



Vascular complications from facial fillers with hyaluronic acid: preparation of a prevention and treatment protocol

Complicações vasculares dos preenchimentos faciais com ácido hialurônico: confecção de protocolo de prevenção e tratamento

JOSÉ CARLOS DAHER ^{1*}

SUELLEN VIEIRA DA-SILVA ¹

AMANDA COSTA CAMPOS ¹

RONAN CAPUTI SILVA DIAS ¹

ANDERSON DE AZEVEDO DAMASIO ¹

RAFAEL SABINO CAETANO COSTA ¹

■ ABSTRACT

Introduction: Over the past two decades, there has been an exponential advancement in treating signs of facial aging. The growing demand for less invasive therapies has stimulated the development of biomaterials toward better products, seeking to fulfill safety criteria, such as biocompatibility and reversibility. Hyaluronic acid (HA) is the most widely used facial filler worldwide, being routine in plastic surgery clinics. Even with low complication rates, it is prudent for the plastic surgeon to be attentive to the signs of vascular occlusion because the interruption of the progression towards necrosis and permanent sequelae depends on rapid medical action. Thus, our service saw the need to create a prevention and treatment protocol, since such complications are serious and sometimes even irreversible. **Methods:** A systematic review of the literature was conducted from January 2003 to January 2018, using descriptors of vascular complications after facial filling with HA and its treatment. **Results:** Filling with HA presents a low potential for complications when performed by qualified professionals. Hyaluronidase, which is currently used off-label, can hydrolyze HA, even in its cross-linked form. If used correctly in a timely manner, it can treat possible vascular complications that would progress to irreversible damage. Accordingly, we prepared a treatment protocol given the current evidence. **Conclusion:** Every plastic surgeon who works with fillers and HA must have a protocol and be aware of the necessary material for early intervention.

Keywords: Hyaluronic Acid; Hyaluronoglucosaminidase; Dermal Fillers; Embolism; Necrosis.

Institution: Hospital Daher Lago Sul,
Brasília, DF, Brazil.

Article received: February 27, 2019.

Article accepted: October 20, 2019.

Conflicts of interest: none.

DOI: 10.5935/2177-1235.2020RBCP0002

¹ Hospital Daher Lago Sul, Brasília, DF, Brazil.

■ RESUMO

Introdução: Ao longo das últimas duas décadas, houve um avanço exponencial no tratamento dos sinais causados pelo envelhecimento facial. A procura crescente por terapias menos invasivas estimulou a evolução dos biomateriais em direção ao produto ideal, buscando preencher os critérios de segurança, tais como biocompatibilidade e reversibilidade. O ácido hialurônico é o produto mais utilizado mundialmente para preenchimento facial, sendo rotineiro nos consultórios de cirurgia plástica. Mesmo com baixos índices de complicações, é prudente que o cirurgião plástico esteja atento aos sinais de oclusão vascular, pois a interrupção da evolução em direção à necrose e seqüela permanente depende da rápida atuação médica. Sendo assim, o nosso serviço vislumbrou a necessidade da confecção de um protocolo de prevenção e tratamento, uma vez que tais intercorrências são graves e algumas vezes até mesmo irreversíveis. **Métodos:** Revisão sistemática da literatura entre janeiro de 2003 a janeiro de 2018, utilizando descritores de complicações vasculares após preenchimento facial com AH e o respectivo tratamento. **Resultados:** O preenchimento com AH apresenta baixo potencial de complicação quando realizado por profissionais habilitados. A hialuronidase, atualmente utilizada off-label, é capaz de hidrolisar o ácido hialurônico, mesmo na sua forma cross-linked. Se utilizada corretamente em tempo hábil, pode tratar possíveis complicações vasculares que naturalmente evoluiriam para danos irreversíveis. Para tanto, confeccionamos um protocolo de tratamento à luz das evidências atuais. **Conclusão:** Todo cirurgião plástico que atua com preenchimentos e ácido hialurônico, deve ter em mãos um protocolo e o material necessário para intervenção precoce. **Keywords:** Hyaluronic acid; Hyaluronoglucosaminidase; Dermal fillers; Embolism; Necrosis.

INTRODUCTION

The aging process is multifactorial and results in simultaneous changes in the various components of the face. The pathogenesis of facial aging can be explained anatomically and is the result of the interaction of intrinsic factors (maturity of soft parts, skeletal atrophy/changes and muscular hyperactivity) and extrinsic factors (gravity and solar damage). Consequently, the smooth confluent appearance of the face is slowly replaced by spiked angles, wrinkles, grooves and prominences. Skeletal changes lead to a general decrease in facial height and moderate enlargement and deepening of the facial structure. The decrease in maxillary height and the increase in orbital volume results in sunken eyes and less space for the insertion of available soft tissue.

Superficial lines that cross the upper limit of the dermis are responsive to dermabrasion, peeling, and lasers. However, dynamic wrinkles respond to muscle inactivation with botulinum toxin or myectomy/

myotomy and can be improved using dermal fillers. Fillers are also useful in treating grooves during their initial stages or as an adjuvant modality to surgery.

The filling of soft parts is an alternative for patients seeking facial rejuvenation with minimal downtime. For young patients, this might be the ideal modality, while for older patients, the combination of filling and surgery is more effective. To date, the ideal filler has not been found, and there is no consensus on its ideal characteristics (Chart 1).

Chart 1. Characteristics of the ideal filler.

Characteristics of the ideal filler	
Non-toxic	Produces natural and noticeable changes.
Biocompatible	Minimal downtime.
Lasting	Predictable.
Reversible	Work well with ageing.
Autologous	Not perceptible to touch.
Ease of use	Safe

The history of facial filling began in 1830, when the German chemist Karl Ludwig, in 1830¹, discovered paraffin. Using this material, in 1899, Gersuny², an Austrian, reported using the substance for esthetic purposes, when he created a testicular prosthesis for a patient who had been treated with orchietomy due to tuberculosis. After that, paraffin became widely used in rhinomodeling, until in 1911² a list of complications that the use of this material could generate emerged. It was then abandoned for cosmetic purposes.

Adipose tissue grafting was initially developed in the late 19th century for facial reconstruction. Neuber, in 1893³, described an autologous fat graft, from the arm, which consisted of fragments of fat tissue to correct facial defects. However, this method only became popular in 1982, after Illouz⁴ described the use of cannulas for vacuum aspiration and grafting of the aspirated product. Several techniques have been proposed since then, and this grafting modality is still widely studied and used by plastic surgeons for facial filling and other areas of the body. In the 1940s, in Japan, injectable liquid silicone was used for breast augmentation. This product gained prominence after being introduced in the United States of America in the 1960s, but in the following years, reports of complications and sequelae of the use of liquid silicone emerged. Its use for cosmetic purposes was banned by the Food and Drug Administration (FDA) in 1979.

Clinical experiments with bovine collagen occurred between 1977-1978, to treat age-related wrinkles. After 6 years of research, the substance was approved by the FDA for aesthetic purposes, under the name Zyderm. Despite the success of this material in the 1980s and it becoming the standard to which all other injectables were compared, it was not an ideal product and had a number of drawbacks. As well as its short duration, all biological materials were derived from organic sources, which can lead to sensitization to foreign animal or human proteins, the transmission of diseases, and immunogenicity. During the following years, there was an evolution of collagen materials, as shown in Chart 2 below:

Chart 2. Evolution of collagen-based fillers.

Collagen-based biological filling	
Zyderm(1981)/Zyplast (1985)	Collagen (bovine)
Dermalogen (1998)	Human collagen matrix
Surgisis (1998)	Pig collagen matrix
CosmoDerm/CosmoPlast (2003)	Collagen (human)

Hyaluronic acid (HA) is a polysaccharide found naturally in the connective tissue of mammals (skin, cartilage, bone, and synovial fluid), with a gelatinous

consistency, high viscoelasticity and high degree of hydration because of its structural characteristics⁵. This material was first described in 1934 by Meyer and Palmer⁶, during the analysis of bovine vitreous humor, which in its natural state is a very good filler but has a short half-life. After minimum chemical changes (cross-linking), it was possible to create a material that was tolerated by the immune system, non-reactive, and had greater longevity. Two techniques were developed to produce the acid: bacterial fermentation or extraction from rooster crest. For large-scale production reasons, the first technique is the most widely used today.

Since FDA approval in 2003, HA has become the most widely used filler in the world due to its properties, such as biocompatibility and reversibility. According to the American Society of Plastic Surgery, in 2014, soft tissue filling increased by 253% when compared to 2000, with HA accounting for 78.3% of all injectable fillers.

METHODS

An extensive search was performed in the MEDLINE, Cochrane, and PubMed databases between January 2003 and January 2018. The keywords used were “dermal fillers”, “vascular complications”, “hyaluronic acid” and “hyaluronidase”. Initially, 49 articles were selected.

The inclusion criteria were:

- Year 2003-2018;
- Clinical trials and case studies;
- HA facial filler;
- Vascular complications;
- Treatment with hyaluronidase.

Exclusion criteria:

- Case reports;
- Filling with other materials besides HA;
- Focus on other complications.
- The results yielded 19 articles.

DISCUSSION

Although infrequent⁷, adverse effects related to the use of HA injections may occur. It is important for all surgeons who work with HA to perfect the infiltration technique and to recognize early complications and master its handling.

The complications of HA filling can be divided into early and late, according to the time of appearance. Those classified as early appear within a period of hours to days. The most common are edema, pain, hyperemia, and ecchymosis⁸. These reactions are usually self-limiting and do not require major interventions. On the other hand, vascular complications that can result in tissue necrosis and loss of vision can occur rarely. These require further attention and follow up due to

the high potential of sequelae⁹. Late complications include biofilms, granulomas, depigmentation, and scarring. (Chart 3)

Chart 3. Complications related to the use of hyaluronic acid.

Early	Tardias
Relate to infiltration:	Infections
Edema	Granulomas
Pain	Nodules
Bleeding	Depigmentation
Ecchymosis	Scars
Inflammatory Reactions	
Allergic Reactions	
Vascular infarction/Tissue necrosis	

Venous obstruction is uncommon but may be observed in some cases where some degree of occlusion is already present¹⁰. It can occur when a large volume of material infiltrates topographies with significant tension, where the tissue is restricted, with the absence of the usual elasticity, as with scars. An accidental intravenous injection may not have repercussions and often goes unnoticed. In contrast, the injection of intra-arterial material can result in flow obstruction, leading to hypoxia in a certain territory and tissue ischemia¹¹.

The signs of vascular occlusion are immediate and usually present with: pale tissue, followed by livedo reticularis, and ischemia. If no intervention is performed, blisters, sores, and tissue necrosis can occur (Chart 4). The most serious complication related to vascular obstruction is a loss of vision, which can happen when there is occlusion of an ophthalmic artery or the retina via a retrograde flow of material injected into the supraorbital area. This is associated with an influx of a large volume at an excessive infusion pressure. The symptoms are immediate and include ocular pain and visual disturbance. Tissue necrosis occurs more in the so-called risk zone, which is the nose, mainly in the glabella. The glabella is supplied by arteries from the supratrochlear, which travels in a medial path to the eyebrows. Due to this anatomical course, it is suggested that there is a greater risk that inadvertent intra-arterial injection may occur¹². The alar topography of the nose is vascularized by terminal branches of the angular artery, a site poor in collateral branches, and is, therefore, a common area of tissue necrosis. Most of the cases reported in the literature occurred in Asia, where there is a high prevalence of filling in risky facial areas¹³.

The first strategy against vascular complications from using HA is prevention. The doctor must be knowledgeable about the vascular anatomy of

Chart 4. Signs of complications x time.

Clinical findings	Time after filling
Skin pallor	Seconds Minutes
Livedo reticularis	Hours
Cyanosis	Hours to days
Blisters	Days to weeks
Barrier loss, ulceration	Dias a semanas

the topography, where infiltration of the material occurs. During an initial visit, it is crucial for patients to question their experience with previous facial procedures. Most of the face is supplied by branches of the external carotid artery, except for the forehead, the central part between the eyes and the upper part of the nose, which are supplied by the ophthalmic artery, and a branch of the internal carotid artery. The arteries involved in complications of the glabella and forehead are the supratrochlear and supraorbital arteries, both of which can lead to eye-related complications. The supra-trochlear artery is constant in most cases, varying its position by a maximum of 5mm. It starts deep in the superomedial part of the orbit and becomes subcutaneous 15 to 25 mm from the supraorbital ridge as it moves superiorly. The supraorbital artery appears at the supraorbital border, vertical to the pupil, becoming subcutaneous 15 to 20 mm above the orbital ridge, heading towards the forehead. Filling in the nasal region should be performed in the deep supraperiosteal plane, below the SAMS, thus avoiding the anastomotic venous network.

The use of cannulas for deep injection is another recommendation since it is less likely that a blind tip thin cannula penetrates an artery compared to a needle. It is prudent to always aspire before infiltrating the material and when withdrawing the needle. Avoid the infiltration of a very large volume (<0.1) of material at an exaggerated pressure, using smaller syringes for flow control, to avoid a possible reversal of flow and retrograde embolism¹⁴.

Even after prevention strategies are undertaken, vascular complications can occur that should be treated immediately. Hyaluronidase is a mucolytic enzyme capable of degrading HA in both its natural and cross-linked form. It hydrolyzes HA, breaking its bonds, generating increased permeability in the skin and connective tissue. Its plasma half-life is approximately two minutes, with it inactivated during its passage through the liver and kidneys¹⁵. However, its effect on subcutaneous tissue is immediate, with a long duration, ranging from 24 to 48 hours.

In 2007, Hirsch¹⁶ et al. reported the first case of vascular occlusion by HA filling, which reverted successfully after the use of the enzyme. In 2014,

DeLorenzi¹⁷ developed an *in vitro* study to assess whether hyaluronidase was able to cross the intact human facial artery wall to hydrolyze the HA filler through small segments of the facial artery, which were filled with a monophasic HA, acquiring the aspect of “sausages”. Then, they were immersed in 300IU of hyaluronidase (manipulated) or saline (control). Only the samples immersed in hyaluronidase displayed degradation of the filler at the end of 4 and 24 hours. Thus, the result indicated that the enzyme could hydrolyze HA even with the vessel wall intact.

Currently, the treatment for vascular accidents by HA requires the use of the enzyme in the entire extension of the lesion. However, there is no standardization of the dose in the literature. In 2007, Soparkar et al.¹⁸ used 375IU of hyaluronidase to dissolve an HA filler in the face of a patient. In their opinion, the recommended dose should vary from 150 to 200IU of hyaluronidase for each 1ml of HA to be removed. In 2014, Rao et al.¹⁹ exposed four types of HA fillers to various concentrations of hyaluronidase *in vitro* and concluded that the enzymatic reaction is time and dose-dependent. The literature recommends early treatment, demonstrating a considerable reduction of its effectiveness after 24h of filling²⁰, which may reach 50%.

We feel that a protocol is required that includes the treatment of these possible complications and adopts the abovementioned knowledge carefully. Given current scientific evidence, we propose the following protocol for treating possible vascular complications:

1. Immediately stop the procedure;
2. Use high doses of hyaluronidase in the affected area;
3. Massage the area;
4. Wait 60 minutes and reassess the possibility of new infiltration.

At the first sign of vascular involvement during the use of HA, the procedure must be stopped. The ACE GROUP, in 2018²¹, recommend the immediate infiltration of hyaluronidase to prevent the progression to tissue ischemia and necrosis, since studies corroborate that the best results are with the early use of the enzyme²², and preferably within the first 4 hours.

The literature emphasizes that it is important to avoid a sub dosage, since the progression of the complication may lead to severe cases, with irreparable consequences²³. High doses (450-1500IU) should be infiltrated across the affected area²⁴, followed by a local massage to dissipate the obstruction.

In Brazil, Hyalozima® 2000utr (Apsen) is available, which must be reconstituted in 5 mL of diluent that accompanies the product, resulting in 400U per mL. Initially, 1mL is aspirated, and after adequate antisepsis and asepsis, 0.1 points must be infiltrated for every extension of the affected area, with needles between 27G

and 30G, and a spacing of 3 to 4cm between the points. The application must be repeated after 60 minutes if there is no improvement in the initial framework, and may be conducted up to 4 times²⁵. The product should be kept cool between 2-8 degrees to ensure its stability. Once opened, the rest of the product should be discarded.

There have been reports of severe allergic reactions to the enzyme. Therefore, patients should be observed for at least 60 minutes after the application of hyaluronidase²¹. Due to its propagation, it should not be infiltrated into areas where botulinum toxin was applied in the last 48 hours.

Patients should be reassessed daily to check for signs of improvement or regression of vascular congestion. Hyperbaric medicine can be useful, as it acts by carrying oxygen to the tissues and is increasingly being used for treating ischemia, which progresses to necrosis^{26,27}.

The monitoring of affected patients involves routine care with surgical wound debridement and surveillance of secondary infections. Patients diagnosed early usually have a satisfactory prognosis. Those with a delayed diagnosis are more likely to have major complications, requiring many weeks of wound care, which can result in different degrees of scarring¹².

CONCLUSION

Although not very common, complications related to the use of HA can be severe and irreversible. The most serious are vascular complications, as they can lead to irreversible sequelae. Therefore, any surgeon using HA for facial fillers must have a treatment protocol and appropriate medications available.

COLLABORATIONS

JCD	Analysis and/or data interpretation, Final manuscript approval
SVS	Analysis and/or data interpretation, Conception and design study, Data Curation, Writing - Review & Editing
ACC	Analysis and/or data interpretation
RCSD	Analysis and/or data interpretation
AAD	Analysis and/or data interpretation
RSCC	Analysis and/or data interpretation

REFERENCES

1. Goldwyn RM. The paraffin story. *Plast Reconstr Surg.* 1980;65(4):517-24.
2. Glicenstein J. The first “fillers,” vaselin and paraffin. From miracle to disaster. *Ann Chir Plast Esthet.* 2007;52:157-61.
3. Klein AW. Techniques for soft tissue augmentation. *Am J Clin Dermatol.* 2006;7(2):107-20.
4. Illouz YG. The fat cell “graft”: a new technique to fill depressions. *Plast Reconstr Surg.* 1986;78(1):122-3.

5. Chong BF, Blank LM, MaLaughlin R, Nielsen LK. Microbial hyaluronic acid production. *Appl Microbiol Biotechnol.* 2005;66(4):341-51.
6. Meyer K, Palmer JW. The polysaccharide of the vitreous humour. *J Biol Chem.* 1934;107:629-34.
7. Alam M, Dover JS. Management of complications and sequelae with temporary injectable fillers. *Plast Reconstr Surg.* 2007;120(6 Suppl 1):98S-105S.
8. Lafaille P, Benedetto A. Fillers: contraindications, side effects and precautions. *J Cutan Aesthet Surg.* 2010;3(1):16-9.
9. Ozturk CN, Li Y, Tung R, Parker L, Piliang MP, Zins JE. Complications following injection of soft tissue fillers. *Aesthet Surg J.* 2013;33(6):862-77.
10. DeLorenzi C. Complications of injectable fillers, part 2: vascular complications. *Aesthet Surg J.* 2014;34(4):584-600.
11. Carle MV, Roe RH, Novack RL. Occlusion caused by cosmetic facial filler injection – reply. *JAMA Ophthalmol.* 2015;133(2):225.
12. Cohen JL. Understanding, avoiding, and managing dermal filler complications. *Dermatol Surg.* 2008;34(Suppl 1):S92-9.
13. Bray D, Hopkins C, Roberts DN. A review of dermal fillers in facial plastic surgery. *Curr Opin Otolaryngol Head Neck Surg.* 2010;18(4):295-302.
14. Beleznyay K, Carruthers JD, Humphrey S, Jones D. Avoiding and treating blindness from fillers: a review of the world literature. *Dermatol Surg.* 2015;41(10):1097-117.
15. Dunn AL, Heavner JE, Racz G, Day M. Hyaluronidase: a review of approved formulations, indications and off-label use in chronic pain management. *Expert Opin Biol Ther.* 2010;10(1):127-31.
16. Hirsch RJ, Cohen JL, Carruthers JD. Successful management of an unusual presentation of impending necrosis following a hyaluronic acid injection embolus and a proposed algorithm for management with hyaluronidase. *Dermatol Surg.* 2007;33(3):357-60.
17. DeLorenzi C. Transarterial degradation of hyaluronic acid filler by hyaluronidase. *Dermatol Surg.* 2014;40(8):832-41.
18. Soparkar CN, Patrinely JR, Skibell BC, Tower RN. Hyaluronidase and restylane. *Arch Facial Plast Surg.* 2007;9(4):299-300.
19. Rao V, Chi S, Woodward J. Reversing facial fillers: Interactions between hyaluronidase and commercially available hyaluronic-acid based fillers. *J Drugs Dermatol.* 2014;13(9):1053-6.
20. Oh EJ, Kang SW, Kim BS, Jiang G, Cho IH, Hahn SK. Control of the molecular degradation of hyaluronic acid hydrogels for tissue augmentation. *J Biomed Mater Res A.* 2008;86:685-93.
21. King M, Aesthetic Complications Expert - Group (ACE). This month's guideline: management of necrosis. *J Clin Aesthet Dermatol.* 2018;11(7):E53-7.
22. Kim DW, Yoon ES, Ji YH, Park SH, Lee BI, Dhong ES. Vascular complications of HA fillers and the role of hyaluronidase in management. *J Plast Reconstr Aesthet Surg.* 2011;64(12):1590-5.
23. DeLorenzi C. New high dose pulsed hyaluronidase protocol for HA filler vascular adverse events. *Aesthet Surg J.* 2017;37(7):814-25. DOI: <https://doi.org/10.1093/asj/sjw251>
24. Landau M. Hyaluronidase caveats in treating filler complications. *Dermatol Surg.* 2015;41(Suppl 1):S347-53.
25. Cohen JL, Biesman BS, Dayan SH, DeLorenzi C, Lambros VS, Nestor MS, et al. Treatment of HA filler-induced impending necrosis with hyaluronidase: consensus recommendations. *Aesthet Surg J.* 2015;35(7):844-9.
26. Alam M, Dover JS. Management of complications and sequelae with temporary injectable fillers. *Plast Reconstr Surg.* 2007;120(6 Suppl 1):98S-105S.
27. Kulikovskiy M, Gil T, Mettanen I, Karmeli R, Har-Shai Y. Hyperbaric oxygen therapy for non-healing wounds. *Isr Med Assoc J.* 2009;11(8):480-5.

***Corresponding author:**

José Carlos Daher

Quadra 07 SHIS, QI 7 Conjunto F, Lago Sul, Brasília, DF, Brazil.

Zip Code: 71615-660

E-mail: daher@hospitaldaher.com.br