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Original article

A retrospective study of dermal fillers associated necrosis and management

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Abstract. *Background:* Dermal fillers, including hyaluronic acid, play an important role in aesthetic medicine. The immunological response is minimal, however, proper technique and pathophysiology associated with neutral and non-allergic reactions must be further studied, as adverse events might still occur leading to numerous and severe complications, such as tissue necrosis. *Methods:* We present a retrospective study with cases of four patients with tissue necrosis, following an aesthetic treatment for either nose correction or lip augmentation. Patients were treated from September 2019 until October 2023 in the Cyprus Facial Surgery office, at the American Medical Center located in Nicosia, Republic of Cyprus. *Results:* All patients had a severe reaction after 15 minutes to 48 hours following the procedure, but no permanent functional damage was reported after treatment with hyaluronidase and heparin injections. *Conclusion:* Mastering the injection technique of hyaluronic acid fillers, having thorough knowledge of the materials used, the timing and type of proper treatment is critical for preventing tissue ischemia and mitigating necrosis.

Key words: dermal fillers, hyaluronic acid, fillers associated necrosis, facial aesthetics

Introduction

Dermal fillers are being used for various reasons to augment and enhance features and areas of the face and are one of the most used materials in aesthetic medicine. Currently an estimation of 160 dermal fillers are available on the market globally, which are classified in biodegradable and non-biodegradable, with different effect duration into temporary, semi-permanent and permanent. The absorbable fillers are metabolized in time by the body making their effect temporary. Types of biodegradable fillers approved by the FDA are HA, collagen, calcium hydroxyapatite (CaHA) and poly-L-lactic acid (PLLA)[1,3]. Non-biodegradable fillers have a permanent effect on the area of injection, which usually triggers a foreign body reaction, that can cause various adverse reactions which can be difficult to manage[1,2]. Hyaluronic acid (HA) is a glycosaminoglycan found also as a natural component of the extracellular matrix. Due to the nature of HA, it has a huge advantage of only minimal immunological response[2]. However, the occurrence of unpredictable adverse reactions requires a better understanding of the pathophysiology that leads to neutral and non-allergic reactions. There may be numerous adverse reactions ranging from minor ones on the injection site, such as bruising and pain, to severe complications, such as tissue necrosis, infections, and retinal artery occlusion. Medical professionals using dermal fillers should be adequately qualified and trained to recognize such complications promptly and be able to solve them quickly[8,9].

One of the serious but rare complications is vascular occlusion which occurs after the injection of the dermal filler material into the arterial blood flow, or resulting from the compression of an adjacent vessel due to voluminous material in the area[3,4]. The onset of the infarct is immediate, especially when an artery is involved, resulting in intense pain and discoloration at

the injection site[7,8,9]. Within the first 24 hours of vascular compromise, there is a decline of oxygen supply due to partial or complete infarction. If left untreated, this can result in the permanent ischemia of the tissue and necrosis.

As treatment, the hyaluronidase enzyme is the gold standard, breaking down the peptide bonds between the long-chained proteins within HA, leading to an increase of mobility of the injected material, leading it to diffuse freely through the tissues in form of oligoproteins[2]. The early injection of hyaluronidase can avert the onset of necrosis induced by compression ischemia from HA[5].

In this article we highlight the various adverse effects and severe events noted to our patients with the use of fillers, and discuss prevention and management[1,3].

Materials and Methods

Patients were recruited and treated at the Cyprus Facial Surgery office from September 2019 to October 2023. The inclusion criteria were severe ischemic reactions to dermal fillers after a liquid rhinoplasty technique and lip augmentation. Photographs before and after the dermal filler injections where captured, informed consents were signed before the procedure, and long term follow ups with pictures were acquired. All products used were stored and kept under the safety guidelines of the manufacturers to ensure their effective use. The products that we used were hyaluronic acid, hyaluronidase, heparin 1500 UI, dexamethasone, aspirin.

Results

This case series comprises of four patients, three female and one male 20, 26, 50 and 41 years of age respectively. In all cases, following a dermal filler injection. Occlusion associated necrosis of the treatment was recorded and resolved after treatment with hyaluronidase within 3 to 14 days. Each patient was monitored 6 months following the treatment. All patients received the same treatment protocol, except the youngest female patient which additionally received treatment with hyperbaric oxygen.

The first case reported was a 26-year-old female that came to our office for a liquid rhinoplasty treatment. An injection of HA based filler was used to correct the tip of the nose. The patient had no complaints right after the procedure and left. After 24 hours the patient complained of excruciating pain and a change in color to blueish with a blanching effect on the superior perioral region and the nasal region (see Figure 1), indicating occlusion of the supply branches of angular triangle vessels. For the first 48 hours she received injections (see Table 1) of hyaluronidase 150 UI every 6 hours on the nasal region and on the periphery to dissolve the intravascular compromise.

Simultaneously, heparin injections were given locally starting with 150 UI every 4 hours for 12 hours, as well as pain medication and an anticoagulation treatment with 350mg of aspirin daily for 1 week. Intravenous dexamethasone was not added to the regimen due to a known history of allergy to cortisone. Her results after 1 month of treatment showed no permanent functional damage but minimal scarring of the nasal tip resulting in a minor cosmetic deformity of the skin.

The second case was a 41-year-old male that wanted to correct the nasal tip with filler injections.

After carefully reading the consent form, the patient signed it, and we proceeded with HA based filler. The patient had no complaints and left the office. After 24 hours the patient started complaining of severe pain and discoloration of the nasal area with livedo pattern and blanching (see Figure 2). We immediately started treatment (see Table 1) with hyaluronidase injections 150 UI every 6 hours in the affected area and on the peripheral branch to dissolve the intravascular spread of the hyaluronic acid, and heparin injections of 150 UI every 4 hours for 12 hours. At 72 hours we continued with IV dexamethasone 8 mg every 8 hours along with pain medications and anticoagulation therapy with 350 mg of aspirin for 1 week. As a result, this patient had a necrotic area of the lateral border of the lateral alar cartilage due to the lack of communication with the office, therefore requiring reconstruction after 12 months of the initial treatment protocol, which the senior author performed with a local flap and autologous alar rim graft to restore nasal

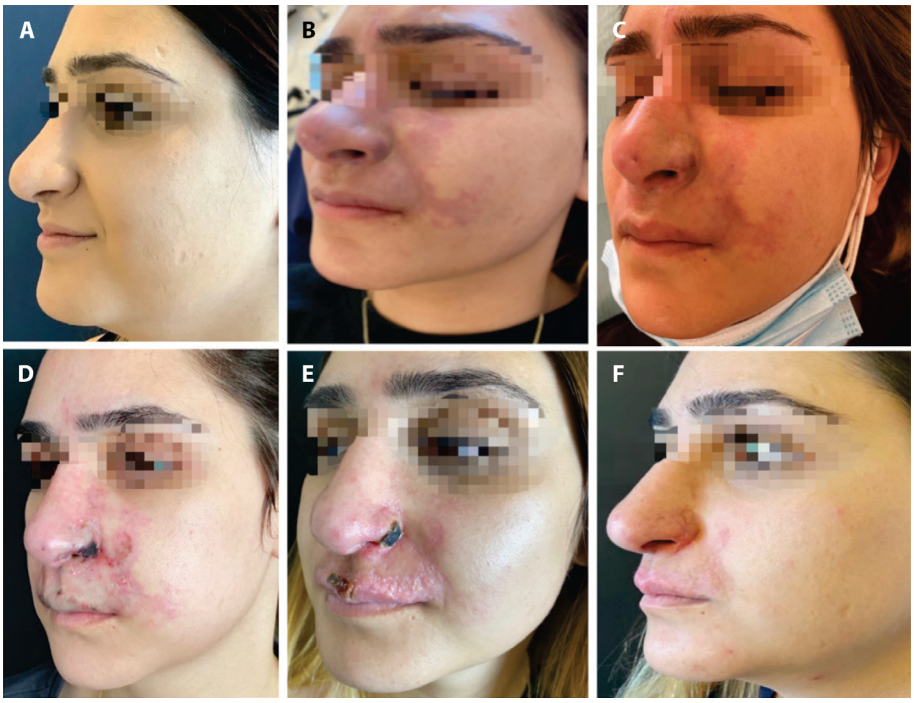

Figure 1. Liquid rhinoplasty with injection of hyaluronic acid. Patient is seen with chronological order from A-F from day of procedure to result of treatment. (A) Before the procedure, (B) 48h after injection of hyaluronic acid at the tip of the nose, with change in color of superior perioral region and nasal region, (C-E) Skin necrosis and progress while on heparin injections for one week, (F) Follow-up 1 month after treatment.

anatomy (see Figure 2D). After a healing period of 1 year, the patient had a satisfactory aesthetic appearance and functionality.

The third case was a 50-year-old female who wanted lip augmentation. Following the standardized procedures in our office, we proceeded with the lip filler injections using a HA based filler. The patient had no complaints and left our office. The patient came back after 15 minutes due to dark purple discoloration on the right side of her upper lip, with the absence of any pain due to lidocaine that was included in the HA based filler (see Figure 3B). After examining the area there was blanching and 150 UI of hyaluronidase were injected (see Table 1). After 6 hours we proceeded with another injection of 150 UI of hyaluronidase on the area of the ischemia. After the first 48 hours the patient received another 90 UI hyaluronidase on the peripheral branches of the affected area, resulting in a complete recovery without any permanent complications (see Figure 3D).

The fourth case was a 20-year-old female with a congenital facial asymmetry that underwent orthognathic surgery and rhinoplasty in July 2022, and wanted a correction of the nasal tip with dermal injections. The patient was informed about the risks and adverse effects of dermal filler injections after any surgical procedure, and signed consents were obtained. After the HA filler injections, the patient had no complaints and left the office. The patient contacted the emergency line after 24 hours of the treatment complaining of excruciating pain, localized ischemia, and blanching. The patient was rushed to our office immediately after the call and we followed the treatment protocol with 320 UI hyaluronidase every 8 hours for the first 24 hours, and heparin injections of 150 UI every 4 hours for 12 hours, then following up for the next 48 hours. The patient was also on Aspirin 350mg for 1 week. After the first 48 hours, epidermolysis of the nose was observed resulting after the vascular compromise (see Figure 4C). The patient was referred

Table 1. Overview of used medication after complications of use of HA based fillers for Case 1, Case 2, Case 3 and Case 4 as well as Outcome of each medication used.

HA based filler cases	Class	Type of treatment	Time period of treatment given	Volume of injection	Use	Outcome of procedure (before and during treatment)	Outcome of treatment
Case 1							
Liquid rhinoplasty treatment	hyaluronidase	Liquid injection	Every 6h	150UI	Enzyme that breaks down hyaluronic acid	good	• No permanent functional damage • Minor deformities of skin • Scarring of nasal tip
	heparin	Liquid injection	Every 4h for 12h, following then for the next 48h	150UI	Prevents blood clots from forming	good	
	Acetylsalicylic acid (Aspirin)	Pill	For 7 days	350mg	Reduces pain and fever	good	
Case 2							
Nasal tip with filler injections	hyaluronidase	Liquid injection	Every 6h	150UI	Enzyme that breaks down hyaluronic acid	poor	• Necrosis of nasal tip • Reconstruction surgery • Functional and aesthetic deformities
	heparin	Liquid injection	Every 4h for 12h, following then for the next 48h	150UI	Prevents blood clots from forming	poor	
	Cortisone (Dexamethasone)	IV	Every 8h	8mg	Treats inflammation, severe allergies, and skin fever	poor	
	Acetylsalicylic acid (Aspirin)	For 7 days	Aspirin	350mg	Reduces pain and fever	poor	
Case 3							
Lip augmentation	hyaluronidase	Liquid injection	Every 6h	150UI	Enzyme that breaks down hyaluronic acid	good	• No complications • No functional or aesthetic deformity
	hyaluronidase			150UI			
	hyaluronidase			90UI			
Case 4							
Nasal tip with dermal injections	hyaluronidase	Liquid injection	Every 6h	320UI	Enzyme that breaks down hyaluronic acid	good	• Fully restored • No functional damage
	heparin	Liquid injection	Every 4h for 12h, following then for the next 48h	150UI	Prevents blood clots from forming	good	

HA based filler cases	Class	Type of treatment	Time period of treatment given	Volume of injection	Use	Outcome of procedure (before and during treatment)	Outcome of treatment
	Acetylsalicylic acid (Aspirin)	Pill	For 7 days	350mg	Reduces pain and fever	good	
	Hyperbaric Oxygen (HBO)	Gas	n.a.	12 dives	Speeds up healing of carbon monoxide poisoning, gangrene, wounds that won't heal, and infections in which tissues are starved for oxygen.	good	

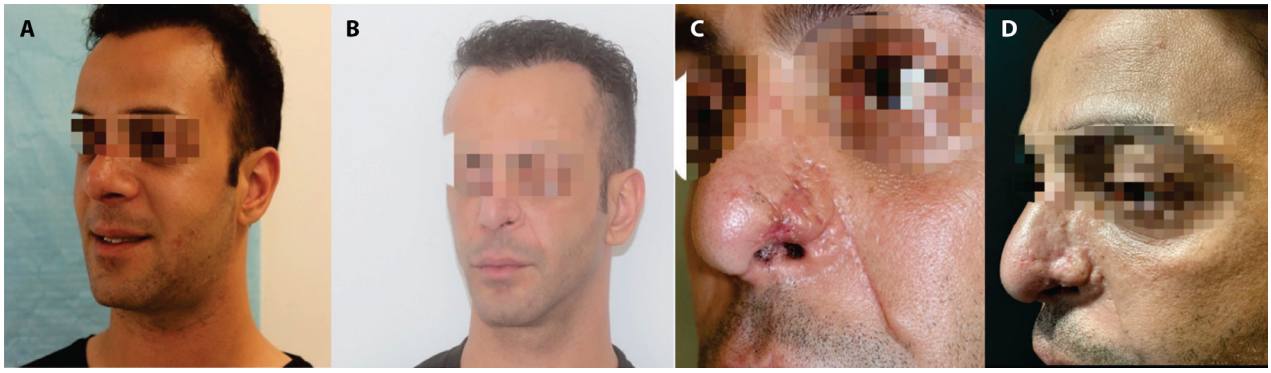

Figure 2. Liquid rhinoplasty with injection of hyaluronic acid. Patient is seen in chronological order from A-D. (A) Immediately after procedure (B) 48h after procedure with discoloration of nasal area and pain (C) One week after treatment with hyaluronidase and heparin injections, (D) Follow-up 1 year after treatment.

to 12 dives of hyperbaric oxygen following the occurrence of epidermolysis (see Figure 4D). After carefully following our treatment protocol the patient had no permanent damage and the ischemic area was fully restored.

Discussion

An increasing number of patients seek injectable fillers especially young ones, therefore the knowledge for the correct use of injectable dermal fillers must be meticulous and precise, as any serious complication might affect the mental health of young patients. Potential complications after each procedure can be severe and lead to necrosis with a rare incidence of 1 out of every 100,000[11]. Enzymes like Hyaluronidase are able to reverse the severe reaction and minimize damage[5,6].

A review article by Y.Z. Chiang, G. Pierone, F. Al-Niaimi revealed that the second most high-risk area of injections is the nasal region (25.5%) and

Figure 3. Lip augmentation with injection of hyaluronic acid. Patient is seen in chronological order from A-E. (A) Before the procedure, (B-C) dark purple discoloration on the right side of the upper lip 15 minutes after procedure, (D) 72 hours after treatment with hyaluronidase injections, (E) Follow-up 1 month after treatment.

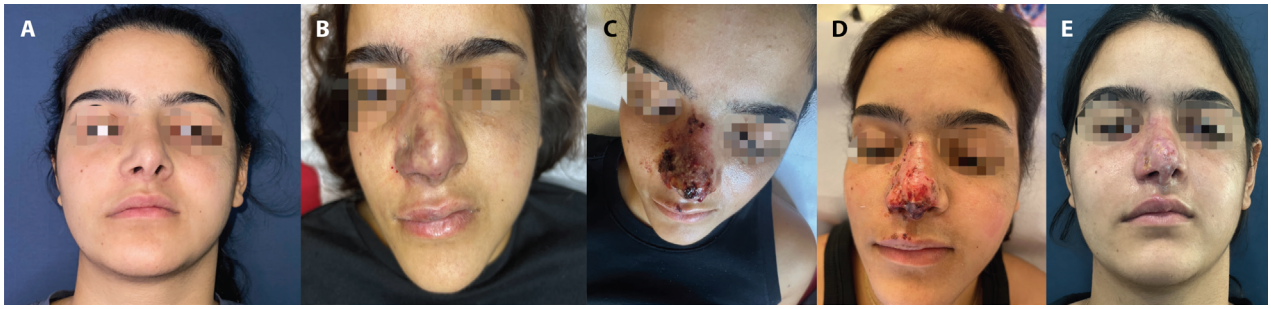

Figure 4. Liquid rhinoplasty with injection of hyaluronic acid. Patient is seen in chronological order from A-E from day of procedure to result of treatment. (A) Before procedure, (B) 24h after injection of hyaluronic acid at the tip of the nose, with blanching, ischemia and change in color of the nasal region. (C) 48h obvious epidermolysis with skin necrosis and vascular compromise of the nasal region, (D) after completing hyperbaric oxygen treatment (E) Follow-up 1 month after treatment.

the glabella region (38,8%), as seen in our case studies three out of four cases were all associated with the nasal region. The necrosis mechanism is assumed to be associated with an increase of pressure followed by the intra-arterial injection. The embolism with the material occurs as it is pushed into the angular artery compromising the blood supply of the superior labial artery to all branches of the facial artery, blocking the perfusion of the nasal region[4,8].

Dr. Bruna Souza Felix Bravo M.D suggests that in the case of filler-induced occlusion, both arterial and venous compromises have a similar pathophysiology mechanism of occlusion, therefore it is crucial to restore the blood flow without delay to avoid any functional damage or tissue necrosis. According to their findings, the authors suggested using 40UI (0,1ml) of hyaluronidase as the gold standard, topically per cm^2 of the affected area, lasting for 24 and 48 hours[10]. Therefore, Dr. Bravo suggests, when performing filler injections, to always have at least one bottle of hyaluronidase in the office to rapidly institute hyaluronidase therapy in case of a hyaluronic acid based vascular compromise.

According to an article written by Joe L Cohen et al.[5] an immediate diagnosis and correct treatment with high doses of hyaluronidase, (at least 200 UI) are critically important in addition to the use of a warm compress with massage to achieve vasodilation which are thought to help[5]. In our case series we found out that using 150 UI, the result was also satisfactory with no functional damage. Within our case series, two of the three cases treated with repeated 150 UI of hyaluronidase responded favorably with the complete resolution of the ischemia avoiding any functional necrosis.

Table 2. Recommended treatment and outcome of each medication.

Medications	Time period of treatment given		Area	Dose	Cases using the medication	Outcome of treatment (poor, good)
Heparin	Every 4h for 12h	Following for the next 48h	Nasal tip	150UI	Case 1	good
					Case 2	poor
					Case 4	good
Hyaluronidase	Every 6h		Nasal region	150UI	Case 1	good
					Case 2	poor
					Case 3	good
					Case 4	good
Aspirin	For 7 Days		Nasal region	350mg	Case 1	good
					Case 2	poor
					Case 4	good
Dexamethasone	Every 8h		Nasal region	8mg	Case 2	poor
Hyperbaric Oxygen (HBO)	n.a.		Nasal region	12 dives	Case 4	good

Deok-Woo Kim et al[6] suggests that the necrotic tissue showed significant improvement after the initiation of hyaluronidase injections within the first 4 hours. The timing of initiation of the hyaluronidase treatment is quintessential in having the best outcome, hence patients are advised to remain in the region for the first 24 hours after dermal fillers. Our patient with the best outcome was treated within 15 minutes with 150 UI hyaluronidase, and after 72 hours the ischemic tissue was fully restored with no functional damage.

Unfortunately, in our study we concluded that patients which presented to the office after 24 hours for hyaluronidase, in which necrosis was already established, had poor recovery, and needed reconstructive surgery to restore their correct anatomy.

The patient that returned to the office within 24 hours and received the recommended treatment protocol of hyaluronidase, aspirin and heparin while undergoing hyperbaric oxygen treatment for a week, had the best outcome and requested no reconstructive surgery, with a full resolution of the symptoms of ischemia within 2 weeks. For this reason, we are in position to present the best protocol for these cases to prevent necrosis and permanent tissue disfiguration.

In our experience if blanching of the area is observed after injection of HA, the immediate use of hyaluronidase to the affected area has the best outcome with the full resolution of the symptoms, and prevents the onset of ischemia, since the HA filler is dissolved before it manages to travel to a distal vasculature resulting in the dissemination of many places, maintaining the vascular supply intact, as seen in the case of Case 3 (see Table 2).

It is critical to have a solid understanding of the acceptable injection depth in each region. Thus, injectable fillers using a needle in the nasal region should always be aspirated, with low injection pressure, subdermal, for optimum safety and minimal amount of HA filler, and if more is required in increments throughout different sessions. Extra caution should be given in operated noses where, as seen in our cases, had higher chances of necrosis than in non-operated patients. In that case, it is safer to inject 8 months to 12 months after the initial surgery, when the vascular supply is re-established and the amount of injection should be minimal, considering that scaring and fibrosis from surgery decreases the vascular net supply where a huge amount of filler can cause compression of the remaining vasculature and may lead to ischemia and necrosis[2]. The use of a canula has a lower chance of injuring a vessel and is thought to be safer[5,6,8].

Conclusion

Dermal fillers are one of the main protagonists in aesthetic medicine, especially for the definition of facial skeletal structures, and providing and restoring volume of the face. An important advancement in aesthetic medicine is using the knowledge on anatomy and physiology, allowing physicians to identify, treat and prevent any complications that arise during the dermal filler injection. Combining knowledge with correct injection skills is cardinal for eliminating and minimizing complications and risks of dermal fillers.

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