronidase Injection

The half-life of hyaluronidase was reportedly 30 minutes in subcutaneous tissue and 2 to 3 minutes in blood vessels.

Table 2 Five consideration factors for hyaluronidase injection

Injected filler degrees of modification	Hyaluronic acid fillers have different degradation times due to various degrees of modification. Both 1,4-butanediol diglycidyl ether and butanediol di-(propan-2,3-dioly) ether should be considered
The efficiency of the different hyaluronidase doses	Various brands of hyaluronidase have different potencies Both 150 and 200 USP are used in the United States, while 1500 IU is often used in Korea
Affected vessels	It is essential to determine which vessels are involved. Hyaluronidase should be subcutaneously injected to the involved vessels, as near as possible
Degradation time	Subcutaneously injected hyaluronidase cannot immediately dissolve the hyaluronic acid filler
Repetitive injection	Subcutaneously injected hyaluronidase disappears after its half-life. Repetitive injection is necessary

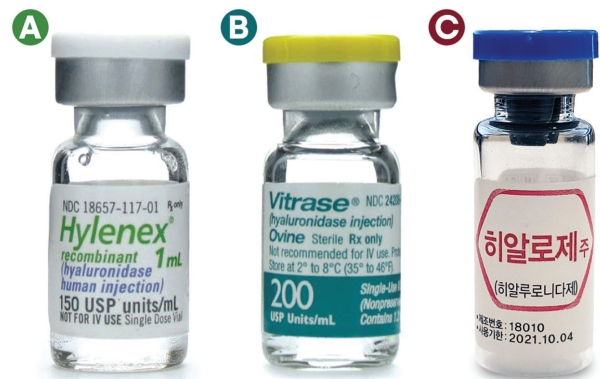


Fig. 2 Various hyaluronidase brands. (A) Hylenex 150 USP, (B) Vitrase 200 USP, and (C) Hyalose 1,500 IU. Each products have different potencies so they should be considered before treatment of filler induced vascular complications.

There have been multiple theories on the immediate deactivation of hyaluronidase upon its injection into a vessel. These reportedly involved antibody formation³ and the anti-HYAL enzyme.² Based on these theories, a subcutaneous hyaluronidase injection is warranted.

Repeated Hyaluronidase Injection

As shown in ►Fig. 1, the hyaluronic acid filler did not degrade immediately after hyaluronidase injection. Therefore, repeated injections every 30 minutes or 1 hour are necessary.

According to the previous study, repeated injections containing the same dosage were more effective.⁴ Hyaluronidase should be injected repetitively subcutaneously near the affected vessels because hyaluronic acid filler does not degrade immediately to hyaluronidase.

Conclusion

Vascular complications are serious sequelae of hyaluronic acid filler injections. Hyaluronidase should be administered immediately. In addition, the degree of filler modification, hyaluronidase potency, and the affected vessel should be determined. Repeated subcutaneous injections were the most effective treatment strategy (► **Table 2**).

Conflict of Interest

W.L. has been an investigator, speaker, and consultant for Joonghun Pharmaceutical, Seoul, South Korea.

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