Vascular complications of hyaluronic acid fillers and the role of hyaluronidase in management

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Summary Skin necrosis following the inadvertent arterial injection of hyaluronic acid (HA) is a serious complication. It is not clear whether or not subcutaneous injections of hyaluronidase decrease skin necrosis in HA-induced vascular complications. We had four cases of HA-induced vascular complications, two of which were treated with hyaluronidase the next day. All of the patients had skin necrosis and scarring. We performed an animal study with rabbit ears in which HA filler was injected into the auricular arteries of both ears. Five rabbits each received a subcutaneous injection of 750 IU of hyaluronidase 4 and 24 h after the filler injection. The hyaluronidase-treated ears in the 4-h intervention group had significantly smaller necrotic areas (p < 0.05), while the 24-h intervention group had no differences in the area of necrosis. Hyaluronidase reduced the vascular complications of HA fillers when used early, but there was no benefit to hyaluronidase injection after 24 h.

Soft-tissue augmentations with injectable fillers are popular aesthetic procedures for patients who desire noninvasive rejuvenation. Among the numerous injectable fillers, hyaluronic acid (HA) fillers have several merits. HA is biocompatible, easy to use and reversible. HA fillers are considered to be safe, although some trivial-to-severe complications can occur.1 Many of the HA filler complications are correctable and technique-related, such as undercorrection, overcorrection and asymmetry. Other serious complications of HA fillers include allergic reactions, infections and skin necrosis.2

Skin necrosis is one of the most serious complications of HA fillers and can result in unaesthetic scar changes. The mechanism leading to tissue necrosis after HA filler injection is not fully understood. There must be extra- and intravascular factors. External vascular compression caused by an excessive amount of viscous fillers can reduce skin perfusion.3 Oedema and inflammation caused by tissue reaction of HA filler ingredients may be attributable to skin necrosis. A small amount of foreign protein in HA filler is known to cause...
an allergic reaction and inflammation. Intravascular factors include direct obstruction of arteries by large-molecular-weight HA fillers and chemical damage of the endothelial lining by HA or impurities in the fillers. Among the above-suggested factors, intra-arterial obstruction is supported by many authors. The glabella is the most common site of necrosis reported after filler injection. Many small arteries arising from supratrochlear arteries provide the blood supply to the glabellar region. The typical patterns of skin necrosis in the glabellar region have a vertical dimension arising from the medial brow, which corresponded to the course of the supratrochlear arteries. The vascular anatomy predisposes the glabella to inadvertent arterial injection of HA filler. The nasal ala is another reported site of necrosis following filler injection. The nasal ala is supplied by the alar branch of angular arteries. Inadvertent injection of HA fillers into the angular arteries in the nasolabial fold area can cause necrosis of the nasal ala, which has a limited collateral circulation.

There is no standard treatment for HA vascular complications; several treatments which have been suggested include massage to disrupt the filler embolus, warm compression, nitroglycerin paste, prostaglandin E1 and injection of hyaluronidase into the area. Hyaluronidase can reduce the effects of unwanted HA filler misplacement. Injection of hyaluronidase in the area of excessively injected HA fillers may correct the unfavourable result within 24 h; however, it is not clear whether or not hyaluronidase decreases skin necrosis in vascular complications associated with HA fillers.

We had four clinical cases of HA-induced vascular complications, some of which were treated with hyaluronidase; however, the efficacy of treatment was not determined. We thus performed an animal study to demonstrate the efficacy of hyaluronidase on HA filler-induced vascular complications.

Materials and methods

Clinical study

Between 2009 and 2011, four patients with vascular complications of HA fillers were retrospectively reviewed. All the patients received HA fillers at private clinics and were transferred to our department for the management of complications. The patients were 26–39-year-old women and received HA filler injections for nasal augmentation.

Animal study

Ten rabbits weighing 3–4 kg were used for the study. The study was approved by the Institutional Review Board of Korea University and performed under guidelines of the Institutional Animal Care and Use Committee. The rabbits were anaesthetised with an intramuscular injection of ketamine (50 mg kg⁻¹, Huons, Seoul, Korea) and xylazine (10 mg kg⁻¹, Bayer Korea, Seoul, Korea). The hair on the ears was shaved. The posterior branch of the posterior auricular vessels was coagulated with electrocautery. The skin on the proximal part of the ear was infiltrated with 1% lidocaine, and a skin incision was made to expose the anterior branch of the posterior auricular artery. The artery was punctured with a 30-gauge needle under a surgical microscope, and 0.25 ml of HA filler (Restylane; Q-Med, Uppsala, Sweden) was injected (Figure 1). The initial small amount of intra-arterially injected HA filler distended the arterial lumen and facilitated intra-arterial positioning of the needle. The HA filler was injected in both ears, and one of the ears was injected subcutaneously with 750 IU of hyaluronidase (Hyluniladase; BMIkorea, Jeju, Korea). The hyaluronidase was injected 4 h after the HA injection in five rabbits (4-h intervention group) and after 24 h in five rabbits (24-h intervention group). The progression of skin changes was photographed, and the final necrotic area was measured. The necrotic areas between the hyaluronidase-injected and control ears were compared statistically using the Wilcoxon signed rank test. A p value < 0.05 was considered statistically significant. Statistical Package for Social Sciences (SPSS) software was used for the statistical analysis.
Results

Clinical study

All four patients had received HA filler injections for nasal augmentation and had skin discolouration within a few hours. Two patients had striking radiating pain along the vascular course during the filler injections, and two patients reported moderate pain after a few hours of the injections. Three patients had skin lesions with either vascular or satellite patterns that were not continuous with the injection site. However, the last patient had a localised skin lesion on the nasal tip, which was the injection site. Two patients received subcutaneous injections of hyaluronidase the day following the procedure; however, the hyaluronidase injections 1 day following HA filler injections were shown not to be effective in the prevention of skin loss. All four patients had some skin necrosis with scar changes (Figure 2).

Animal study

As soon as the HA filler was injected intra-arterially, the ears appeared pale along the arterial course. However, the ears gradually turned dark blue and were clearly darker in colour than normal after 2–3 h.

In the 4-h intervention group, the treated ears and the vessels became pink, but the untreated ears and vessels remained blue–black on day 7 (Figure 3). Ear skin necrosis was evident 2–3 weeks post-procedure. The treated ears had no skin necrosis in three rabbits. Small areas of skin necrosis (<0.2 cm²) were noted in two rabbits; the mean necrotic area was 0.04 ± 0.06 cm² (Figure 4). The five untreated ears had large areas of skin necrosis; the mean necrotic area was 10.1 ± 7.3 cm². The difference between the treated and untreated ears in the 4-h intervention group was statistically significant (p < 0.05; Figure 5).

In the 24-h intervention group, all the ears had large areas of skin necrosis, regardless of the treatment. The treated ears had mean necrotic areas of 11.3 ± 4.1 cm²,

Figure 2  (A) A 39-year-old female with an HA filler injection on her nose developed pain and a blue skin discolouration. The skin lesion developed along the vascular course (3-day post-injection view). (B) A 30-year-old female with HA filler injection on her nose developed skin necrosis on the radix, nasal tip, and left lower eyelid (17-day post-injection view). (C) A 29-year-old female with a HA filler injection on her nose developed pain and skin discolouration, and received a hyaluronidase subcutaneous injection the next day. Skin necrosis developed on the glabella, nasal dorsum, and ala along the vascular course (7-day post-injection view). (D) A 26-year-old female with HA filler injection on her nasal tip developed pain and skin discolouration, and received a hyaluronidase subcutaneous injection the next day. The nasal tip skin was crusted, and a split thickness skin necrosis was developed (6-day post-injection view).
and the untreated ears had mean necrotic areas of $10.1 \pm 2.4 \text{ cm}^2$. The difference between the treated and untreated ears in the 24-h intervention group was not statistically significant ($p > 0.05$; Figure 5).

**Discussion**

In the clinical cases, all the patients received HA fillers at private clinics and were transferred to our department for the management of complications. The patients were aware that they had received HA filler injections. Many commercial HA fillers are available and each product has varying molecular weight, cross-linking properties and trace protein. It is important to describe these properties in these cases. However, the product name was not known to us, which was a limitation of our clinical studies. In Korea, more than 13 brands of HA fillers are approved by the Korean Food and Drug Administration; Restylane and Juvederm (Allergan, Irvine, CA, USA) are among the most popular fillers. However, some unapproved fillers, probably imported illegally, may be used by some clinicians at a low price.

Two patients received hyaluronidase subcutaneous injections the day after the procedure. The treatment was performed by clinicians who had injected HA fillers. The amount of injected hyaluronidase was not documented.

Three patients had skin lesions with either vascular or satellite patterns that were not continuous with the injection site. We had a strong suspicion that the above three patients had inadvertent arterial injection of HA fillers. However, the other patient had a localised skin lesion on the nasal tip which was the injection site, and the cause of necrosis was not apparent. The other proposed mechanisms leading to necrosis were pressure necrosis due to excessive filler injection, external vascular compression, tissue oedema and inflammation.

In the animal model, the posterior branch of the posterior auricular artery was ablated because rich arterial anastomoses prevent tissue ischaemia. When we did not coagulate the posterior branch of the posterior auricular artery, the arterial injection of HA filler did not create significant skin necrosis if the area was $<1 \text{ cm}^2$ in size. We could assume that the glabella and nasal ala of the clinical cases had limited collateral circulation.

In a preliminary study, we also injected HA filler around the vessels with high tissue pressure to simulate a vascular compression model and into the vein to simulate a venous obstruction model; however, neither injection resulted in skin necrosis of the rabbit ear.

HA is a biodegradable, non-immunogenic and natural polysaccharide abundant in synovial fluid, vitreous humour and extracellular matrix. The molecular weight of HA ranges between several thousand and millions. The natural
form of HA is known to have a very short half-life (several hours) in the body.16 Commercially available HA fillers are chemically cross-linked, which makes HA more viscous and stable in tissue. The particle size of HA fillers ranges from 20 to 1000 μm, and the size of the HA filler used in our study was 250 μm.17 The particle sizes of HA fillers match arteriole sizes of subdermal plexus (100–400 μm).18 HA fillers can obstruct numerous arterioles which form the subdermal plexus, resulting in tissue necrosis. Ligation of a cutaneous artery does not produce tissue necrosis in the face; the obstructed vessels must be small and sufficient in number to preclude collateral circulations.

Vascular complications after HA filler injections have most commonly been reported in the glabellar area. Inadvertent injection of HA fillers into the supratrochlear artery may cause pain, skin discolouration and skin necrosis. In Asia, the subcutaneous HA fillers are frequently injected for purposes of nasal augmentation. The radix, dorsum and tip of the nose are frequent sites of HA filler injection. Specifically, the alar base and nasolabial folds are injected for a youthful appearance. The HA fillers are injected deep to the subcutaneous tissues in the case of nasal and paranasal augmentation; deep injections have an increased likelihood of encountering the axial artery, which may explain why we have many cases of HA vascular complication involving the nasal area.

The optimal time of hyaluronidase injection in the case of HA vascular complications was not determined, but it is wise to use hyaluronidase as early as possible. A case report demonstrated that a hyaluronidase injection rescued impending necrosis following a HA injection: 75 IU of

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**Figure 4** Two weeks after the HA filler injection into the anterior branch of the posterior auricular artery. (A) Hyaluronidase was injected subcutaneously 4 h after the HA injection. (B) Hyaluronidase was not injected.

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**Figure 5** The necrotic area was significantly smaller in the hyaluronidase-injected ears in the 4-h intervention group. In the 24-h intervention group, the difference in the necrotic area between control and hyaluronidase-injected ears was not significant. * Significant difference for \( p < 0.05 \).
hyaluronidase was injected 6 h after a HA filler injection. According to an experimental study, the degradation ratio of cross-linked HA in 100 IU of hyaluronidase after 24 h was 50%, and it depended on the amount of hyaluronidase. We demonstrated that subcutaneously injected hyaluronidase rescued impending necrosis caused by intra-arterially injected HA filler. The subcutaneously injected hyaluronidase would diffuse into the obstructed vessels and degrade the HA filler. The embolised vessels would restore blood flow if the HA filler is degraded without significant endothelial damage.

HA filler injections are safe procedures, and severe complications are rare; however, physicians should be aware of the potential risks of vascular complications. As early subcutaneous injection of hyaluronidase recovers the skin from impending necrosis, it is important that physicians recognize the signs of impending necrosis at an early stage.

Conclusions

Inadvertent vascular injections of HA filler cause pain, a skin colour change to blue and resultant skin necrosis. Hyaluronidase can reduce the vascular complication of HA fillers if used early, but there is no benefit in injecting hyaluronidase the day after the HA filler injection.

Ethical approval

The study was approved by the Institutional Review Board of Korea University, and performed under guideline of Institutional Animal Care and Use Committee.

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None.

Conflict of interest

None declared.

References
