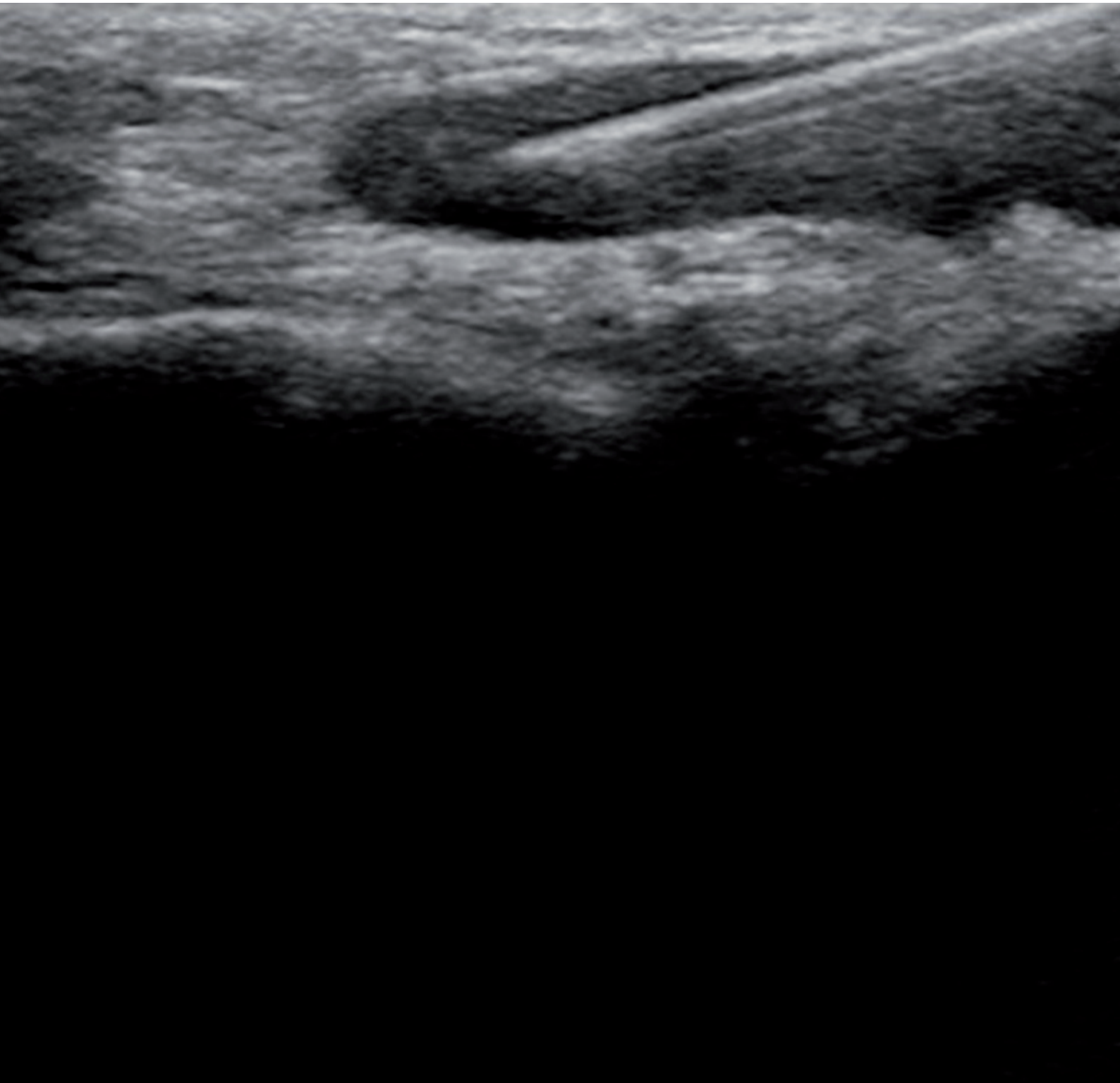
Leonie W. Schelke

Strategies to Improve the Safety of Filler Treatments



Strategies to Improve the Safety of Filler Treatments

Strategieën ter verbetering van de veiligheid van fillerbehandelingen

Leonie Waltraut Schelke

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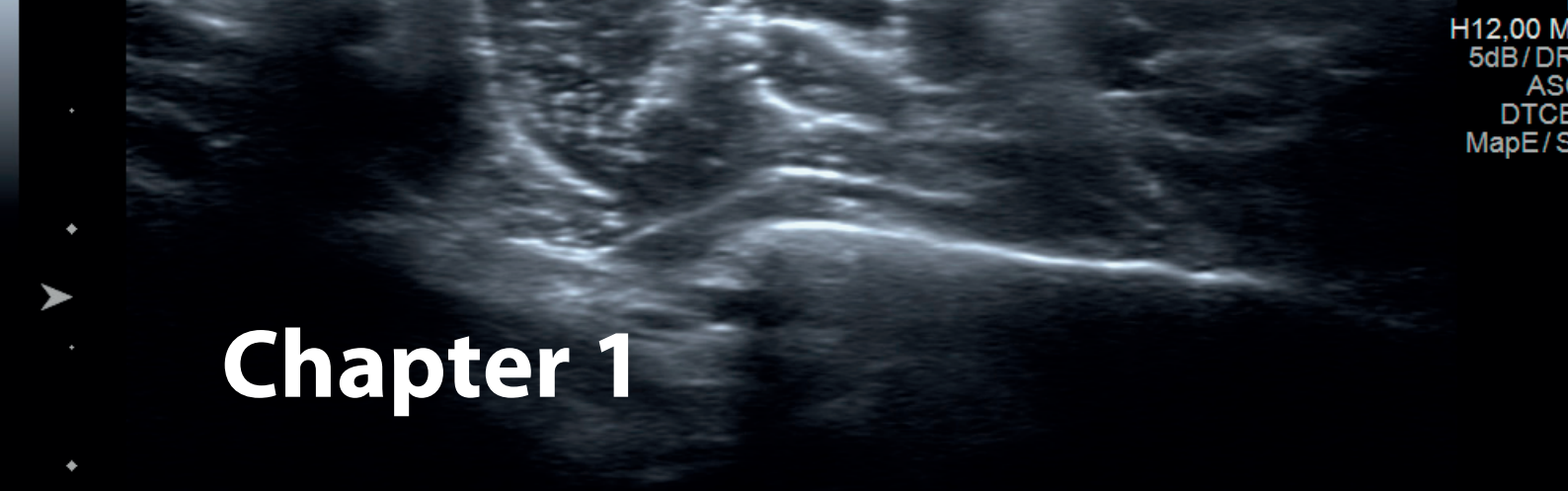
Prologue

In 2006 I realized that permanent fillers gave rise to much more problems than anticipated. Also I realized that in dealing with these problems, I should not make the same mistake that I and all other doctors did when we started using these permanent fillers. We worked without a solid scientific basis!

Yet, in 2006 patients had problems with filler and had to be helped. I was willing to accept this challenge. So, for the past thirteen years I have devoted much of my time in finding ways to improve the care for patients with filler problems. First, off course, I faced the problems of diagnosis and treatment. After introducing ILT, the ways to improve diagnostics became pressing. I dived further into ways ultrasound can improve our diagnostic and therapeutic accuracy. Finally I realized that we can use ultrasound also in prevention of problems with fillers.

Science in cosmetic medicine is still in its infancy. This partly because it is a relatively new area in medicine. But also because of the nature of its subjects, who are not willing to allow experiments with their exterior. This means that research in this field of medicine is largely exploratory, descriptive and theory-building.

This thesis relates the scientific journey that I made from 2006 onwards.



Chapter 1

General Introduction

Fillers

Cosmetic medicine is a continuously expanding field, including minimally invasive treatments with soft tissue fillers. According to the American Society of Aesthetic Plastic Surgery, over 1.4 million filler treatments were performed 2017[1], which is a 2,9% increase compared to 2016 and a 40,6% increase compared to 2012. In the Netherlands the estimated number of filler injection treatments performed in 2016 was almost 140.000[2].

There is a variety of fillers available [3]. To subdivide them, different categories of filler types are being proposed. The most common grouping is made in terms of biodegradable (moderate and long duration) versus non-biodegradable fillers [3,4,5] .

Non-biodegradable fillers do not resorb. They are injected in small amounts to fill in superficial wrinkles. They provoke a tight fibrotic reaction around the filler particles to keep them in place and to enhance the permanent result. Examples of these type of fillers are silicon oil (medical grade, a polymer of dimethylsiloxanes), polymethylmethacrylate (PMMA, Artecoll™) [6,7] , hydroxyethyl methacrylate (HEMA, Dermalive™), and dermapolymeren [8].
Thereafter, permanent hydrogel fillers such as polyalkylimide and polyacrylamides came on the market around 2000. They are meant to replace volume-loss and are injected in larger amounts subcutaneously. Formation of fibrosis around the material occurs, which should keep the filler in place [9].

Bio-degradable fillers are meant to break down in the body in a reasonable time. The first resorbable fillers were collagen based fillers. Their effect lasted only for a few months. To prevent hypersensitivity, skin testing was required [10]. Hyaluronic acid fillers were brought onto the market in 2003 and are the most commonly used fillers since then. Hyaluronic acid (HA) is a naturally occurring linear polysaccharide composed of repeating disaccharide units of N-acetylglucosamine and D-glucuronic acid. HA fillers are hydrophilic as they have the capacity to bind water [11]. They are resorbable but depending on particle size and cross-linking (mainly with butanediol diglycidyl,BDDE), the rate of degradation may vary from months up to one and a half or two years' time [12,13]. Hyaluronic acid fillers have the unique advantage of reversibility when injected with hyaluronidase [11, 14,15].
There are significant differences among the different HA fillers. These include HA concentrations, cross-link chemistry, quantity of cross-linkers, and amount of uncross-linked HA-all of which may play an important role in the behavior of these materials during and after injection [16].

Fillers with biodegradable particles that stimulate the body to produce its own collagen have a longer duration of effect; these type of fillers are also called bio-stimulatory products[3,4]. They consist of polyesters and stimulate fibroblast activity and collagen type 1 and 3 production, thereby thickening the dermis, and are then degraded and removed by hydrolysis, solubilization, and phagocytosis by macrophages [17]. The most commonly used are poly lactic acid, polycaprolactone and calcium hydroxyapatite [18]. On average they are being resorbed after 18 -24 months [58]. Chitosan, a linear polysaccharide, is currently under investigation for use as a dermal filler[19,20].

Fillers currently being used in the Netherlands are hyaluronic acid fillers and the so-called bio-stimulatory fillers such as poly lactic acid, polycaprolactone and calcium hydroxyl appetite. Outside Europe and the

United Stated, the fillers mentioned in Table 1 are still being used[21]. This should be kept in mind as this may lead to unexpected side effects.

Table 1. Fillers substances currently in use worldwide.

Filler substance	Bio-degradable	Brand names
hyaluronic acid	yes	e.g. Hylaform, Restylane, Juvederm, Teosyal, Stylage, Boletero, Princess, Perfectha, Matridur, Hyacorps, Hyamax, Surgiderm, Esthelis, Glytone, Prevelle Silk, Emervel, Visagel, Rofilan Hylan Gel, Hydrafill, Puragen, Macrolane
Collagen	yes	Zyderm, Zyplast, Cosmoderm, Isolagen, Evolance
poly-lactic acid	yes	New-Fill, Sculptra
calcium hydroxy apatite	yes	Radiesse
polycaprolactone	yes	Ellanse
polyvinyl alcohol	yes	Bio-in-blue
polyalkylimide	no	Bio-alcamid, Amazing Gel, Interfall, BeautiCal
polyacrylamide	no	Aquamid, Outline
dimethylsiloxane	no	Silikon 1000, SilSkin, PMS 350, Bioplastique
polymethyl methacrylate	no	Artecoll, Artefill, Metacrill
hydroxyethyl methacrylate	no	Dermalive, Dermadeep
dermapolymeren	no	unknown

Regulation of soft tissue fillers

Fillers are classified as medical devices by Regulatory Agencies (the Medical Devices Directives in Europe and the Food and Drug Administration in the US), as their primary intended action is mechanical ("filling effect") [4,22]. Medical devices are defined by the fact that they do not achieve their principal intended action in or on the human body by pharmacological, immunological or metabolic means. It is important to note that devices may be supported in their filling effect by these means.

In 1970, the Medical Devices Directive (MDD) was established. In the early years, supervision regarding the quality control of this Directive was lacking. As this gave rise to safety problems regarding pacemakers and artificial heart valves, the monitoring of safety and quality compliance was improved in 1993. However, the MDD is mainly based on the principle of “Good Manufacturing” instead of pre-market approval. One of the reasons for this is the fact that out of the more than 500.000 different medical devices, the largest part is of low risk, and safety and quality are warranted by a safe production process. A pre-market approval requires a lot of investments and is thought to slow down innovation[22,23].

Under the current system, Notified Bodies are responsible for reviewing CE Marking applications, and grant approval for products to be placed on the market in Europe. This notification process is limited, and requires only copies of labelling and approval certificates (CE and Declaration of Conformity)[22,23].

After marketing, manufacturers need to comply with post marketing surveillance regulations. It is the responsibility of the company how to obtain report data through post marketing surveillance. Reported side effects and recalls are not publicly disclosed. A competent management of post-marketing surveillance in reporting and monitoring of adverse events of fillers is still lacking, leading to a delay in the reporting and publishing of adverse events[23,24].

In 2005, dermal fillers were re-classified as class III (the highest class) in the EU Medical Device Directive[25]. In 2010, the MDD was reinforced with additional requirements, especially around the need to demonstrate clinical effectiveness. Clinical data for safety and effectiveness should be sourced from 1) clinical investigation(s) of the device concerned, 2) clinical investigations or other studies reported in the scientific literature of a similar device for which equivalence to the device in question can be demonstrated, 3) published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated. In general, in the case of fillers clinical investigations should be performed unless it is duly justified to rely on existing clinical data [24].

Despite the modifications in 2005, there is still a need to strengthen the assessment, registration and manufacturing quality of medical devices leading to better patient safety and outcomes [25]. In the Netherlands, the use of permanent fillers for cosmetic procedures was forbidden in 2015. A National Implant Registry for cosmetic implant medical devices (as with the hip, knee and ankle registries) was introduced in July 2017[26,27].
New European requirements will be implemented in the Netherlands by 26 May 2020. Products classified as high risk, including fillers, will need a stricter admissions procedure with enhancement of clinical evaluation [28]. The transparency and accountability for the management of post-marketing surveillance will be improved by a European Database on Medical Devices (Eudamed)[28].

In the United States, according to the Food and Drug Administration (FDA), fillers are also classified as medical devices. Approval standards for devices were established by Congress in the Medical Device Amendments of 1976. To obtain FDA approval, dermal fillers have gone through the controlled clinical testing for safety and effectiveness required for high-risk devices. Pre-market testing is carried out on an average of 120 patients, and many products are also subject to long-term safety studies after marketing. In addition, the FDA maintains a publicly available database of all reported side effects and recalls. Dermal fillers are approved for use in the US only by prescription. There are currently 10 dermal fillers on the market in the US, compared to approximately 160 EU approved fillers[29].

The minimal requirements in the EU for clinical efficacy and safety has given rise to unforeseen complications caused by fillers. The lack of an adequate post marketing surveillance system has led to a delay in identifying these complications. This has caused a substantial number of patients to suffer serious complications from EU-approved dermal fillers. A survey conducted by the British Association of Aesthetic Plastic Surgeons (BAAPS) reported 38,5% of plastic surgeons in the UK seeing patients in that

year who had experienced complications with a permanent facial filler and 23% of plastic surgeons reported having patients in that year who required surgery to correct the complications caused by permanent fillers [30,31]. Due to severe adverse events, in the Netherlands, the Inspection of Health forbid the use of polyalkylimide hydrogels in 2007 and the use of a heavily cross-linked hyaluronic acid filler in 2012. Since 2015, the use of permanent fillers for cosmetic treatments is forbidden in the Netherlands[32,33,34].

Complications

All dermal fillers have a potential risk of complications. These complications may be due to a product - host interaction or caused by a wrong injection technique[4,18].

Product - host interaction

Known adverse events due to the product - host interaction are allergic reactions, the formation of foreign body granulomas and other types inflammatory responses such as abscesses or panniculitis [35].

An allergic reaction is an early onset reaction. In literature, these type I hypersensitivity reactions have been reported in hyaluronic acid fillers and collagen- based products. The onset of reaction occurs within minutes or hours after injection due to an immunoglobulin E (IgE)-mediated immune response to the dermal filler[14]. This may manifest as erythema of any degree, induration, tenderness, or swelling with or without pruritus, but after initial or repeated exposure, angioedema or anaphylactic reactions may occur [36]. For collagen based fillers, to prevent hypersensitivity, skin testing is required. To date, approximately 3.0% of the patients tested have had a hypersensitivity reaction at implantation sites [8]. For hyaluronic acid based fillers (HA) skin testing is not necessary. In literature, a percentage of 0,8% is reported[14].

Late onset adverse events associated with dermal fillers may manifest from weeks to many months, even years, after an injection of a dermal filler[18,21]. Clinically these present as nodules with or without apparent inflammatory reactions (figures 1-3), or as abscesses (figure 4).
Subcutaneously injected materials will always trigger the host's innate immune system, resulting in a (normal) foreign body reaction. This reaction consists of protein adsorption on the implant surface, inflammatory cell infiltration, macrophage fusion into foreign body giant cells, fibroblast activation and ultimately, if phagocytose will fail, fibrous encapsulation[37]. The foreign body reaction is a complex phenomenon and is not yet fully understood [38]. It is described that macrophages and foreign body giant cells may persist for the lifetime of the implant. With biocompatible materials, the composition of the foreign body reaction in the implant site may be controlled by the surface properties of the biomaterial, the form and the volume of the implant [39, 40] .

Over time, due to the degradation process or the chemical characteristics of the product, late onset adverse events associated with dermal fillers may appear. The proposed hypothesis of foreign body granulomas involves the host's immune response to the amount, impurities or irregularities of the injected material [37]. This systemic reaction may be caused due to the resistance of the enzymatic breakdown or phagocytosis of filler material [41]. The engulfed material remains sequestered in a capsule

of monocytes and macrophages, leading to the secretion of cytokines and inflammatory products to attract more macrophages [42]. These macrophages eventually fuse to form multinucleated foreign body giant cells, characteristic of granulomas. As it is a systemic process, typically all injected sites at the time are involved [43]. Systemic granulomatous reactions are rather mediated by T-lymphocytes rather than humoral antibodies. Previously reported incidences of granulomatous reactions were in the range 0.02–2.8% [15,43,44,] whereas granulomatous reactions are more frequent after treatment with permanent filler materials [45].

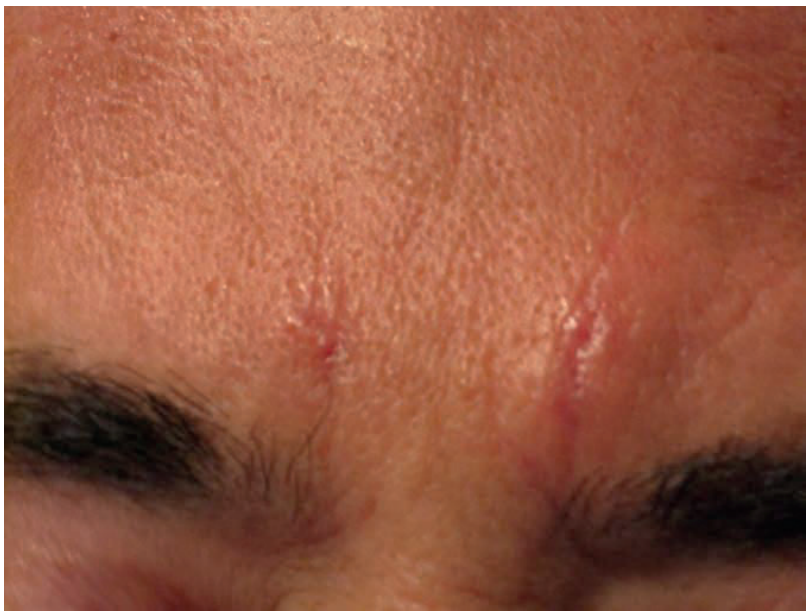


Figure 1. Filler complication. A string of nodules is apparent along the frown lines.

In recent years, as an alternative hypothesis, biofilms have been proposed to play a role in the formation and progression of foreign body reactions [46]. Filler implants can be infected by injection of skin flora directly into the material during the procedure, or they can be seeded with bacteria through contiguous direct extension or hematological spread [47,48]. Biofilms are heterogeneous structures that comprise bacteria embedded within a strong extracellular matrix of secreted polysaccharides including hyaluronic acid .[6] They function as self-maintaining organisms that grow, respond to stimuli, and maintain a resistant homeostatic environment. Biofilms can present clinically as erythematous granulomas but can also lead to localized pyogenic infections, presenting as deep abscesses or cellulitis [49,50] (figure xx) Histologic examination is preferably performed to examine the nature of the implanted material, characteristics of the inflammatory response, and even the bacterial species. The absence of bacteria does not, however, preclude the possibility of a bio film formation. Although there are publications in favor of a bio film proving the contamination of filler material with bacteria, some other publications disagree with these findings. Whether the focus of chronic inflammation is a response to either a foreign body or a collection of chronic bacteria has to be established [3, 40, 47,50,51,52].

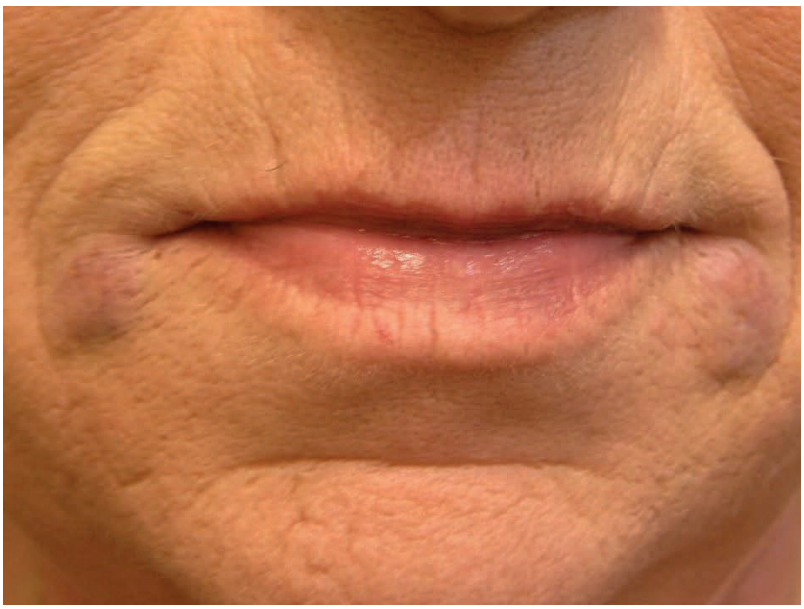


Figure 2. Filler complication. Two elastic nodes at both corners of the mouth. No signs of inflammation are present.

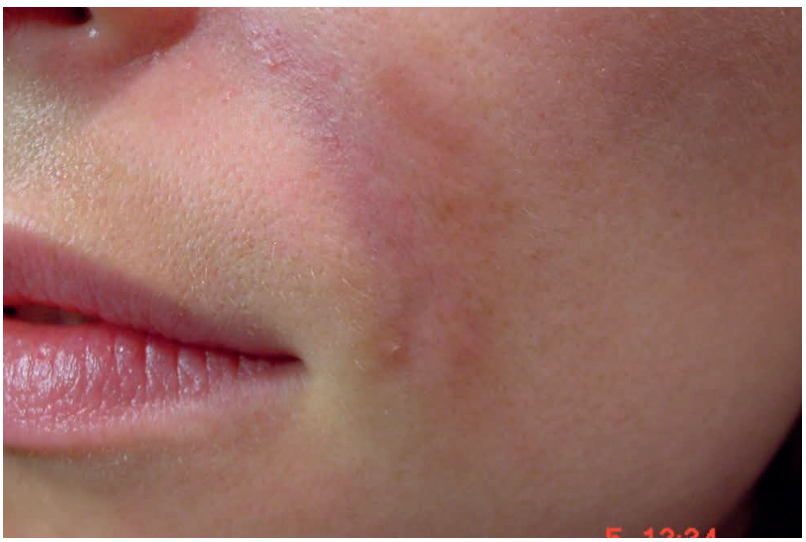


Figure 3. Filler complication. Inflammatory reaction expressed as erythema with a purplish hue. Also palpable subcutaneous nodules were present.

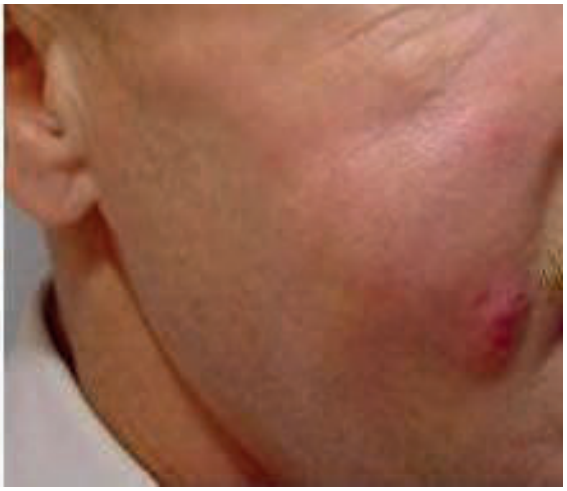


Figure 4. Filler complication. An inflamed area on the right cheek with edema, erythema and medio-caudally formation of an abscess.

Technique dependent complications

An incorrect injection technique may lead to adverse events such as overcorrection (figure 5), accumulation of the filler (nodules), dislocation of the filler[53] (figure 6), edema especially in the malar region and vascular adverse events [17,43,54].

Prevention to avoid these complications is of utmost importance [18]. Knowledge of facial anatomy is one of the key points but one has to remember that induvidual variations do exist. Adequate injection technique (slow injections, never too much pressure) and the use of safe materials such as cannulas is also recommended [17].

Non-inflammatory nodules may appear caused by improper technique and placement of the filler [4,15, 55]. This can result from injecting too superficially or injecting large volumes in one location without paying attention to the dynamics of the underlying muscles, leading to accumulation or dislocation of the filler material. The so called Tyndall effect, a bluish discoloration, may appear if hyaluronic acid fillers are injected too superficially into the skin. The filler is a clear gel so when light reflects through the skin, a bluish appearance may be visible [44].

Malar edema is a chronic form of edema, reported with filler injections in the infraorbital hollow in the lid/cheek junction area [17] .This reaction arises as a consequence of direct pressure of fillers on the lymphatics and the patient's pre-existing compromised lymphatic drainage in the suborbicularis oculi fat. Malar edema can last from days to months, or be permanent and is often refractory to treatment. This reaction can be prevented by using filler material that is less viscous, and by placing a small volume of filler material deep into the malar septum (pre-periosteal level) to avoid severing the ligament which may provoke edema. This technique requires expertise and a great knowledge of the local anatomy [17].

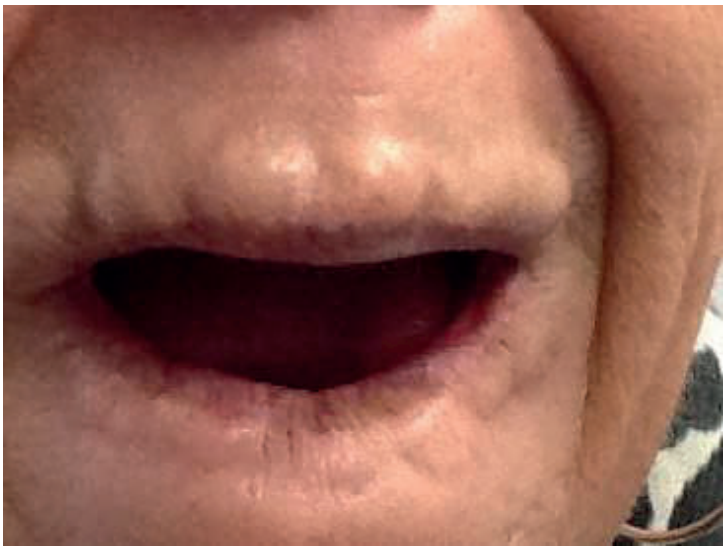


Figure 5. Filler complication. Numerous nodules in the upper and lower lip are the result of overcorrection.

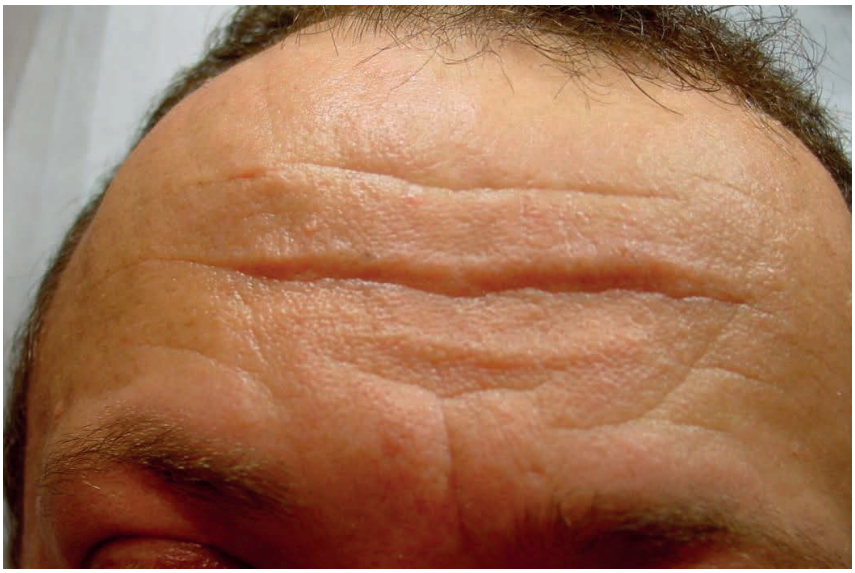


Figure 6. Filler complication. A horizontal thickening is observed right above a deep mimical forehead line. This complication results from dislocation of the filler product due to muscular activity.

Vascular adverse events may happen if material is injected into or compromising a vessel. It has been suggested that the minor signs of vascular compression may be misinterpreted as injection related

bruising, pain and swelling [56]. In its most serious form, intravascular injection or vascular compression of filler material can lead to skin necrosis or, in rare cases, blindness [57]. The underlying mechanism is thought to be related to high pressure intra-arterial injection, whereby the filler material is injected proximal to the origin of the retinal artery[55]. Subsequent release of the pressure causes embolism of the filler material into the central retinal artery or retrograde movement of filler material through collateral arteries into the retinal arteries, blocking blood supply to the retina [58]. In the Netherlands, the first patient left with irreversible blindness of one eye after a filler treatment was reported in September 2016 [59].

Current treatment options

In general, two treatment regimens to treat filler complications are advised: medication (local or systemic) [3,47,61] or surgical removal of the material [7, 38]. An overview of these options is given in table 2.

Medication can be useful to suppress the adverse immune response towards the filler material but do not remove the filler itself. Allergic reactions can be treated with a course of oral anti-histamine. In severe episodes or cases of anti-histamine resistant cases, a short course of oral corticosteroid can be used[14,36]. In the rare case of an anaphylactic reaction, an emergency kit containing epinephrine pens should be available in the treatment room.

Glucocorticoids have been used extensively to prevent the foreign body reaction due to their efficacy and wide spectrum of activities as they target neutrophils, macrophages, mast cells, lymphocytes and fibroblasts [46]. Granulomas may be treated at first with high concentrations of intralesional steroids in the nodules (20 to 40 mg/ml) at a 2- to 4 weeks interval [5, 14,42, 63]. Skin depressions and pigmentary changes may occur and the patient has to be aware of this side effect, which can be leveled temporarily with collagen or hyaluronic acid fillers. Intralesional 5-fluorouracil (5FU) injection is advised as well. 5FU is supposed to have an apoptotic effect on the inflammatory cells making up the infiltrate [14, 64]. However, recurrence after intralesional injections is common. Systemic granulomatous reactions are often difficult to treat and often requires systemic corticosteroids treatment with or without removal of the filler if possible[65].

For other Inflammatory adverse events, the main treatment advice is to use antibiotics [13], preferably from the macrolide group 1, as these will treat bacterial inflammatory reactions and suppress foreign body responses by up-regulating the production of anti-inflammatory mediators[66,67]. In addition, based on this same two-fold principle, minocycline may be used in less severe inflammatory adverse events. After the inflammatory response has disappeared, removal of the filler material may be considered.

In case of technique dependent complications, removal of the filler material is the best treatment option. Hyaluronic acid fillers come with the advantage of being dissolvable with hyaluronidase [13,15]. For all other fillers, surgical excision may remove (parts of) the material but often with tissue damage and scarring as a cosmetically undesirable result [68]. Skin testing is recommended in the use of non-recombinant animal-sourced hyaluronidase to avoid hypersensitivity reactions [18,44].

As soon as any signs of vascular compromise are observed, filler injections should be stopped immediately [57]. The cardinal signs of vascular occlusion are pain and acute changes of skin color. Blanching or pallor of skin tends to suggest an arterial occlusion, whereas red/bluish discoloration is more indicative of venous congestion [13]. Recommendations for treating HA filler-induced vascular adverse events are to inject hyaluronidase in a high dose up to 1500 units. Hyaluronidase treatment should be considered regardless of the fillers used as it can potentially reduce tissue edema and vessel-occluding pressure. Further treatment suggestions are to massage vigorously, apply warm compresses and topical nitroglycerin paste and start oral aspirin [57,58,59,60,69]. In the event of impending retinal ischemia, it is advised to inject hyaluronidase also in the retrobulbar area [56,58]. Despite several published guidelines and recommendation, skin necrosis due to a vascular adverse event will often leave the patient with scarred tissue. The outcome of retinal ischemia is even worse; out of 98 documented cases, vision was restored in only 2 patients [57,60].

Table 2. Adverse events and their treatment options

Adverse event	**Prevention**	**Treatment options**
Allergic reaction	Skin testing	Systemic: antihistamine / steroids In case of HA*: intralesional hyaluronidase
Malar edema	Respect contra-indication: edema present in particular peri-ocular	Manual lymphatic compression In case of HA*: intralesional hyaluronidase
Non-infectious inflammatory response	Respect contra-indications: auto-immune disease, active herpes or viral infection.	Intralesional: steroids / 5FU** Systemic: steroids / minocycline Remove filler if possible
Infectious inflammatory response	Respect contra-indication: active current bacterial or viral infection. Sterile skin preparation	Systemic: antibiotics, macrolide Remove filler if possible, after inflammation is subsided
Dislocation	Correct injection technique	Remove filler if possible
Non-inflamed nodules	Correct injection technique	Remove filler if possible
Vascular adverse event: necrosis	Know your anatomy, avoid large bolus, use a cannula instead of a needle, inject slowly with minimal pressure	In case of HA*: intralesional hyaluronidase For others fillers: remove filler if possible
Vascular adverse event: visions loss	Know your anatomy, avoid large bolus, use a cannula instead of a needle, inject slowly with minimal pressure	Massage, hyaluronidase high dose retrobulbar and at the site (also for non-HA*), nitroglycerine paste, warm compresses, oral aspirin, refer to ophthalmologist

*HA = hyaluronic acid fillers ** 5-Fluorouracil

Aims of this thesis

The Department of Dermatology of the Erasmus Medical Center Rotterdam is the sole referral center for dermal filler complications in the Netherlands. Since 2009 there is a specialized outpatient clinic. The general aim of this thesis is to gain more knowledge about the diagnosis and treatment options of the different filler complications that are referred here.

In Chapter 2 we report the different complications of a polyaklylimide hydrogel filler. This filler was supposed to be safe when brought into the market but gave rise to severe complications years after usage.

In Chapter 3 we examine the extruded polyalkylimide hydrogel histologically, as well as the type of immune response and the change of filler substance over time. When we were able to remove this products after years of being in vivo, the most striking observations was its change in color. At the time of injection the polyalkylimide gel was transparent. When taken out, it was white or yellowish, anything but transparent. Our hypothesis was that this would be a result of a foreign body reaction and that the initial bio-compatibility was compromised.

Chapter 4 focuses on the efficacy of a new treatment modality, the intralesional laser therapy (ILT), invented by the plastic surgeon Daniel Cassutto. Formerly, patients with problems of permanent filler had to be treated by excision of the material. In a retrospective study we investigated the results of ILT in our patient group from 2011-2016. Our hypothesis was that ILT is a viable initial treatment before surgery should be considered.

In Chapters 5.1 – 5.4 we evaluate the use of ultrasound imaging as a diagnostic tool for filler detection and as an improvement in the treatment of filler complications. For many dermatologists ultrasound imaging is an almost daily used part of their practice for diagnosis and treatment of venous problems. In our center for dermal filler complications we have used this modality since the start in 2011. In an effort to relate our findings to colleagues via scientific journals, we detected that a uniform terminology was lacking. Therefore, a nomenclature for sonographic description of filler images is being developed and proposed in 5.4.

References

1. American Society for Aesthetic Plastic Surgery (ASAPS). 2016 Cosmetic Surgery National Data Bank Statistics. Available at: https://www.surgery.org/sites/default/files/ASAPS-Stats2017.pdf
2. Decates T, de Wijs L, Nijsten T, Velthuis P. Numbers on injectable treatments in the Netherlands in 2016.J Eur Acad Dermatol Venereol. 2018 2018 Aug;32(8):e328-e330
3. Vanaman M, Fabi SG, Carruthers J. Complications in the Cosmetic Dermatology Patient: A Review and Our Experience (Part 1).Dermatol Surg. 2016 Jan;42(1):1-11.
4. Zielke H, Wölber L, Wiest L, Rzany B. Risk profiles of different injectable fillers: results from the Injectable Filler Safety Study (IFS Study). Dermatol Surg. 2008 Mar;34(3):326-35; discussion 335.
5. Colombo G, Caregnato P. Stifanese R, Ferrando G. Destructive granulomatous reaction to polyacrylamide lip Injection: Solution for a complex case. Aesth Plast Surg (2011) 35:662–665
6. Uchida Y, Yoshii N, Kubo H, et al. Facial paraffinoma after cosmetic paraffin injection. J Dermatol 2007;34:798–800
7. Ferneini EM, Hapelas S, BS, Watras J. Ferneini AM, Weyman D, Fewins J. Surgeon's Guide to Facial Soft Tissue Filler Injections: Relevant Anatomy and Safety Considerations.. J Oral Maxillofac Surg 75:2667.e1-2667.e5, 2017
8. Lowe NJ, Maxwell CA, Lowe P, Duick MG, Shah K. Hyaluronic acid skin fillers: adverse reactions and skin testing. J Am Acad Dermatol. 2001 Dec;45(6):930-3.
9. Andre P, Lowe NJ, Parc A. Adverse reactions to dermal fillers: a review of European experiences. J Cosmet Laser Ther 2005;7:171–176
10. Cockerham K1, Hsu VJ . Collagen-based dermal fillers: past, present, future. Facial Plast Surg. 2009 May;25(2):106-13.
11. Kim JE, Sykes JM. Hyaluronic acid fillers: history and overview. Facial Plast Surg. 2011 Dec;27(6):523-8.
12. Rayess HM, Svider PF, Hanba C, Patel VS, DeJoseph LM, Carron M, Zuliani GF. A Cross-sectional Analysis of Adverse Events and Litigation for Injectable Fillers. JAMA Facial Plast Surg. 2018;20(3):207-214
13. Herrmann JL Hoffmann RK, Ward CE, Schulman JM, Grekin RC. Biochemistry, Physiology, and Tissue Interactions of Contemporary Biodegradable Injectable Dermal Fillers. Dermatol Surg 2018;0:1–13
14. Beleznay K1, Carruthers JD, Carruthers A, Mummert ME, Humphrey S. Delayed-onset nodules secondary to a smooth cohesive 20 mg/mL hyaluronic acid filler: cause and management. Dermatol Surg. 2015 Aug;41(8):929-39.
15. Rzany B, Becker-Wegerich P, Bachmann F et al. Hyaluronidase in the correction of hyaluronic acid-based fillers: a review and a recommendation for use. J Cosmet Dermatol 2009; 8: 317–3.
16. San Miguel Moragas J, Reddy RR, Alfaro FH, Mommaerts MJ. Systematic review of “filling” procedures for lip augmentation regarding types of material, outcomes and complications, Journal of Cranio-Maxillo-Facial Surgery 43 (2015) 883e906

17. Funt DK. Avoiding Malar Edema During Midface/Cheek Augmentation with Dermal Fillers. J Clin Aesthet Dermatol. 2011 Dec; 4(12): 32–36.
18. Lemperle G, Rullan PP, Gauthier-Hazan N. Avoiding and treating dermal filler complications. Plast Reconstr Surg. 2006 Sep;118(3 Suppl):92S-107S.
19. Halimi C, Montembault A, Guerry A, Delair T, Viguier E, Fulchiron R, David L. Chitosan solutions as injectable systems for dermal filler applications: Rheological characterization and biological evidence. Eng Med Biol Soc. 2015;2015:2596-9.
20. Ji DY, Kuo TF, Wu HD, Yang JC, Lee SY. A novel injectable chitosan/polyglutamate polyelectrolyte complex hydrogel with hydroxyapatite for soft-tissue augmentation. Carbohydr Polym. 2012 Aug 1;89(4):1123-30.
21. G. Lemperle, N. Gauthier-Hazan. Foreign body granulomas after all injectable dermal fillers: part 2. Treatment options Plast Reconstr Surg, 123 (2009), pp. 1864-1873
22. COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning medical devices. EUR-Lex Access to European Union law
23. Wetgeving medische hulpmiddelen: een stand van zaken. Sluijters B, Frank S. Tijdschrift voor Gezondheidsrecht (2001) 25:57–66
24. European Commission DG Health & Consumers Directorate B -Consumer Affairs Unit B2 – Health technology and Cosmetics MEDICAL DEVICES: Guidance document MEDDEV 2.5/10 January 2012 Guideline for authorized representatives
25. Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007. Official Journal of the European Union
26. Ministerie van Volksgezondheid, Welzijn en Sport. Handreiking medische hulpmiddelen. 12-12-2017
27. Verordening 2017/745 van het Europees Parlement en de Raad van 5 april 2017 betreffende medische hulpmiddelen, tot wijziging van Richtlijn 2001/83/EG, Verordening (EG) nr. 178/2002 en Verordening (EG) nr. 1223/2009, en tot intrekking van Richtlijnen 90/385/EEG en 93/42/EEG van de Raad. Publicatieblad van de Europese Unie
28. Ministerie van Volksgezondheid, Welzijn en Sport. Verdiepende sessie Klinisch onderzoek MHM. Opbrengsten en actiepunten. Woensdag 14 februari 2018
29. U.S. Department of Health and Human Services. U.S. Food and Drug Administration. Unsafe and Ineffective Devices Approved in the EU that were Not Approved in the US. May 2012
30. BAAPS, 1 in 4 surgeons fixing botched permanent filler ops, British Association of Aesthetic Plastic Surgeons Offers Safety Guidelines for Injectables (June 2009), available online at http://www.baaps.org.uk/about-us/press-releases/491-1-in-4-surgeonsfixing-botched-permanent-filler-ops.
31. BAAPS, Surgeons' demands published in British Medical Journal: Fillers Less Regulated than Tattooing and Acupuncture - Call to Make Them Prescription (July 2009), available online at http://www.baaps.org.uk/about-us/press-releases/498-surgeons-demandspublished-in-british-medical-journal
32. Geertsma RE, de Bruijn ACP, van Drongelen AW, Hollestelle ML, de Jong WH et all. Mate van voorkomen en ernst van complicaties bij het gebruik van permanente vullers bij rimpelbehandelingen. RIVM-briefrapport 078/2006 VGC/AH/RG/ccc

33. Inspectie Gezondheidszorg en Jeugd. Ministerie van Volksgezondheid, Welzijn en Sport. Inspectie voor de Gezondheidszorg waarschuwt voor rimpelvulmiddelen. 18 Mei 2006
34. Inspectie Gezondheidszorg en Jeugd. Ministerie van Volksgezondheid, Welzijn en Sport. Meer producten van fabrikant van Hyacorp filler verboden. Nieuwsbericht 19-04-2016.
35. Urdiales-Galvez F, Delgado NE, Figueiredo V, Lajo-Plaza JV, Mira M et all. Treatment of Soft Tissue Filler Complications: Expert Consensus Recommendations. Aesth Plast Surg (2018) 42:498–510
36. Bhojani-Lynch T. Late-Onset Inflammatory Response to Hyaluronic Acid Dermal Fillers. Plast Reconstr Surg Glob Open. 2017 Dec; 5(12): e1532.
37. Nicolau PJ. Long-lasting and permanent fillers: biomaterial influence over host tissue response. Plast Reconstr Surg 2007;119:2271–86
38. Lemperle G, Gauthier-Hazan N. Foreign body granulomas after all injectable dermal fillers: part 1. Possible causes. Plast Reconstr Surg, 123 (2009), pp. 1842-1863
39. Alijotas-Reig J, Fernández-Figueras, MT, Puig L. Inflammatory, immune-mediated adverse reactions related to soft tissue dermal fillers. Sem Arth Rheum 43(2013)241–258
40. J.M. Anderson, A. Rodriguez, D.T. Chang, Foreign body reaction to biomaterials. Semin. Immunol. 20 (2) (2008 Apr) 86-100.
41. Mukta Sachdev, YN Anantheswar, BC Ashok, Sunaina Hameed, and Sanjay A Pai. Facial Granulomas Secondary to Injection of Semi-Permanent Cosmetic Dermal Filler Containing Acrylic Hydrogel Particles J Cutan Aesthet Surg. 2010 Sep-Dec; 3(3): 162–166.
42. Kadouch JA, Vos W, Nijhuis EWP, Hoekzema R. A Granulomatous Foreign-Body Reactions to Permanent Fillers: Detection of CD123+ Plasmacytoid Dendritic Cells. J Dermatopathol 2015;37:107–114
43. Chiang YZ, Pierone G, Al-Niaimi F. Dermal fillers: pathophysiology, prevention and treatment of complications. J Eur Acad Dermatol Venereol. 2017 Mar;31(3):405-413
44. Alijotas-Reig J, Garcia-Gimenez V. Delayed immune-mediated adverse effects related to hyaluronic acid and acrylic hydrogel dermal fillers: clinical findings, longterm follow-up and review of the literature. JEADV, 2008;22:, 150–161
45. Sáncheza O, Rodríguez-Suredaa V, Domíngueza C, Fernández-Figuerasc T, Vilchesa A, Llurbaa E, Alijotas-Reiga J. Study of biomaterial-induced macrophage activation, cell-mediated immune response and molecular oxidative damage in patients with dermal bioimplants. Immunobiology 217 (2012) 44– 53
46. Lemperle G, Nicolau P, Scheiermann N. Is there any evidence for biofilms in dermal fillers? Plast Reconstr Surg. 2011 Aug;128(2):84e-85e.
47. Ibrahim O, Overman J, Arndt KA, Dover JS. Filler Nodules: Inflammatory or Infectious? A Review of Biofilms and Their Implications on Clinical Practice. Dermatol Surg. 2018 Jan;44(1):53-60.
48. Beer K, Avelar R. Relationship between delayed reactions to dermal fillers and biofilms: facts and considerations. Dermatol Surg 2014;40:1175–9.
49. Rohrich RJ, Monheit G, Nguyen AT, Brown SA, et al. Soft-tissue filler complications: the important role of biofilms. Plast Reconstr Surg 2010;125:1250–6.
50. Saththianathan M, Johani K, Taylor A, et al. The role of bacterial biofilm in adverse soft-tissue filler reactions: A combined laboratory and clinical study. Plast Reconstr Surg.2017;139:613–621.

51. Morais JM, Papadimitrakopoulos F, Burgess DJ. Biomaterials/Tissue Interactions: Possible Solutions to Overcome Foreign Body Response. AAPS J. 2010 Jun; 12(2): 188–196.
52. Wang Y, Guan A, Isayeva I, Vorvolakos K,et all. Interactions of Staphylococcus aureus with ultrasoft hydrogel biomaterials. Biomaterials 95 (2016) 74-85
53. Jordan DR, Stoica B. Filler Migration: A Number of Mechanisms to Consider. Ophthal Plast Reconstr Surg 2015;31:257–262
54. Funt D, Pavicic T. Dermal fillers in aesthetics: an overview of adverse events and treatment approaches. Clin Cosmet Investig Dermatol. 2013 Dec 12;6:295-316.
55. Alshaer Z, Alsaadi Y, Mrad MA. Successful Management of Infected Facial Filler with Brucella. Aesthetic Plast Surg. 2018 Jun 11.
56. Rayess HM, Svider PF, Hanba C, Patel VS, DeJoseph LM, Carron M, Zuliani GF. A Cross-sectional Analysis of Adverse Events and Litigation for Injectable Fillers. JAMA Facial Plast Surg. 2018;20(3):207-214
57. Cavallini M, Gazzola R, Metalla M, Vaienti L. The role of hyaluronidase in the treatment of complications from hyaluronic acid dermal fillers. Aesthet Surg J. 2013 Nov 1;33(8):1167-74
58. DeLorenzi C. New High Dose Pulsed Hyaluronidase Protocol for Hyaluronic Acid Filler Vascular Adverse Events. Aesthet Surg J. 2017 Mar 17; 1-12
59. Schelke L, Fick M, van Rijn LJ, Decates T, Velthuis P, Niessen F. Permanent eenzijdig visusverlies na een cosmetische filler behandeling van de rug (Case report). Ned Tijdschr Geneeskd. 2017;161:D1246.
60. Beleznay 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
61. Dastoor SF, Misch CE, Wang H-L. Dermal fillers for facial soft tissue augmentation. J Oral Implantol 2007;33:191–204
62. Wolfram D., Tzankov A., Piza-Katzer H. Surgery for Foreign Body Reactions due to Injectable Fillers. Dermatology. 2006;213(4):300-4.
63. Souza TAB, Colomé LM, Bender EA, Lemperle G. Brazilian Consensus Recommendation on the Use of Polymethylmethacrylate Filler in Facial and Corporal Aesthetics. Aesthetic Plast Surg. 2018 Jun 5. doi: 10.1007/s00266-018-1167-1.
64. Wiest LG, Stolz W, Schroeder JA. Electron Microscopic Documentation of Late Changes in Permanent Fillers and Clinical Management of Granulomas in Affected Patients. Dermatol Surg 2009;35:1681–1688
65. Graivier MH, Bass LM, Lorenc ZP, Fitzgerald R, Goldberg DJ, Lemperle G. Differentiating Nonpermanent Injectable Fillers: Prevention and Treatment of Filler Complications. Aesthet Surg J. 2018 Apr 6;38(suppl_1):S29-S40
66. Ming Zeng A, Zhi-Yong L., Ma J, Cao P.P, Wang H., Cui Y.H., Liu Z. Clarithromycin and dexamethasone show similar anti-inflammatory effects on distinct phenotypic chronic rhinosinusitis: an explant model study. BMC Immunology (2015) 16:37
67. Nozoe K, Aida Y, Fukuda T, Sanui T, Nishimura F. Mechanisms of the Macrolide-Induced Inhibition of Superoxide Generation by Neutrophils. Inflammation, Vol. 39, No. 3, June 2016: 1039-1046

68. Cassuto D, Pignatti M, Pacchioni L, Boscaini G, Spaggiari A, De Santis G. Management of complications caused by permanent fillers in the face: A treatment algorithm. Plast Reconstr Surg. 138: 215e, 2016
69. Coleman SR. Avoidance of arterial occlusion from injection of soft tissue fillers. Aesthet Surg J. 2002;22:555–557

Chapter 2

Complications after Treatment with Polyalkylimide

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Complications after Treatment with Polyalkylimide

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BACKGROUND Polyalkylimide is a nonresorbable, biocompatible polymeric filler that has been used for several years to treat soft tissue deficits. The literature has shown a minor complication rate. We noticed that complications typically appear several years after injection.

OBJECTIVE To evaluate the complications reported after treatment with polyalkylimide.

METHODS AND MATERIALS We describe a retrospective evaluation, reported by members and candidate members of the Dutch Society of Cosmetic Medicine, of complications after use of polyalkylimide.

RESULTS In total, 3,196 patients were treated, and 4,738 treatments were performed, from which 154 complications (patient complication rate 4.8%, treatment complication rate 3.3%) were reported. The most common complication was inflammation; other complications were hardening, migration, and accumulation of the product. In some patients, skin biopsy followed by histologic examination was performed.

CONCLUSION Treatments with polyalkylimide have been reported to give rise to complications years after treatment. Even though the study described is a retrospective evaluation, we consider an overall complication rate of 4.8%, the severity of the complications, and the difficulty in treating them too high a risk for a cosmetic treatment. The Dutch Society of Cosmetic Medicine advises against the use of polyalkylimide.

The Dutch Society of Cosmetic Medicine is a society of physicians working in the cosmetic field. One of the principles of the Society is that registration of complications from fillers may lead to better physician performance and greater safety for patients, especially because European and Dutch legislation do not require long-term studies or follow-up for fillers to be registered and brought on the market.

Polyalkylimide gel is a nonresorbable, biocompatible polymeric gel that has been used for several years to treat soft tissue deficits.[1] It consists of 96% apyrogenic water and 4% polyalkylimide. The compound has a reticulated structure that resembles the adipose tissue in which it is commonly implanted; it has a pH of 7 and an oxidative value of almost 0.[2] Polyalkylimide can be injected under the skin for soft tissue replacement. Polyalkylimide is described as an endoprosthesis; after implantation, a thin membrane of 0.02 mm of collagen is formed around the material, connecting it to the surrounding tissue and keeping the material together. Even a long time after implantation, the gel can be removed by puncturing the membrane and squeezing the gel out. In early publications and data, polyalkylimide is described as a safe filler. Possible complications mentioned are an infection rate of 0.06%.

In The Netherlands, starting from 2001, polyalkylimide has been used for cosmetic treatments. As complications after treatment with polyalkylimide have been reported more often,[3,4] members and candidate members of the Dutch Society of Cosmetic

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Medicine were asked to evaluate all of the complications after treatment with polyalkylimide.

The aim of this study was to investigate the relative risk of complications with treatment with polyalkylimide for cosmetic reasons.

Materials and Methods

We describe a retrospective study of the complications reported after facial treatment with polyalkylimide between October 2001 and March 2007. A questionnaire was sent to 40 physicians, all members of the Dutch Society of Cosmetic Medicine. They were asked for data including total number of patients treated, total number of treatments performed, and total number of complications. They were also asked to specify complications: inflammation (and if available cause of inflammation), hardening of the capsule (autoimmune disease, micro-inflammation), migration (area of migration), accumulation of the material (area), or any other.

A subgroup consisted of lipodystrophy in patients with human immunodeficiency virus (HIV).

Results

Forty questionnaires were sent; 20 (50%) were returned. The number of patients treated varied between 0 and 1,051, with an average of 320. The number of treatments varied between 0 and 1,051 with an average number of 474 treatments. In total, 154 complications were reported, with an average of 15 per physician. A total number of 3,196 patients received 4,738 treatments, and 4.8% of the patients developed a complication (Table 1).

TABLE 1. Complications in 3,196 Patients and 4,738 Polyalkylimide Treatments

Complications	*Amount* n	*Patients* %	*Treatments* %
Total	154	4.8	3.3
Inflammation	63	2.0	1.3
Accumulation	31	1.0	0.7
Hardening of the capsule	31	1.0	0.7
Migration	21	0.7	0.4
Other	8	0.3	0.2

Inflammation

The most common complication reported was inflammation (2.0%). Most were not directly related to the injection procedure and did not occur within days or weeks after the treatment, but years later, mainly after surgical facial procedures in the face, such as dental procedures or infections in the head and neck region (Figure 1).

Accumulation of the Product

The complication rate of accumulation of the product was 1.0%. This typically occurs years after treatment.

Hardening of the Capsule

Hardening of the capsule was seen in 1.0% of the patients; this is generally a visible and disturbing disfigurement for patients.

Migration

In 0.7% of the patients, migration was reported, and it occurred mainly in the cheek area and the marionette lines. In some case, the material was injected

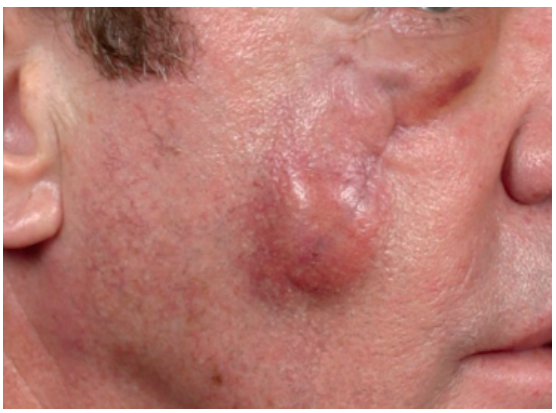

Figure 1. Complication (infection) of polyalkylimide.

TABLE 2. Complications in 270 Patients with Human Immunodeficiency Virus Treated with Polyalkylimide

Complications	*Amount,* n	*Patients, %*
Total	17	6.3
Inflammation	9	3.3
Accumulation	4	1.5
Hardening of the capsule	1	0.4
Migration	3	1.1

in the lower cheek and corners of the mouth and migrated as far as the lower eyelid and tear trough.

Subgroup of Lipodystrophy

Polyalkylimide is used to treat medication-induced lipodystrophy in patients with HIV. In The Netherlands, polyalkylimide used to be the first choice of treatment because of its characteristics of permanency and use for large-volume deficits and patient costs. Complications reported in this patient group showed a higher incidence of inflammation (Table 2) and less hardening of the product.

Histology

Biopsies taken from lesions that developed at polyalkylimide injection sites showed a mild chronic, granulomatous inflammatory reaction with some histiocytes surrounding the material. There was little or no acute inflammation, but some of the biopsies showed fibrosis (Figure 2).

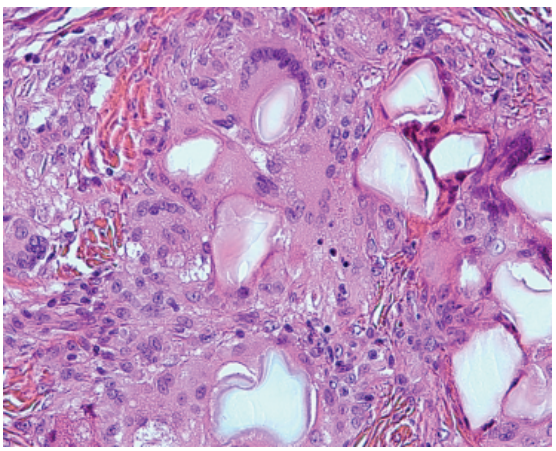

Figure 2. Histologic findings.

Discussion

Procedures and fillers used for cosmetic indications should be as safe as possible. The patient complication rate of polyalkylimide in this retrospective study was 4.8%. The treatment complication rate was 3.3%, because sometimes more than one treatment per patient was performed.

These percentages may be considered too high,[5] especially when taking into account the health risk of inflammation and the difficulty of treating disfiguring complications such as hardening and migration.

Inflammation was reported most frequently (2% per patient) and was mostly not treatment related but occurred 2 to 4 years later. Infections in the head and neck region and surgical facial procedures such as dental procedures or after a face lift were mentioned as possible related events, but in half of the patients, no possible cause of infection was found. Laboratory evaluation of the material showed in most cases no bacterial growth; in some cases *Staphylococcus aureus* was found, suggesting a secondary infection of *Staphylococcus aureus*.

Hardening of the capsule leaves the patient with visible disfigurement. The cause of this complication is not known. Causes of hardening of filler may be micro-inflammation due to a biofilm of bacteria[6] or an autoimmune response, but in most cases, no known cause or trigger was reported.

Migration occurred especially in such areas as the marionette lines and the cheeks. In several cases, the material was injected in the lower cheeks and corners of the mouth and migrated to the lower eyelid. The distance of the product movement strongly suggests migration. Muscle activity might be a factor in this process.

Although the gel can be removed by puncturing and squeezing it out, in several cases of hardening and inflammation, this was not a simple or sufficient procedure to treat the complication.

Earlier literature describing treatments with polyalkylimide report good results, with a minor complication rate (inflammations, treatment related).[7–9] Current small studies mention complications of inflammation 1 year or longer after treatment.[3,4,10] Because most complications are reported years after implantation of the material, numbers may be underestimated. The numbers given are based on a simple retrospective evaluation with a 50% response rate to the questionnaire. Nevertheless, the (candidate) members felt that the complications reported were too frequent and severe to ignore, leading to the advice of the Dutch Society of Cosmetic Medicine not to use polyalkylimide.

Cosmetic medicine is a strongly developing speciality. Every year, more treatments are performed. Legislation and regulation of fillers used for these procedures are not as strict as, for example, for medication and are often lacking long-term clinical trials and follow-up.

Fillers with a nonresorbable profile may lead to unforeseen complications that may be difficult to restore. In case of fillers indicated for volume loss, larger amounts of product are being used, and alternatives with a nonpermanent profile are available. Physicians working in the cosmetic field should try to cope with the lack of law by trying to work together and share knowledge on complications on an (inter)national level.

References

1. Pacini S, Ruggiero M, Morucci G, et al. Polyalkylimide, a novel prosthetic polymer, does not interfere with morphological and functional characteristics of human skin. Plast Reconstr Surg 2003;111:489–91.
2. Pacini S, Ruggiero M, Morucci G, et al. Polyalkylimide: a novelty for reconstructive and cosmetic surgery. Ital J Anat Embryol 2002;107:209–14.
3. Karim RB, Hage JJ, van Rozelaar L, et al. Complications of polyalkylimide 4% injections (Bio-Alcamid): a report of 18 cases. J Plast Reconstr Aesthet Surg 2006;59:1409–14.
4. Alijotas-Reig A, Garcia-Gimenez V. Delayed immune-mediated adverse effects of polyalkylimide dermal fillers. Clinical findings and long-term follow-up. Arch Dermatol 2008;144:637–42.
5. Fulton JE. Complications of laser resurfacing. Dermatol Surg 1998;24:91–9.
6. Christensen L. Normal and pathologic tissue reactions to soft tissue gel fillers. Dermatol Surg 2007;33(s2):S168–75.
7. Lafarge C, Rabineau P. The polyalkylamide gel; experience with Bio-Alcamid. Semin Cutan Med Surg 2004;23:236–40.
8. Lahiri A, Waters R. Experience with Bio-Alcamid, a new soft tissue endoprosthesis. J Plast Reconstr Aesthet Surg 2007;60: 663–7.
9. Ramon Y, Fodor L. Preliminary experiences with Bio-Alcamid in HIV facial lipoatrophy. Dermatology 2007;214:151–4.
10. Goldan O, Georgiou I, Grabov-Nardini G. Early and late complications after a nonabsorbable hydrogel polymer injection: a series of 14 patients and novel management. Dermatol Surg 2007;33:S199–206.

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Chapter 3

Polyalkylimide: A Nonstable Filler Over Time

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Polyalkylimide: A Nonstable Filler Over Time

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BACKGROUND Polyalkylimide hydrogel is supposed to be a permanent, biocompatible implant. However, years after subcutaneous implantation clinical complications are seen.

OBJECTIVE To increase the understanding of the changes that occur over time in this subdermal implanted filler.

MATERIALS AND METHODS The extruded filler material of 34 patients was evaluated by histologic examination.

RESULTS In most patients who had cosmetic disturbances but no complaints, histology showed no immune cells in or around the filler material. In patients with an acute inflammatory response, giant cell invasion was seen in and around the filler material. Patients with chronic complaints showed a neutrophilic cell influx in the extruded filler. In all patients, degeneration and calcification of the material was noted. The polyalkylimide hydrogel changed over time, both macroscopically and microscopically. As in most of the patients no immune response was seen around the filler material, this may indicate that the material is biocompatible.

CONCLUSION The authors conclude that a dermal filler should not be judged solely on its biocompatible characteristics but also on the degradation process over time in the human body.

The authors have indicated no significant interest with commercial supporters.

Polyalkylimide (Bio-alcamid) is a nondegradable hydrogel used for soft tissue replacement. This filling substance is described as a biocompatible endoprosthesis.[1] Polyalkylimide has been used on a wide scale from approximately the year 2000 onward. In the Netherlands, its use has been discouraged after the publication in 2007[2] and a warning by governmental institutions[3] because of the types and rate of complications. The Dutch representative (AB Medical) stopped supplying the substance shortly afterward.

In 2007, the frequency of complications in the Netherlands was rated at 4.6%.[2] However, between 2007 and 2016, the authors have experienced a steady influx of new patients with complications from the substance to the outpatients' clinic. The complication rate is probably much higher than first described. In a retrospective study published in 2012 looking back for 7 years after treatment with polyalkylimide, George and colleagues report a complication rate of 50%.[6] Complications described due to polyalkylimide are inflammatory reactions, hardening, dislocation, and accumulation of the product.[2,4–6] The last 2 are probably caused by dynamics of the underlying muscles.[7] Two theories have been proposed about the pathophysiology of the inflammatory reactions. Some view this as a foreign body response others regard this as a reaction to biofilm formation around the hydrophilic gel.[8–10]

Early tests with this substance suggested a favorable biocompatibility.[11] In vitro tests with the fresh product showed a very low interference with cell viability, absence of tissue necrosis,[4] and no involvement of neutrophilic lymphocytes, monocytes, and macrophages, such as is regularly seen in foreign body responses.[12] With subcutaneous injections in human

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skin, no significant changes were observed on cell proliferation and cell function 12 weeks after placement of the implant.[10] At the present time, 16 years after the introduction of polyalkylimide as an injectable filler, considering the high complications rate and the type of complications, it must be concluded that over a period of years, this substance is either nonbiocompatible or nonstable; maybe even both propositions apply.

To increase the understanding of the changes that occur over time in this subdermal implanted filler, the authors evaluated the material that they extruded from patients with complications years after a treatment of polyalkylimide.

Methods

During 2012 to 2015, all patients who consulted the outpatient clinic and presented themselves with complications due to polyalkylimide were evaluated with ultrasound. Information about the amount of product used, the location and depth of injection, and the occurrence of an acute inflammatory reaction was gathered. Taking into account the degree of cosmetic disfiguration in a patient's face and complaints suggesting any (low grade) inflammatory reaction such as itching, swelling, redness, tenderness or pain, and results from the ultrasound examination, it was advised either to leave the filler at rest or to evacuate the product by 18 G needle puncture under ultrasound guidance. Filler material was evacuated from 40 patients and sent for histologic examination.

All patients gave informed consent for the material to be examined. The material was fixed in formaldehyde 4% in phosphate buffer saline. The material was stained with hematoxylin–eosin and examined by light microscopy.

Results

A total of 41 samples of extruded materials were collected. Seven of these were not included in this study due to wrong handling or preparation of the material or when it turned out to be a different product than polyalkylimide. In the remaining 34 patients (7 men and 27 women), the polyalkylimide gel fillers had been injected more than 8 years before.

Macroscopically, the extruded filler has a different aspect compared with the original transparent gel that was injected years ago. None of the samples were transparent. Some were whitish and gel-like, but most of them were yellowish and creamy, much like a purulent substance (Figure 1).

The histological findings are given in Table 1. In all the polyalkylimide preparations examined, the material collected showed some degree of degradation, varying from mild to severe (Figure 2). The polyalkylimide particles become smaller and show irregular edges, making a dehydrated impression. In most samples, dehydration and calcification in the degenerated gel were seen. Calcification was not seen in the intact filler parts.

Furthermore, 3 different types of immunological reaction were seen. In all patients, the reaction toward the polyalkylimide filler corresponded with the clinical aspect of the patient in the following ways:

(1) A total of 25 patients with accumulation of dislocation of the product and hardening of the filler. These patients had no signs of inflammation; actually, they had no physical complication at all besides a disturbing cosmetic aspect. In these patients, no immune cells were seen in or around the filler material. Calcification was seen in the degenerated, dehydrated filler parts.

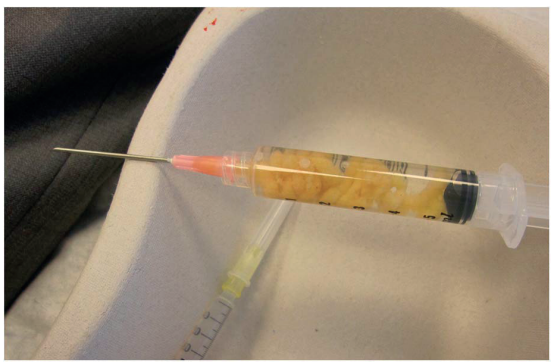

Figure 1. Nontransparent extruded filler.

TABLE 1. Histology Related to Type of Complication

No. of Patients	*Type of Complication*	*Histology*
25	Cosmetic disfiguration	Calcification and dehydration
5	Chronic response	Neutrophils, calcification, and dehydration
4	Acute inflammatory response	Giant cells, calcification, and dehydration*

*One of these 4 patients was HIV+ and besides giant cells, also neutrophils and bacterial influx (streptococci) were seen at histology.

(2) A total of 4 patients with an acute inflammatory response, clinically visible as swelling, redness, and pain. The material was collected at the time of inflammation. Histologically, in and around the filler, material giant cell invasion was seen. No other immune cells were seen; calcification was noticed (Figure 3, A and B).
(3) A total of 5 patients with physical complaints of the filler material as changing mild swelling, tingling feeling, itching, and awareness of the material when temperature drops. The extruded filler material showed a neutrophilic cell influx, and some giant cells but no other immune cells were seen (Figure 4, A and B). Calcification was seen in the material.

Discussion

Polyalkylimide hydrogel is supposed to be a permanent, biocompatible implant. Yet, years after subcutaneous implantation clinical complications are seen, most commonly dislocation, accumulation, hardening, and more rarely, an acute inflammatory response.

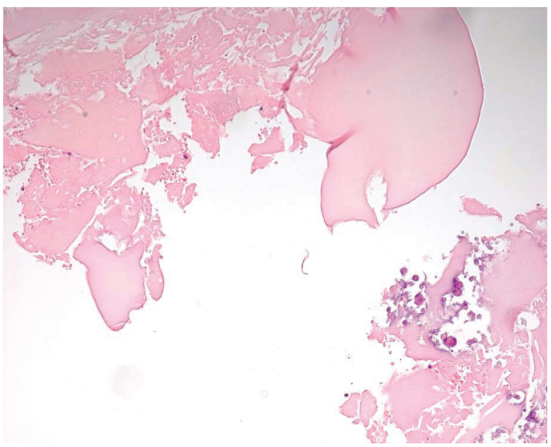

Figure 2. Amorphous mass (polyalkylimide) showing degeneration at the lower right site, no immune cells present.

The former 2 the authors assume to be due to underlying muscular activity, leading to either upward movement of the filler or spherical accumulation of the filling substance at 1 central point. Today, these types of complications are considered to be the result of wrong placement of the filler. Subcutaneous injection of volumizing implants is known to lead to these kind of problems.[13] The extruded product of these patients showed no immune cell reaction in or around the implant. This is in concordance with the initial report about polyalkylimide implants, where none or only a very minor inflammatory response with a fibrotic layer around the material was shown.[14] This was found 3 months after implantation[15]; in this study more than 8 years.

Degeneration of the product was seen in all patients, although the degree of degeneration may vary. Even in the same patient, with all the filler material injected at the same time, different histological samples showed a different degree of degeneration. This is in accordance with the clinical aspect of the evacuated material; per patient the filler material may have a different aspect, varying from a purulent substance to a dry and powdery material. Dehydration probably accounts for the nontransparent appearance of the removed product. Polyalkylimide hydrogels have a high capacity for the exchange of water molecules with the surrounding tissue.[16] In vitro, dehydration and calcification of hydrogels have been described.[17,18] Hydrogels which are dehydrated change in structure.[18–20] It seems, however, that this does not automatically lead to complications because the authors observed some degree of dehydration inside the gel in the histology of all patients.

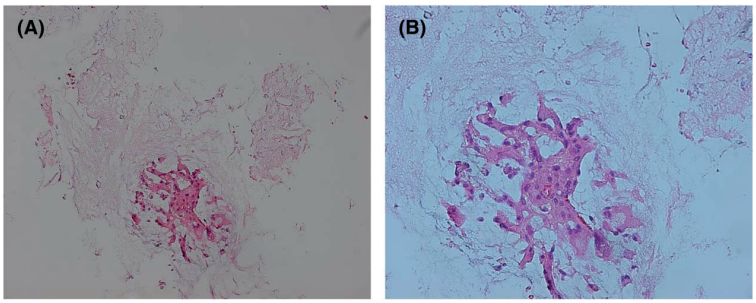

Figure 3. (A) Amorphous mass (polyalkylimide) degenerated surrounded with giant cells exclusively. (B) Detail of panel (A).

The authors also observed calcium deposits in all samples. The role of calcium in implants is unclear. In some orthopedic biomaterials, calcium deposits are appreciated for the stimulation of osteoclasts. In vitro tests with other biomaterials show that it can act as a potent stimulus of neutrophil activation, as well as causing fibroblast cytotoxicity.[16] Calcium phosphate can drive an inflammatory response and should be carefully monitored and controlled in biomaterials.[17] Although in vitro studies for biomaterials including acrylate hydrogels are available, these are not specific for dermal filler applications and in vitro studies cannot be extrapolated to an in vivo situation.[20]

Five patients in the group had chronic complaints. On histological examination, they showed neutrophilic influx around the filler material. As neutrophils are assumed to be involved at the first stage of a foreign body response, the authors suggest that these patients were stable for a long time and developed an immune impulse toward the filler as the result of an unknown stimulus.

Four patients who presented themselves with acute onset of inflammatory response corresponded histologically with a giant cell influx. It is known that dermal fillers will induce a foreign body reaction where at first neutrophils and later on macrophages and foreign body giant cells may attach to the surface of the filler material.[21,22,23] It is described that these macrophages and foreign body giant cells may persist for the lifetime of the implant. With biocompatible materials, the composition of the foreign body reaction in the implant site may be controlled by the surface properties of the biomaterial, the form, and the volume of the implant.[23,24] Polyalkylimide was used subcutaneously in large volumes for facial volume loss. Size disparity between the biomaterial surface and the attached cell may induce frustrated phagocytosis.[11] This process does not involve engulfment of the biomaterial but does cause the extracellular release of leukocyte products in an attempt to degrade the biomaterial. The authors hypothesize that this may lead to an ongoing cell infiltration in the hydrogel noticeable as a chronic giant cell reaction. It is uncertain what causes the acute inflammatory response and if a bacterial biofilm is involved.[25,26] Only 1 of 4 patients had a bacterial influx, which explains the presence of neutrophils found in histology.

The authors may conclude that in all patients the polyalkylimide hydrogel filler changed over time, both

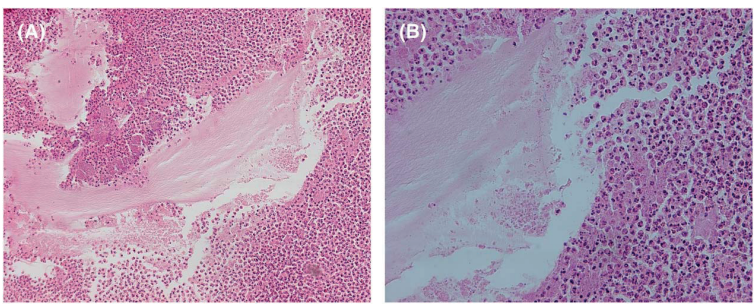

Figure 4. (A) Amorphous mass (polyalkylimide) surrounded by neutrophils exclusively. (B) Detail of panel (A).

macroscopically and microscopically. This indicates that the material is unstable over time. Furthermore, on histological examination, different types of immune reaction were seen corresponding to the different clinical presentations.

Why some patients do respond with (acute or chronic) inflammation and others do not, remains unclear. A possible explanation might be an immune response caused by a sterile (secondary) inflammatory response or a low grade biofilm.

In most of the patients, however, no immune response was seen around the filler material, indicating that the material is biocompatible. Other characteristics of the product may be responsible for the complications seen. The authors conclude that a dermal filler should not be judged solely on its biocompatible characteristics but also on the degradation process over time in the human body.

References

1. Pacini S, Ruggiero M, Cammarota N, Protopapa C, et al. Polyalkylimide, a novel prosthetic polymer, does not interfere with morphological and functional characteristics of human skin fibroblasts. Plast Reconstr Surg 2003;111:489–91.
2. Schelke LW, van den Elzen HJ, Canninga M, Neumann HAM. Complications after treatment with polyalkylimide. Dermatol Surg 2009;35:1625–8.
3. Health and safety legislation (13-02-2015) prohibition of the use of permanent fillers for aesthetic use (Nieuwsbericht | 13-02-2015 Inspectie voor de Volksgezondheid: Verbod permanente rimpelvullers voor cosmetische toepassing).
4. Goldan O, Georgiou I, Grabov-Nardini G, Regev E, et al. Early and late complications after a nonabsorbable hydrogel polymer injection: a series of 14 patients and novel management. Dermatol Surg 2007;33 (Suppl 2):S199–206; discussion S206.
5. Nadarajah JT, Collins M, Raboud J, Su DS, et al. Infectious complications of Bio-Alcamid filler used for HIV-related facial lipoatrophy. Clin Inf Dis 2012;55:1568–74.
6. George DA, Erel E, Waters R. Patient satisfaction following Bio-Alcamid injection for facial contour defects. J Plast Reconstr Aesthet Surg 2012;65:1622–6.
7. Kim H, Bae IH, Ko HJ, Choi J, et al. Novel polydioxanone multifilament scaffold device for tissue regeneration. Dermatol Surg 2016;42:63–7.
8. Lemperle G, Nicolau P, Scheiermann N. Is there any evidence for biofilms indermal fillers? Plast Reconstr Surg 2011;128:84e–5e.
9. Alijotas-Reig J, Miró-Mur F, Planells-Romeu I, Garcia-Aranda N, et al. Are bacterial growth and/or chemotaxis Increased by filler injections? Implications for the pathogenesis and treatment of filler-related granulomas. Dermatology 2010;221:356–64.
10. Rohrich RJ, Monheit G, Nguyen AT, Brown SA, et al. Soft-tissue filler complications: the important role of biofilms. Plast Reconstr Surg 2010; 125:1250–6.
11. Gibas I, Janik H. Review: synthetic polymer hydrogels for biomedical applications. Chem Chem Technol 2010;4:297–304.
12. Dini L, Panzarini E, Miccoli MA, Miceli V, et al. In vitro study of the interaction of polyalkilimide and polyvinyl alcohol hydrogels with cells. Tissue and Cell 2005;37:479–87.
13. Lemperle G, Rullan PP, Gauthier-Hazan N. Avoiding and treating dermal filler complications. Plast Reconstr Surg 2006;118(3 Suppl): 92S–107S.
14. Ramires PA, Miccoli MA, Panzarini E, Dini L, et al. In vitro and in vivo biocompatibility evaluation of a polyalkylimide hydrogel for soft tissue augmentation. J Biomed Mater Res B Appl Biomater 2005;72:230–8.
15. Formigli L, Zecchi S, Protopapa C, Caporale D, et al. Bio-alcamid: an electron microscopic study after skin implantation. Plast Reconstr Surg 2004;113:1104–6.
16. Lamberti G, Barba AA, Cascone S, Dalmoro A, et al. Chapter 8: An engineering point of view on the use of the hydrogels for pharmaceutical and biomedical applications: materials science. In: Majee SB, editor. *Emerging Concepts in Analysis and Applications of Hydrogels*. London: Intech; 2016.
17. Chirila TV, Gridneva Z, Morrison DA, Barry CJ, et al. Spontaneous calcification of acrylic hydrogels in abiotic calcifying edia and the relevance of ionic solute effects. J Mat Sci 2004;39:1861–4.
18. Chirila TV, Zainuddin DJT, Hill T, Whittaker AK, et al. Effect of phosphate functional groups on the calcification capacity of acrylic hydrogels. Acta Biomater 2007;3:95–102.
19. Yuk H, Zhang T, Parada GA, Liu X, et al. Skin-inspired hydrogel-elastomer hybrids with robust interfaces and functional microstructures. Nat Commun 2016;7:12028.
20. Sekine Y, Ikeda-Fukazawa T. Structural changes of water in a hydrogel during dehydration. J Chem Phys 2009;130:034501.
21. Alijotas-Reig J, Fernández-Figueras MT, Puig L. Inflammatory, immune-mediated adverse reactions related to soft tissue dermal fillers. Sem Arth Rheum 2013;43:241–58.
22. Anderson JM, Rodriguez A, Chang DT. Foreign body reaction to biomaterials. Semin Immunol 2008;20:86–100.
23. Morais JM, Papadimitrakopoulos F, Burgess DJ. Biomaterials/tissue interactions: possible solutions to overcome foreign body response. AAPS J 2010;12:188–96.
24. Wang Y, Guan A, Isayeva I, Vorvolakos K, et al. Interactions of *Staphylococcus aureus* with ultrasoft hydrogel biomaterials. Biomaterials 2016;95:74–85.
25. Tuson HH, Weibel DB. Surface morphology bacteria material: bacteriae surface interactions. Soft Matter 2013;9:4368–80.
26. Wang Y, da Silva Domingues JF, Subbiahdoss G, van der Mei HC, et al. Conditions of lateral surface confinement that promote tissue-cell integration and inhibit biofilm growth. Biomaterials 2014;35:5446–52.

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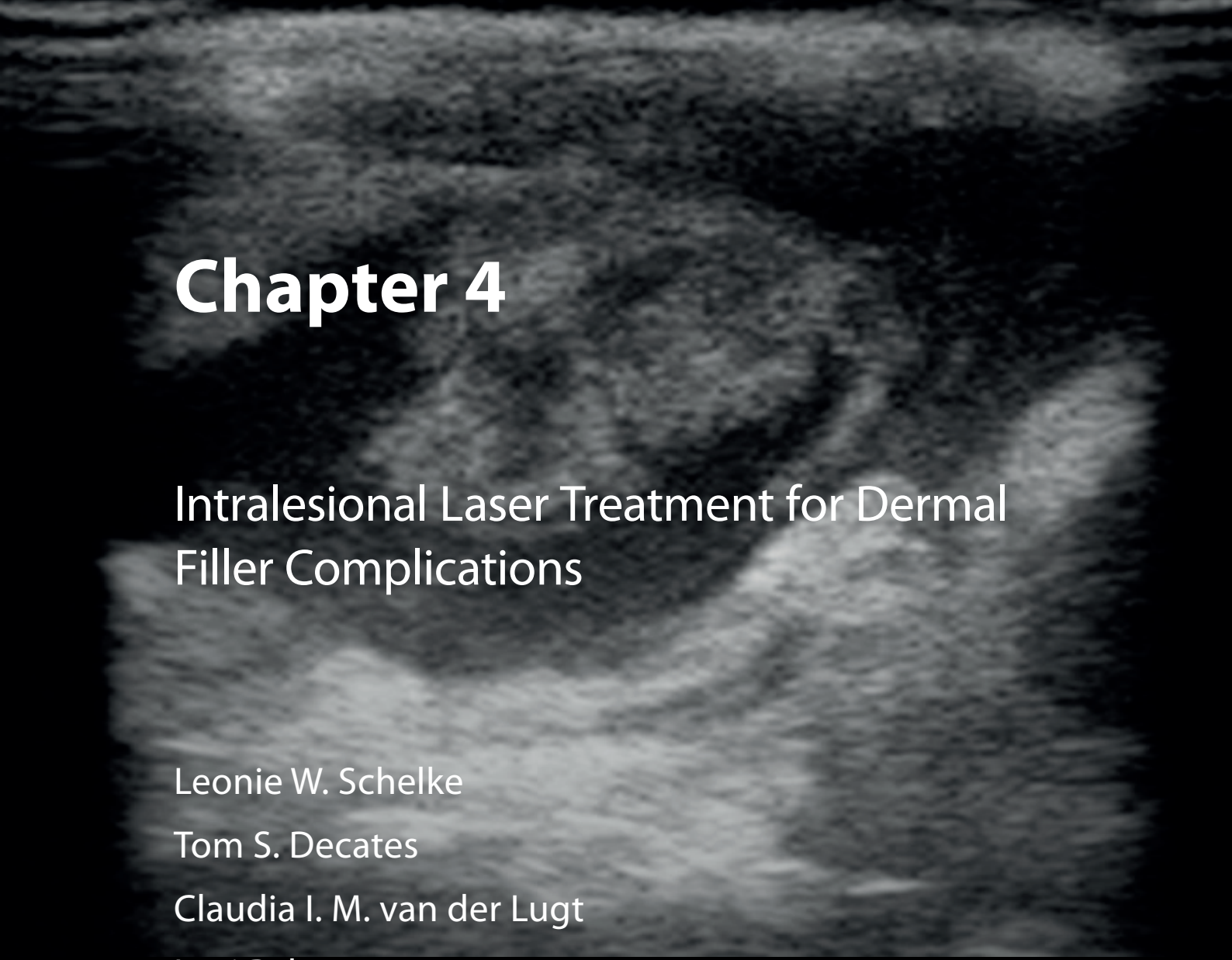

Chapter 4

Intralesional Laser Treatment for Dermal Filler Complications

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Intralesional Laser Treatment for Dermal Filler Complications

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Background: For complications caused by filler treatments, in general, two treatment regimens are advised: systemic drugs and surgical removal of the material. Another possible treatment option would be removal of the material by intralesional laser treatment.
Methods: Two hundred forty-two patients with complications caused by fillers were treated with intralesional laser treatment.
Results: In the majority of patients, an improvement was achieved (92 percent), in 9 percent the complication was resolved, and in 3 percent it was not improved (unknown in the rest).
Conclusion: Considering the large number of patients treated until now and the efficacy and good safety profile of this treatment, the authors plead that intralesional laser treatment may be considered as a treatment option before surgery. (*Plast. Reconstr. Surg.* 141: 1361, 2018.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, IV.

Although there is ongoing popularity of dermal filler use and an increasing number of treatments performed, much is unknown about complications with regard to their rate, possible causes, and optimal treatment options. As filler treatments are mainly performed as a cosmetic treatment in healthy clients, not only the treatment itself but also the options if any complications occur should be safe and must avoid severe side effects.

Looking at the literature, there is no consensus about the nature of these complications or treatment modalities.[1] One hypothesis of the cause of complications is a chronic foreign body response[2,3]; another theory is biofilm formation around dermal fillers, probably consisting of skin bacteria.[4,5] Both are thought to cause an inflammatory response.

In general, two treatment regimens are advised: systemic drugs[1,6] and surgical removal of the material.[2,7] Drugs can be useful to suppress the adverse reactions toward the filler material but they do not remove the filler itself. The drugs used are antibiotics, preferably from the macrolide group 1, as these will treat bacterial inflammatory reactions and suppress foreign body responses by up-regulating the production of antiinflammatory mediators.[8,9] The latter can also be treated with corticosteroids systemically or injected intralesionally. Surgical excision may remove (parts of) the material but often with tissue damage and scarring as a cosmetically undesirable result.

Another possible treatment option for filler complications has been developed and described by Cassuto et al.[10,11] This treatment modality—intralesional laser treatment—is capable of removing the foreign substance in a microinvasive manner. In this article, we describe our treatment outcomes with intralesional laser treatment for dermal fillers.

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PATIENTS AND METHODS

In the period between 2011 and 2016, 590 patients consulted our clinics for filler complications. Of these patients, 90 percent ($n = 531$) were women and 10 percent ($n = 59$) were men. Each patient's history was taken, especially complaints, onset of adverse event, medication, and earlier treatment regimens. All patients were evaluated with ultrasound examination. With ultrasound, information about the type of filler, the amount, the injection technique, the location and dislocation of the product, and the presence of an acute inflammatory reaction was gathered. Taking into account the degree of cosmetic disfiguration in a patient's face, the patient's complaints, and results from the ultrasound examination, patients were advised either to leave the filler at rest or to have the product evacuated (Fig. 1). All patients gave informed consent for the treatment performed. In 41 percent of the treatments, evacuation of the product was performed with the aid of intralesional laser treatment.

Intralesional Treatment

In our outpatient clinic, two types of lasers are used: a 810-nm-wavelength diode laser and a 1470-nm-wavelength diode laser (continuous wave) (Quanta System, Milan, Italy). Both lasers are developed and used for endovenous laser treatments. The 810-nm laser targets hemoglobin, and the 1470-nm laser heats water in blood and vein wall, secondarily destroying the vein wall.

In endovascular laser treatment of varicose veins, different wavelengths are used (810 and 1470 nm). Not the wavelength of the device but the amount of energy and heat delivered to the varicose veins is thought to be most important for achieving success.[12–14] This will probably account for the intralesional treatment, and we found no obvious difference in efficacy for these two different wavelengths.

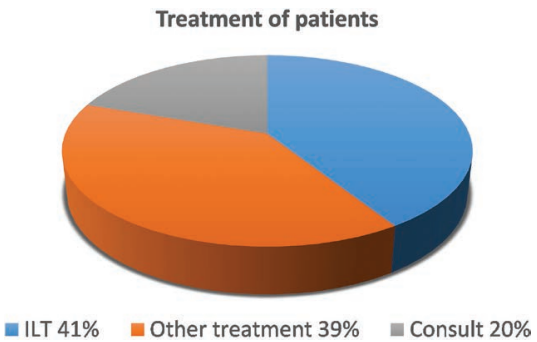

Fig. 1. Treatment of patients. *ILT,* intralesional laser treatment.

The intralesional laser treatment procedure for dermal fillers consists of inserting a fiberoptic laser into the area of the product. The laser power setting for both lasers depends on the diameter of the fiber used and is on average 3 to 6 W for the 810-nm laser and 0.6 to 0.8 W for the 1470-nm laser, both in continuous-wave mode. Delicate areas such as orbital regions, glabella, and locations that have been treated with corticosteroid injections before were treated with reduced power to avoid skin burns. The fiber diameter may vary between 200 and 600 μm; the smaller diameter is preferable. If the product is not clinically easily felt or seen, the fiber insertion can be performed under ultrasound guidance. Intradermal anesthesia at the skin entry point is commonly used in all instances. As the pain sensation of the patient is helpful to adjust the delivered energy into the filler, anesthesia is limited to the skin entrance. If too much heat is being delivered to the filler material or if the fiber is not in the right place, heat may be diffused into the surrounding tissues, risking tissue damage or pigmentation.[11] The patient is instructed to warn the operator if pain or excessive heat is sensed. During the intralesional laser treatment procedure, softening of the product is noticed, which is used as an endpoint. After the laser procedure, the heat-liquefied filler can be (partly) squeezed out by manual compression through an 18-gauge needle entry point or through a small incision made by a no. 11 scalpel (Fig. 2).

As we broadly follow the treatment regimen proposed by Cassuto et al., we have made some additions to their technique based on filler types: hydrophobic and hydrophilic fillers. They behave differently in tissue, but they have also been injected differently into the tissue.

Hydrophilic Fillers

Almost all nonresorbable hydrophilic fillers and resorbable hyaluronic acid fillers with large particles are used as volumizers and are often injected as a bolus. On ultrasound, they appear as hypoechoic pockets or cysts. Known filler types that give rise to complications in this category are polyalkylimide and polyalkylimide fillers and heavily cross-linked hyaluronic acids. Histologic examination indicates that these fillers tend to dehydrate over time. Dehydration may be one of the explanations why these types of fillers are difficult to remove. Before introducing the fiber into the filler, 1 to 10 ml (depending on the pocket

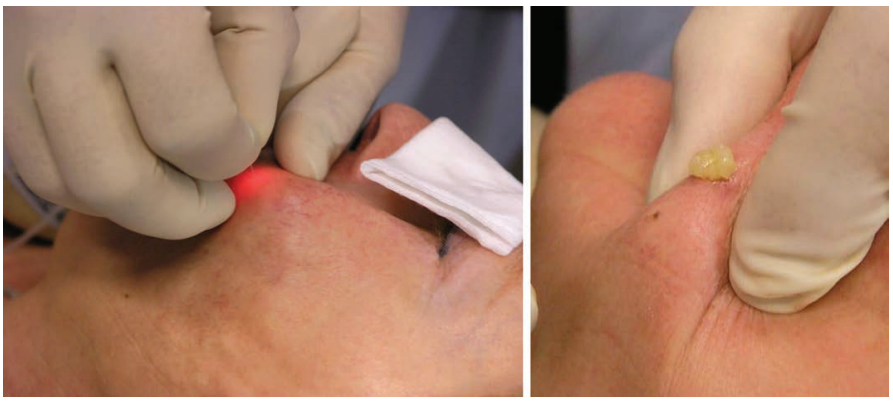

Fig. 2. (*Left*) The laser fiber is inserted in the filler. (*Right*) The heat-liquefied filler is squeezed out.

size) of 0.9% sodium chloride is injected into the filler depot, if needed under ultrasound guidance (Fig. 3). During heat delivery by the intralesional laser treatment fiber, the injected fluid is bubbling, also visible with ultrasound. [**See Video, Supplemental Digital Content 1**, which demonstrates the intralesional laser treatment procedure including corresponding ultrasound imaging. The intralesional laser treatment of a hydrophilic filler (polyalkylimide) is shown. As it is done under ultrasound guidance, the fiber tip can be inserted accurately in the filler pocket. When the clinical endpoint (softening of the product) is reached, the heat-liquefied filler can be squeezed out by manual compression, in this case through an 18-gauge needle entry point, available in the "Related Videos" section of the full-text article on PRSJournal.com or, for Ovid users, available at ***http://links.lww.com/PRS/C758***.] After the laser procedure, the pocket is irrigated again with saline solution to mechanically flush out as much material as possible.

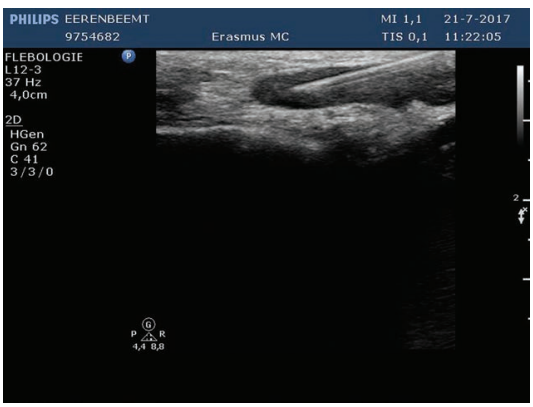

Fig. 3. Injection in filler depot under ultrasound guidance.

Hydrophobic Fillers

The most commonly used hydrophobic fillers are polymethylmethacrylate, hydroxyethylmethacrylate, and silicone oil (polydimethylsiloxane). The injection technique used is mainly infiltrating small particles into the tissue, leading to a fibrotic tissue response. The fiber is inserted into the area of the material, by drilling small holes. Little

Video. Supplemental Digital Content 1 demonstrates the intralesional laser treatment procedure including corresponding ultrasound imaging. The intralesional laser treatment of a hydrophilic filler (polyalkylimide) is shown. As it is done under ultrasound guidance, the fiber tip can be inserted accurately in the filler pocket. When the clinical endpoint (softening of the product) is reached, the heat-liquefied filler can be squeezed out by manual compression, in this case through an 18-gauge needle entry point, available in the "Related Videos" section of the full-text article on PRSJournal.com or, for Ovid users, available at ***http://links.lww.com/PRS/C758***.

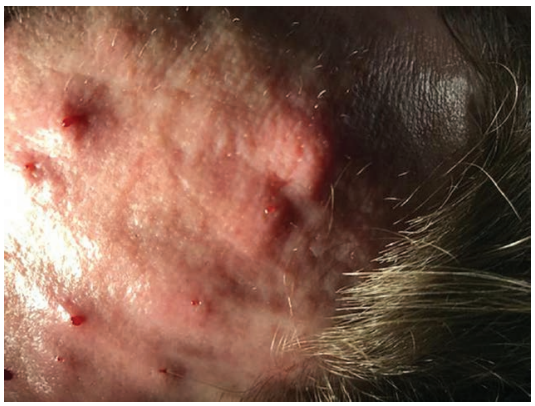

Fig. 4. Little droplets of silicone oil after intralesional laser treatment.

droplets dripping out of the insertion openings show filler material (Fig. 4).

Posttreatment Recommendations

For hydrophobic fillers, heat compression followed by gentle massage to push out more product is advised for the first hours after treatment. For hydrophilic fillers, because the skin entrance is much larger (because of a stab incision with a no. 11 blade or an 18-gauge needle), it is advised to leave the skin at rest to prevent inflammatory reactions. For all treatments, our postoperative advice is not to apply any cream or makeup until the entrance skin opening has healed, to prevent any secondary infection. Oral macrolide antibiotic treatment is given to patients at risk such as patients under corticosteroid treatment and immunocompromised patients (e.g., human immunodeficiency virus). Downtime is normally 2 to 4 days after treatment. A sensitive area such as the lips will give rise to a more pronounced swelling and could take 5 days to heal.

RESULTS

From January of 2011 to September of 2016, 590 patients visited our clinic. Of these 590 patients, 242 patients (214 women and 28 men) were treated with intralesional laser treatment. The mean age of these patients was 52 years (range, 25 to 78 years). On average, 1.7 treatments were performed per patient (Fig. 5).

Most complications treated with intralesional laser treatment were caused by polyalkylimide. Clinical symptoms to filler treatment complications were inflammatory reactions, visible lumps and nodules, dislocation and accumulation of the product, and hardening. In Figure 3, the complications treated with intralesional laser treatment are listed per filler for the fillers used most often (Fig. 6).

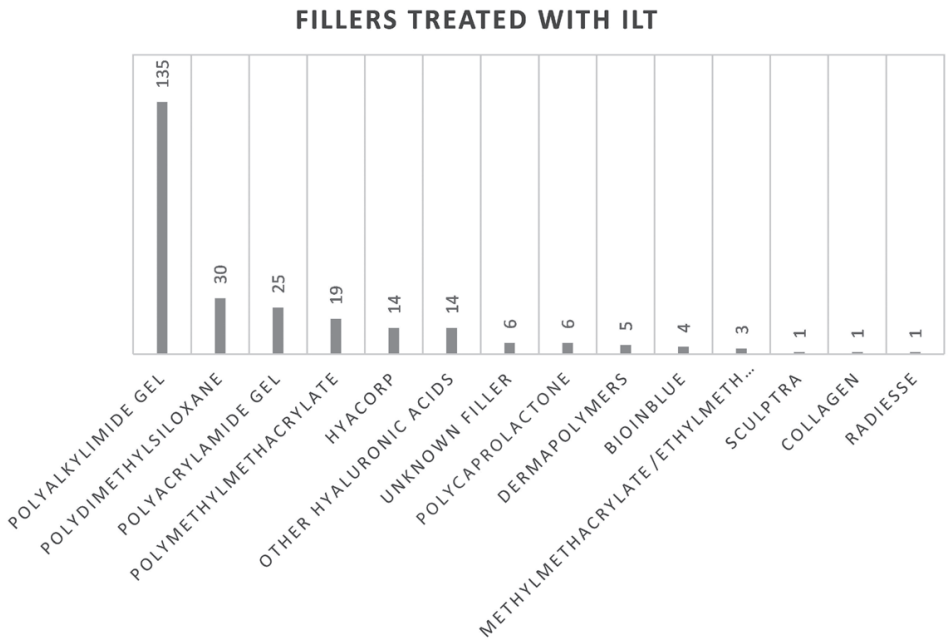

Fig. 5. Fillers treated with intralesional laser treatment (*ILT*).

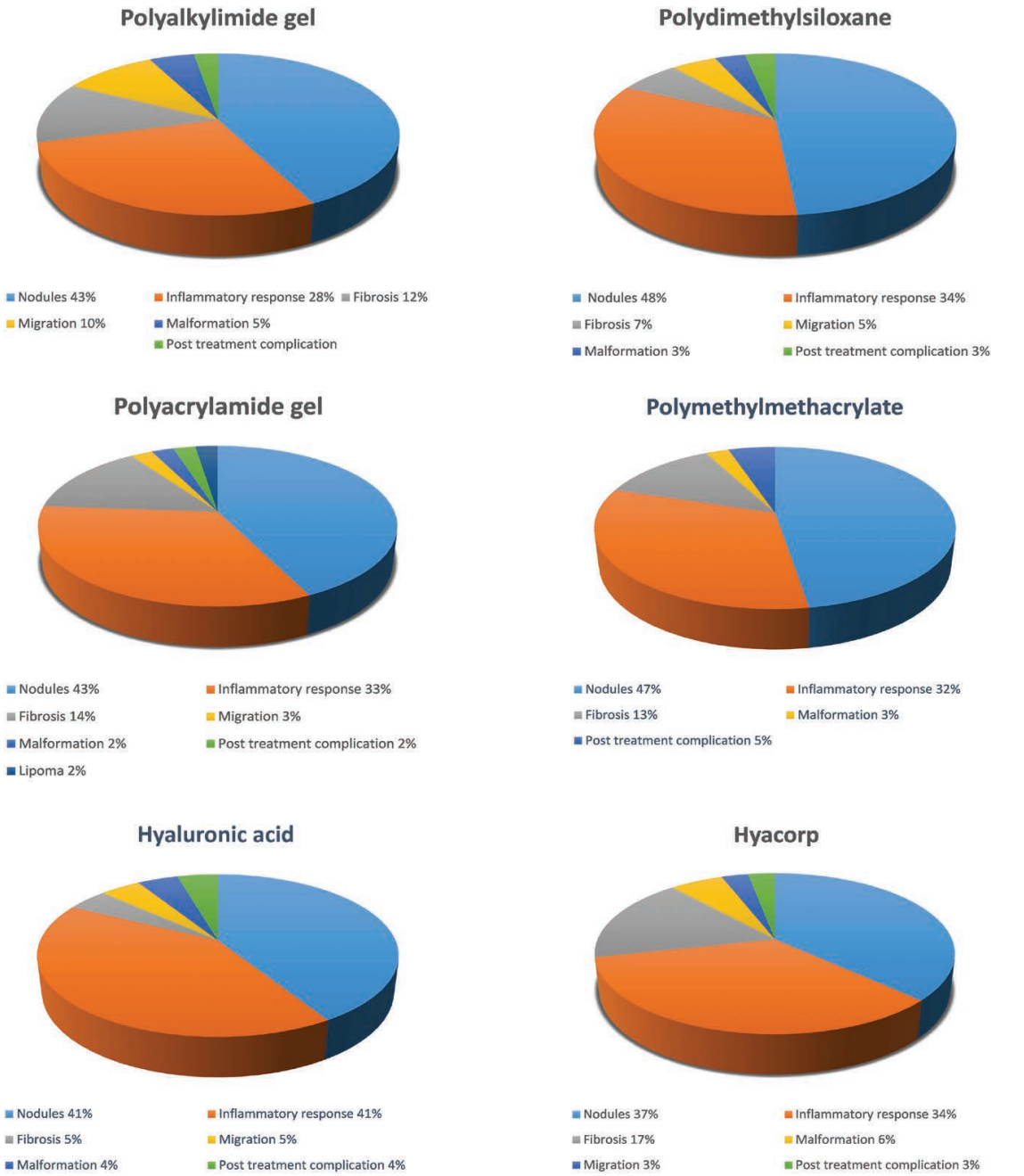

Fig. 6. Complications per filler for the six most common fillers.

It is interesting to note that 11 percent of the patients visiting our polyclinic had a complication caused by injections with resorbable hyaluronic acid fillers. Half of these complications are attributable to wrong injection techniques resulting in dislocation of product caused by dynamics of the underlying muscles, excessive edema of the lower eye lid region, or inflammatory responses when volumes that are too large are injected (mostly hyaluronic acid products

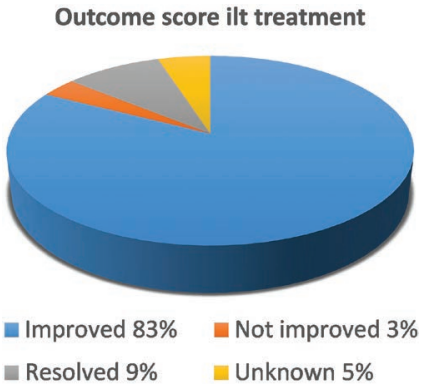

Fig. 7. Outcome score of intralesional laser treatment (*ilt*).

with a high viscosity and stiffness). The other 50 percent of the complications were attributable to cross-linking (up to 63 percent) of some hyaluronic acid products that were too strong, thus creating the same complications as seen with permanent fillers. In cases of volumes that are too large and products with excessive cross-linking, hyaluronidase alone was not successful in dissolving the filler, and intralesional laser treatment followed by hyaluronidase injection was necessary to remove it.

After treatment, patients were asked whether the treatment improved their cosmetic and physical complaints (Fig. 7). To stay in line with the article by Cassuto et al., this was defined as follows:

Resolved: All symptoms are completely cured or judged tolerable by the patient.
Improved: Cosmetic disturbances and lump visibility are reduced to a degree judged tolerable by the patient. Interrupting the steroid therapy without recurrence is possible.
Not improved: no cosmetic and/or physical improvement (Fig. 8).

The improvement can also be seen with a follow-up ultrasound examination. Hydrophilic fillers decrease in pocket size or disappear, although fibrosis is mostly remaining (Fig. 9). The tight fibrotic tissue formed around hydrophobic fillers prevents ultrasound passage (shadowing). After intralesional laser treatment, the visibility of the tissue improves (e.g., teeth become visible again with follow-up ultrasound examination) (Fig. 10).

Patients not improved are mostly patients with an inflammatory reaction after intralesional laser treatment who visited a first aid department of a nearby hospital (not familiar with these types of problems) and, because of the drain placed as a treatment, without any follow-up or wound procedure management, were left with a scar in their face. Furthermore, fillers injected in the orbital region are more difficult to remove, leading to less satisfying results (Fig. 11).

Fig. 8. (*Left*) Before intralesional laser treatment. (*Right*) Improvement after intralesional laser treatment.

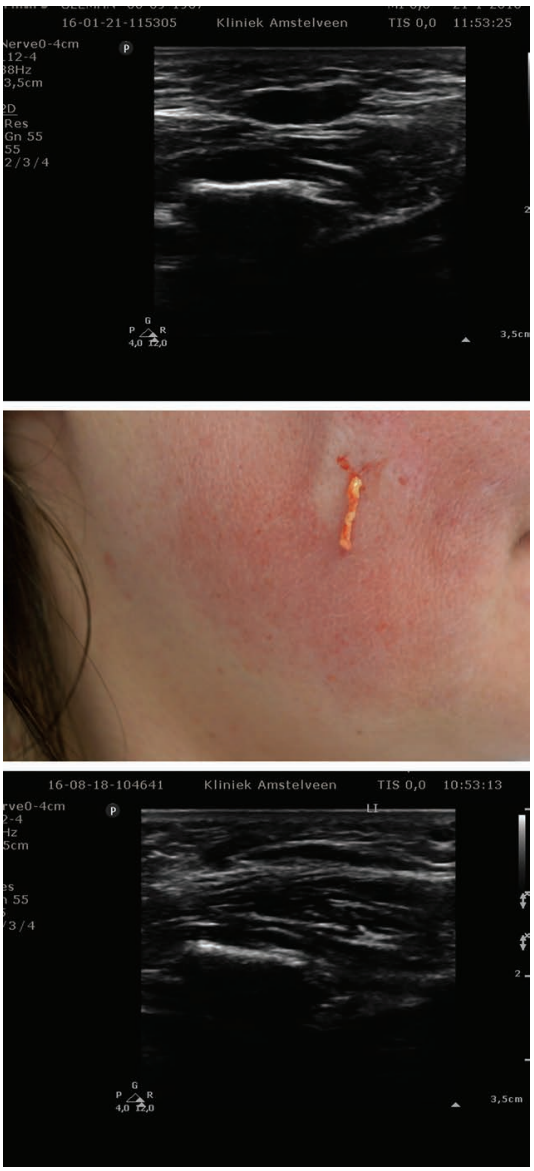

Fig. 9. (*Above*) Hydrophilic filler (*black pocket* on screen) before intralesional laser treatment. (*Center*) Hydrophilic filler is squeezed out after intralesional laser treatment. (*Below*) Decreased pocket size of hydrophilic filler on screen.

Complications Caused by Intralesional Laser Treatment

Inflammatory reactions as a complication caused by intralesional laser treatment are seen. As there is still no consensus about the cause of this reaction, a macrolide was given as treatment to cover any bacterial infection and an acute inflammatory response as well. Ibuprofen was given for its pain-reducing and antiinflammatory characteristics. After a couple of days, the abscess could be evacuated by puncture. Normally, this will leave no visible scarring. Immunocompromised patients are more prone to develop post–intralesional laser treatment inflammatory responses.

One patient with large pockets of polyalkylimide injected in the lower orbital region (under the eyelids) was left with an open wound for months. Because of an excess of heat applied into this sensitive area, which had also been treated with cortisone injections previously, damage was done to the overlying skin. In combination with the large amount of filler remaining, there was a very slow healing response. If treating delicate areas such as the periorbital region (lower eyelid region), glabella, or skin treated previously with cortisone injections, the temperature should be adjusted lower.

One patient had persistent skin hyperpigmentation after the intralesional laser treatment. This can be prevented by making an insertion hole with a no. 11 scalpel and then inserting the fiber into the pocket of the filler, ensuring that no heat is applied to the skin surface. Placing the tip of the fiber on the skin and heating the fiber thereafter may cause a slight burning reaction that should be prevented in these cases and those with Fitzpatrick skin type III and higher.

DISCUSSION

There is still much to learn about complications caused by filler treatments. The relationship between product and the host response at the time of injection and during the degradation process is still not clear[15,16]; thus, treatment options are difficult to standardize. However, in case of complications, it seems logical to at least remove as much filler product as possible.

In 2009, a small number of patients (n = 20) treated with intralesional laser treatment were described by Cassuto et al.[10] In 2016, the same authors published an article regarding a large number of treated patients (n = 219) who experienced an improvement of their complaints.[11] We underscore these outcomes with our data.

Almost all patients noted an improvement after intralesional laser treatment, although not always as much as they hoped for. There may be remainders of the filler or of fibroses. Taking this into account, the minimally invasive manner of the treatment and the limited downtime add to the attractiveness of this method. Considering

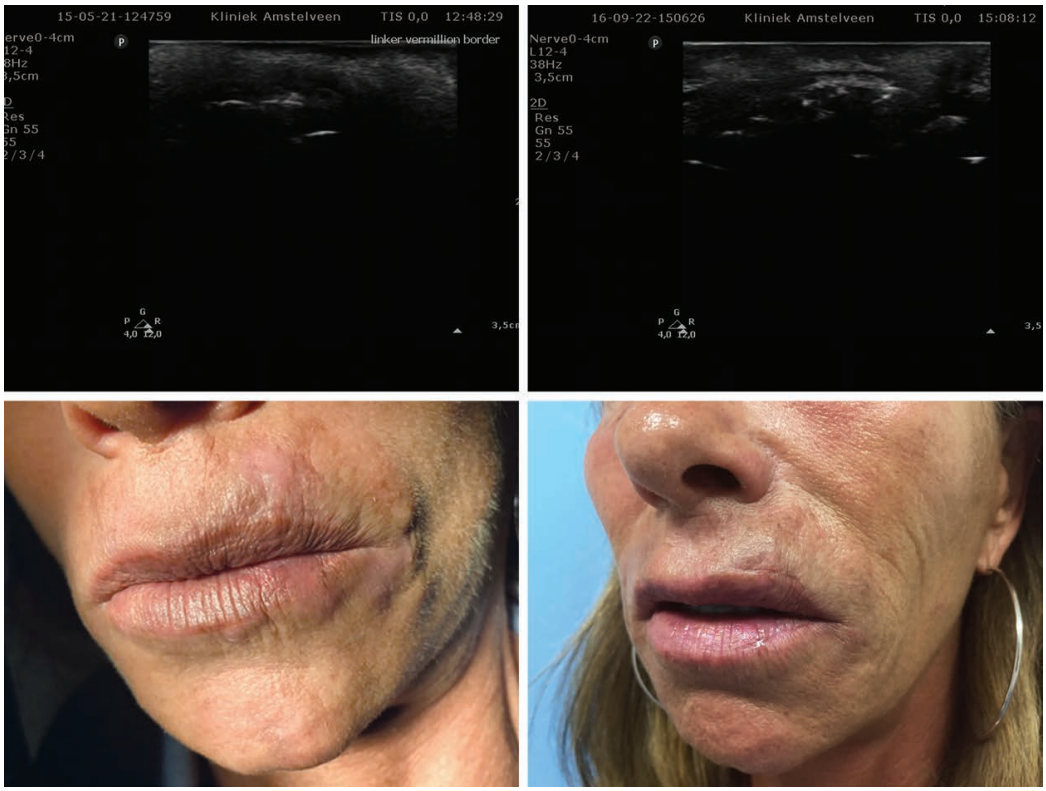

Fig. 10. (*Above*, *left*) Fibrotic tissue around silicone oil prevents most ultrasound wave passing through (shadowing). (*Above*, *right*) After intralesional laser treatment, more ultrasound waves can pass through. (*Below*, *left*) Before intralesional laser treatment of silicone oil. (*Below*, *right*) After intralesional laser treatment of silicone oil.

Fig. 11. (*Left*) Before intralesional laser treatment. (*Right*) After intralesional laser treatment, showing less improvement in the orbital region.

the large number of patients treated until now, and the efficacy and good safety profile of this treatment, we plead that intralesional laser treatment should be considered as a treatment option before surgery.

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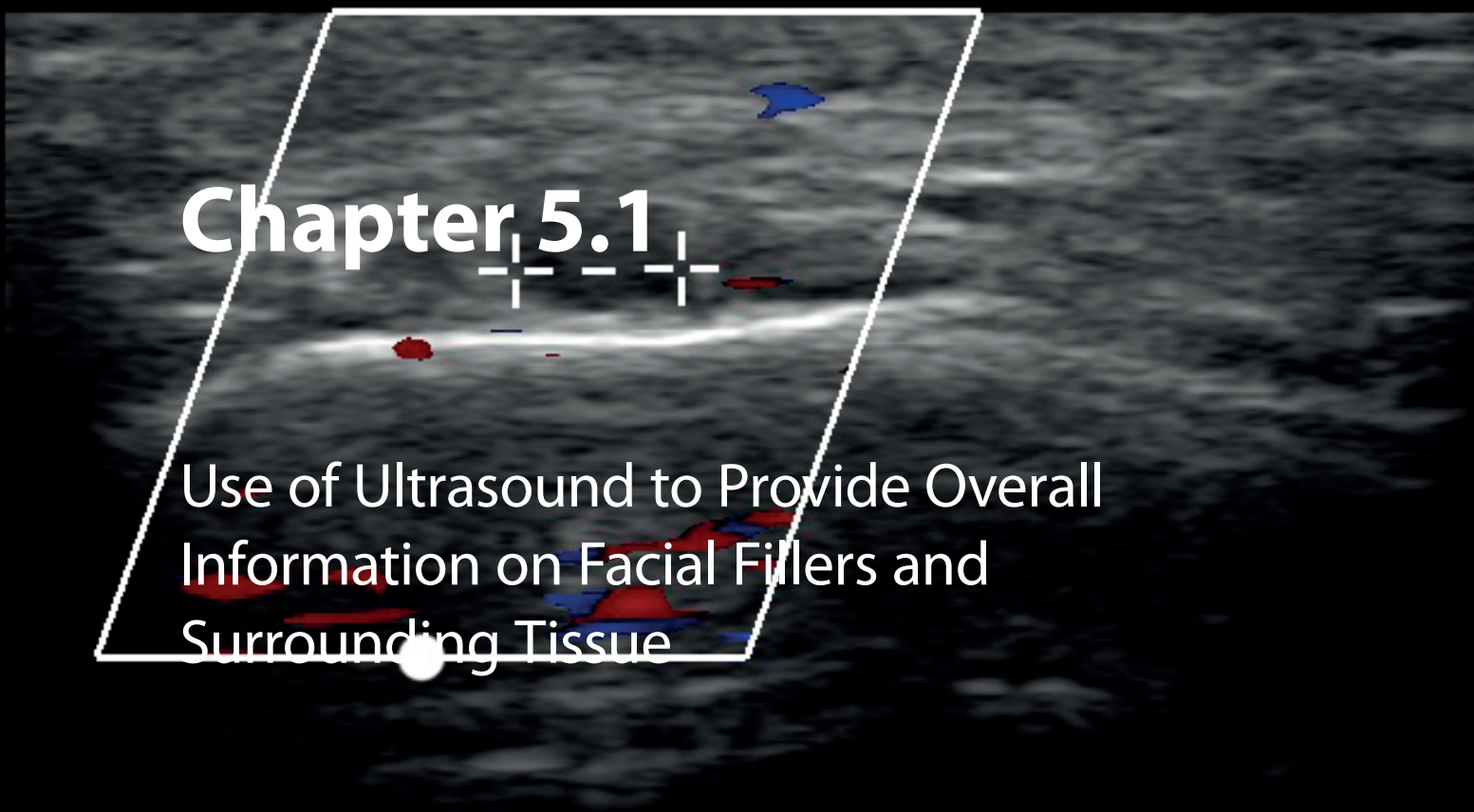
PATIENT CONSENT

Patients provided written consent for the use of their images.

REFERENCES

1. Ibrahim O, Overman J, Arndt KA, Dover JS. Filler nodules: Inflammatory or infectious? A review of biofilms and their implications on clinical practice. *Dermatol Surg.* 2017. [E-pub ahead of print.]
2. Nicolau PJ. Long-lasting and permanent fillers: Biomaterial influence over host tissue response. *Plast Reconstr Surg.* 2007;119:2271–2286.
3. Kadouch JA, Vos W, Nijhuis EW, Hoekzema R. Granulomatous foreign-body reactions to permanent fillers: Detection of CD123+ plasmacytoid dendritic cells. *Am J Dermatopathol.* 2015;37:107–114.
4. Saththianathan M, Johani K, Taylor A, et al. The role of bacterial biofilm in adverse soft-tissue filler reactions: A combined laboratory and clinical study. *Plast Reconstr Surg.* 2017;139:613–621.
5. Rohrich RJ, Monheit G, Nguyen AT, Brown SA, Fagien S. Soft-tissue filler complications: The important role of biofilms. *Plast Reconstr Surg.* 2010;125:1250–1256.
6. Vanaman M, Fabi SG, Carruthers J. Complications in the cosmetic dermatology patient: A review and our experience (part 2). *Dermatol Surg.* 2016;42:12–20.
7. Wolfram D, Tzankov A, Piza-Katzer H. Surgery for foreign body reactions due to injectable fillers. *Dermatology* 2006;213:300–304.
8. Zeng M, Zhi-Yong L, Ma J, et al. Clarithromycin and dexamethasone show similar anti-inflammatory effects on distinct phenotypic chronic rhinosinusitis: An explant model study. *BMC Immunol.* 2015;16:37.
9. Nozoe K, Aida Y, Fukuda T, Sanui T, Nishimura F. Mechanisms of the macrolide-induced inhibition of superoxide generation by neutrophils. *Inflammation* 2016;39:1039–1048.
10. Cassuto D, Marangoni O, De Santis G, Christensen L. Advanced laser techniques for filler-induced complications. *Dermatol Surg.* 2009;35(Suppl 2):1689–1695.
11. Cassuto D, Pignatti M, Pacchioni L, Boscaini G, Spaggiari A, De Santis G. Management of complications caused by permanent fillers in the face: A treatment algorithm. *Plast Reconstr Surg.* 2016;138:215e–227e.
12. Malskat WS, Stokbroekx MA, van der Geld CW, Nijsten TE, van den Bos RR. Temperature profiles of 980- and 1,470-nm endovenous laser ablation, endovenous radiofrequency ablation and endovenous steam ablation. *Lasers Med Sci.* 2014;29:423–429.
13. Weiss RA, Weiss MA, Eimpunth S, Wheeler S, Udompunturak S, Beasley KL. Comparative outcomes of different endovenous thermal ablation systems on great and small saphenous vein insufficiency: Long-term results. *Lasers Surg Med.* 2015;47:156–160.
14. Boersma D, Smulders DL, Bakker OJ, van den Haak RF, Verhoeven BA, Koning OH. Endovenous laser ablation of insufficient perforating veins: Energy is key to success. *Vascular* 2016;24:144–149.
15. Christo SN, Diener KR, Bachhuka A, Vasilev K, Hayball JD. Innate immunity and biomaterials at the nexus: Friends or foes. *Biomed Res Int.* 2015;2015:342304.
16. Tang L, Hu W. Molecular determinants of biocompatibility. *Expert Rev Med Devices* 2005;2:493–500.



Chapter 5.1

Use of Ultrasound to Provide Overall Information on Facial Fillers and Surrounding Tissue

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Use of Ultrasound to Provide Overall Information on Facial Fillers and Surrounding Tissue

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BACKGROUND Information on fillers and their behavior over time in the different layers of tissue is limited. Ultrasound may be used to visualize these fillers and their surrounding tissue to broaden knowledge.

OBJECTIVE To evaluate the use of ultrasound as a diagnostic and research tool to obtain information on facial fillers and their behavior in human tissue.

METHODS AND MATERIALS Patients with a history of facial filler treatment were examined using ultrasound in an outpatient setting.

RESULTS Seventy-two patients were examined. Hydrophilic fillers were echo visible, whereas tissue-generating fillers, permanent and resorbable, could be detected according to their tissue-generating reaction within the tissue. Filler characteristics such as longevity and reaction within the tissue and complications such as migration and granulomas could be visualized.

CONCLUSION The use of ultrasound may provide information to broaden our knowledge of facial fillers and may improve the performance and safety of filler treatments.

The authors have indicated no significant interest with commercial supporters.

In current clinical practice, rejuvenation of the face with soft tissue fillers is increasingly shifting from treating single lines and wrinkles toward volume restoration and filling of larger facial areas to enhance facial appearance.[1–3] Similarly, there is a shift from volumetric correction of the dermis or subcutaneous layers toward injections at a deeper muscular and supraperiosteal level.[4]

Although some attention has been paid to the different categories of fillers, their longevity, mode of action, degradability, histological findings, and clinical effect,[5,6] our knowledge of their behavior over time in the different layers of tissue and their complications is limited.[7,8]

Ultrasound is a noninvasive, easy-to-use, reproducible technique used to visualize subcutaneous body structures.[9,10] Sound waves, produced using an ultrasound transducer, travel into the body. Whenever a sound wave encounters structures or material with a different density, part of the sound wave is reflected back to the transducer and is detected as an echo. The strength of the reflection determines the brightness; white for a strong reflection or echo (hyperechogenic, as seen for gases or bone), black for a weak echo (hypoechogenic, e.g., fluids), and varying shades of gray for everything in between (Table 1).

Because facial fillers have their own characteristics and density, ultrasound may be used to visualize these materials and provide information to broaden our knowledge.[11]

The aim of this study was to assess the use of ultrasound as a diagnostic tool to provide information on filler dimensions such as echo visibility of

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TABLE 1. Glossary of Terms

Anechoic	Echo free, the sound wave is totally absorbed or totally reflected by the material, and its image appears totally black on the monitor
Cystic	An anechoic, well-defined, acoustic enhancement (e.g., any fluid-filled structure, urinary bladder)
Echogenic	Capable of producing echoes
Echogenicity	Degree of brightness of a structure displayed on the ultrasound
Finely textured	Fine-grained heterogeneous internal echoes within a structure
Heterogeneous	Nonuniform echo pattern throughout the structure being imaged
Homogeneous	Uniform echo pattern throughout the structure being imaged
Hyperechoic	Image echoes that are brighter than surrounding tissue and appear white on the monitor (e.g., bone, fibrous tissue, calcium hydroxyapatite)
Hypoechoic	Echoes that are not as bright as surrounding tissue and appear gray to dark on the monitor (e.g., fluid-filled structures, vessels)
Isoechoic	Structures compared are of equal echogenicity
Shadowing	Failure of the sound beam to pass through an object so only shadowing is seen behind it (e.g., bone, gas, calcifications, air)

different fillers, the location of fillers over time, degradation, and possible complications such as migration and hardening.

Methods

In this study, patients were included as they presented themselves to our outpatient clinic. Seventy-two individuals with a history of filler treatment(s), permanent and resorbable, were examined. Before ultrasound examination, a history was taken, and a clinical examination and palpation of the face and, if possible, implanted filler was performed.

During full-face ultrasound examination, skin and tissue underneath were explored for (different) fillers. Information was gathered on their echo visibility, injected plane and location, and possible tissue reaction. Furthermore, visibility of possible complications, such as migration, granulomas, and hardening, was assessed.

Two of 72 patients had their initial filler treatment, including post-treatment visits, done under ultrasound guidance.

The ultrasound (LOGIQ e B-mode, Linear Probe 12L-RS, GE Healthcare, Chalfont St. Giles, UK) 13 MHz, two-dimensional-mode imaging with a linear array probe was used. For each patient, the technician performing the ultrasound, the physician examining the patient and interpreting the results, and the ultrasound device being used were the same.

Tissue and ultrasound markings (e.g., exact location and scan angle) were established before measurements took place and were noted to ensure reproducibility.

Results

Seventy-two patients were examined (Table 2). Some patients had received treatments with different types of fillers. In all patients, the filler was visible. A summary of the visibility of investigated fillers is described in Table 3.

Hyaluronic Acid

Hyaluronic acid (HA) is a hydrophilic resorbable gel. It may be used in the superficial layers of the skin, as well as in the deeper layers, to treat subcutaneous volume loss. In this study, we only examined the latter. Because HA is a hydrophilic gel, it is less reflective than the surrounding tissue and is visible as a fairly distinct hypoechogenic (black) lesion with some hyperechogenic (linear) reflections.

TABLE 2. Numbers of Different Fillers at Ultrasound Examination

Filler	*Numbers at Ultrasound Examination*
Hyaluronic acid	7
Lipofilling	2
Calcium hydroxyapatite	2
Polylactic acid	2
Silicone oil	3
Polymethylmethacrylate	2
Polyalkylimide	57

Lipofilling

Autologous body fat can be used to treat facial volume loss. Fat implants are visible with ultrasound as a well-defined, compact, finely textured area and are isoechogenic to slightly hyperechogenic (Figure 1).

Calcium Hydroxyapatite

Calcium hydroxyapatite is a biostimulator and enhances collagen production. It may be injected at the dermal and subcutaneous level, where it will improve skin texture over time, or on the supraperiosteal level to improve skeleton volume loss. Calcium phosphate was injected in the deep dermal and subcutaneous planes (first upper mm of picture) approximately 3 months previously (Figure 2). Ultrasound shows greater density on the treated right area. The finely textured, hyperechogenic tissue reflects most sound waves back (possibly because of calcium), preventing ultrasound penetration (shadowing). On the left side, the transition toward greater sound wave penetration is visible, marking the untreated skin.

TABLE 3. Ultrasound Findings of Examined Fillers

Product	*Depth of Injection*	*Sites of Injection*	*Follow-ups,* n	*Common Findings on Ultrasound*	*Characteristic*
Bio-Alcamid polyalkylimide	Subcutaneous	Cheeks, chin	3	Anechoic to hypoechoic lesions with distinct echogenic walls	Hydrophilic
Voluma hyaluronic acid	Subcutaneous, periosteal	Cheeks, temple	2	Hypoechogenic area with some hyperechogenic reflections	Hydrophilic
Lipofilling, autologous	Subcutaneous	Cheeks	1	Isoechogenic to slightly hyperechogenic	Fatty tissue
Sculptra polylactic acid	Periosteal	Temples	3	Indirect effect of increase of tissue	Tissue generating
Radiesse calcium hydroxyapatite	Deep dermal	Nasolabial folds, cheeks		Shadowing due to calcium particles?	Tissue generating
Silicon oil	Deep dermal	Nasolabial folds, lips	2	Shadowing due to dense fibrous tissue	Induces a fibrotic tissue reaction
Artecoll polymethylmethacrylate	Deep dermal	Nasolabial folds	2	Shadowing due to dense fibrous tissue	Induces a fibrotic tissue reaction

Bio-Alcamid, Polymekon, Brindisi, Italy; Voluma, Juvederm, Allergan, Irvine, CA; Sculptra, Dermik Laboratories, Bridgewater, NJ; Radiesse, Merz Pharma, Frankfurt am Main, Germany; Artecoll, Rofil Medical, Breda, The Netherlands.

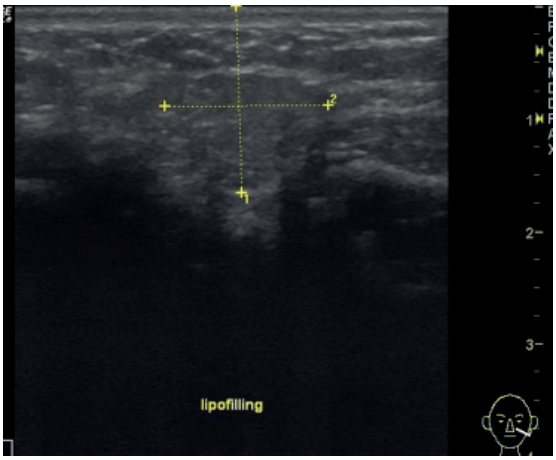

Figure 1. Autologous fat implant in the cheeks.

Polylactic Acid

Polylactic acid (PLA) is a biostimulator and enhances collagen production. It may be injected at the subcutaneous or supraperiosteal level to improve (skeleton) volume loss. PLA is a solid substance that is diluted in water at the time of injection. The water is absorbed within 2 weeks. PLA itself could not be detected by ultrasound but its filling effect, based on collagen production, may be visible over time. One patient had received a first treatment of the temples with PLA 7 weeks previously. We measured the distance between the skin and the bone of the temple area with ultrasound (Figure 3, the upper side of the picture is skin, the bottom is bone). The patient returned 8 weeks after a second treatment with PLA; ultrasound measurement shows an increase in distance between the skin and the bone (Figure 4), indicating a tissue-generating effect.

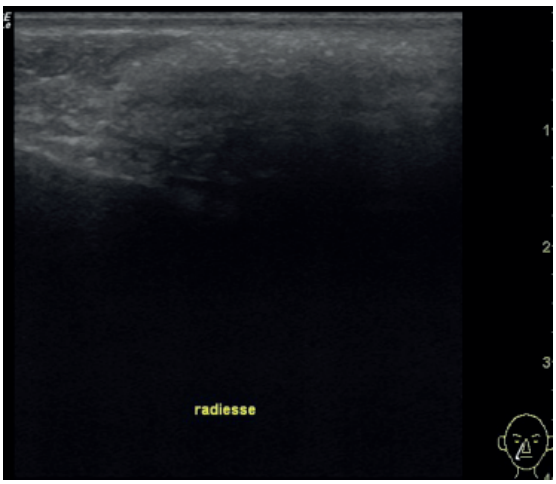

Figure 2. Hyperechogenic calcium phosphate, injected 3 months before in the deep dermal and subcutaneous planes, prevents ultrasound penetration. In the untreated skin on the left side, ultrasound penetration is visible.

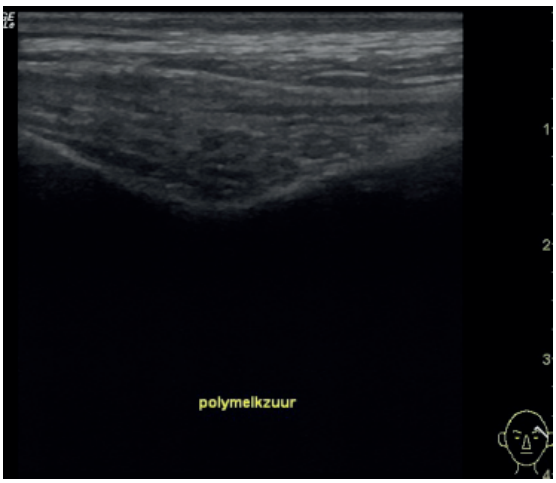

Figure 3. Polylactic acid injected 7 weeks before above the periosteal level of the temple. The distance between the skin and the bone of the temple area was measured using ultrasound.

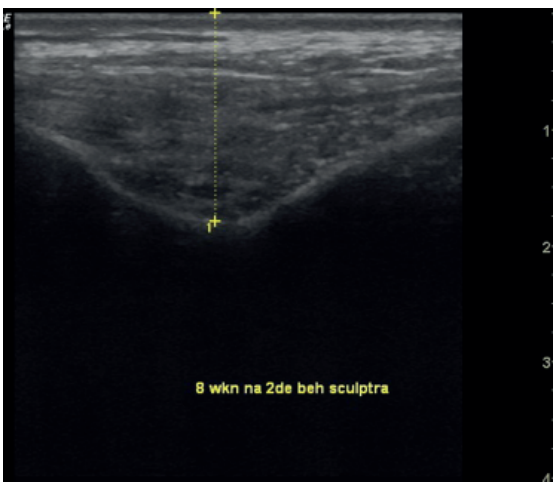

Figure 4. Follow-up ultrasound to measure the increase in the distance between the skin and the bone 8 weeks after a second treatment with polylactic acid.

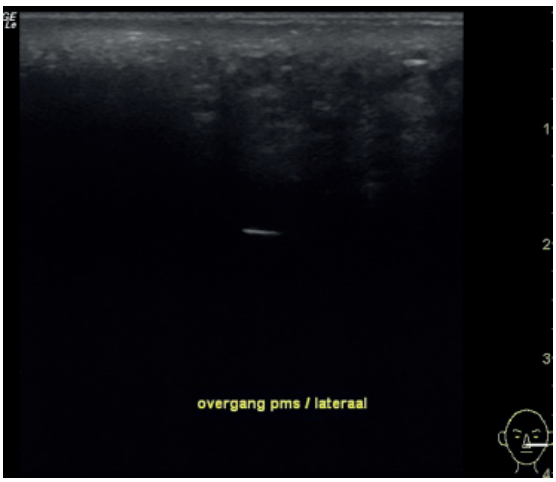

Figure 5. The tight fibrotic tissue due to silicon oil prevents ultrasound passage. The borders of the fibrotic reaction are clearly marked by echo waves passing through the untreated skin.

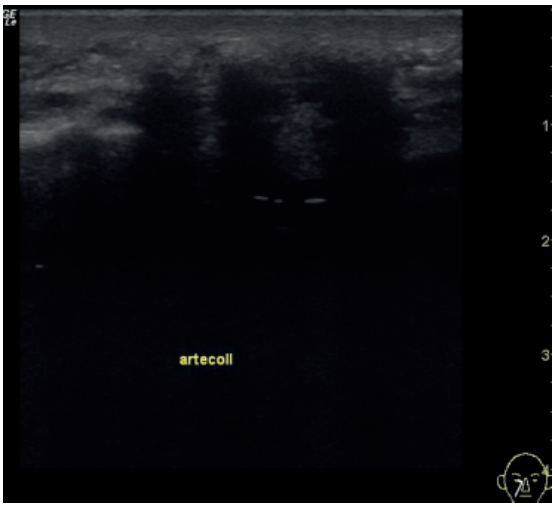

Figure 6. The tight fibrotic tissue due to polymethylmethacrylate prevents ultrasound passage.

Silicone Oil

Silicone oil is injected using a microdroplet technique into the skin and induces a fibrotic reaction leading to nonresorbable, fibrotic tissue surrounding the silicone oil. Figure 5 shows silicon oil, injected more than 10 years previously in the nasolabial fold. During clinical examination, there are no visible signs of overcorrection or granulomas. On palpation, firmer, homogeneous skin tissue can be felt underneath the nasolabial fold. With ultrasound, we cannot detect any product, but the tight fibrotic tissue can be marked, because it does not allow any sound wave to pass through, leaving the structures and tissue underneath unrevealed (shadowing). The borders of the fibrotic reaction toward the right side of the picture are clearly marked by echo waves passing through the skin showing the deeper structures.

Polymethylmethacrylate

Polymethylmethacrylate (PMMA) is a permanent product that induces a fibrotic tissue reaction and is mainly injected into the subcutaneous layer.

Figure 6 shows PMMA, injected more than 10 years previously into the nasolabial fold. With examination, the fibrotic tissue reaction can be seen, and on palpation, firmer, homogeneous skin tissue can be felt underneath the nasolabial fold. Ultrasound shows an image of shadowing due to the fibrotic reaction similar to that seen with silicone oil.

Polyalkylimide

Most of the patients presented to our clinic with complications after treatment with polyalkylimide.

Polyalkylimide is a nonresorbable, biocompatible, hydrophilic gel consisting of 96% water and 4% polyalkylimide. It can be injected subcutaneously to correct volume loss. On ultrasound, the hydrophilic polyalkylimide appears as an anechogenic (cystic) black lesion with distinct, echogenic walls (left side of Figure 7).

Complications

During facial ultrasound examination, the following complications due to fillers were visible (Table 4).

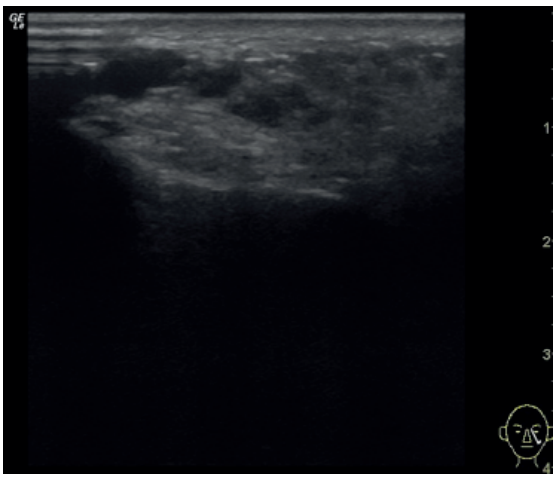

Figure 7. The hydrophilic polyalkylimide appears as a cystic black lesion. Fibrotic hardening of the product can be seen on the right side as a more grayish reflection around and within the product.

Hardening of the Filler: During clinical examination, hardening can be felt and is often visible. With ultrasound, the fibrotic hardening of a product will reflect more sound waves than polyalkylimide alone and can be seen as a more grayish reflection around and within the product (right side of Figure 7).

Migration of Filler: Migration is a possible complication. In a patient treated with polyalkylimide to correct volume loss in the cheeks, a disfiguration of bulging appeared in the lower eyelid and was seen and palpable (Figure 8). As shown in Figure 7, with ultrasound we were able to identify the bigger, original depot of polyalkylimide in both cheeks followed by a droplet pattern of polyalkylimide migrating upward toward the medial lower eyelid.

Granuloma Formation: A possible complication of fillers based on tissue regeneration is a granuloma, which can be noticeable in the skin and is palpable as a hard nodule (Figure 9).

With ultrasound (Figure 6) a small, slightly more echogenic oval shaped area is visible within the fibrotic anechogenic tissue, indicating remaining product.

Placement of Filler: One patient presented with persistent swelling and irritation of the left lower eyelid after treatment with HA in the deeper planes of the orbital rim and cheekbones. Swelling had initially been treated successfully with hyaluronidase injections and prednisone orally but recurred after stopping therapy.

With ultrasound, pockets of HA were located in the deeper subcutaneous layers. The filler was placed correctly, but one deeper pocket was seen to be situated directly near a vessel on the ultrasound (Figure 10). Hyaluronidase was injected under ultrasound guidance in this pocket. At follow-up, the swelling had disappeared, and the pocket of HA had almost disappeared; declining pressure on the vessels is visible with color flow (Figure 11).

In two patients, ultrasound examination was used after the treatment filler procedure. Both patients were treated with HA for volume restoration; one patient was treated with 2 mL of HA in each temple;

TABLE 4. Ultrasound Findings of Adverse Events (AEs)

Product	*AE*	*Ultrasound Finding*	*Time Frame AE*
Bio-alcamid (polyalkylimide)	Migration	Pattern of small, hypoechogenic droplets	2–6 years after treatment
Bio-alcamid (polyalkylimide)	Fibrotic hardening	Stronger fibrotic reflections seen as a more grayish color around and within the filler	2–6 years after treatment
Voluma hyaluronic acid	Wrong placement	Compression of vessel	Directly after treatment
Artecoll polymethylmethacrylate	Granuloma	Slightly hyperechogenic oval shaped area	Years after treatment

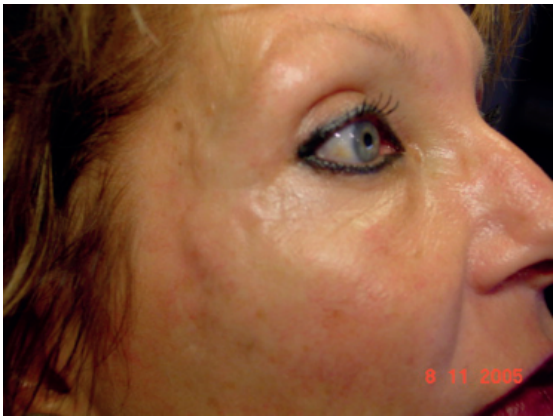

Figure 8. Hardening and migration of polyalkylimide from the cheek to the area under the eyelid.

the other patient was treated with 2 mL of HA in each cheek bone. Before treatment, exploration of the treatment area was performed with ultrasound; arteries and veins in the superficial and medial level were located. No other fillers or abnormalities were seen. The distance between the skin and the bone was measured.

Just before injection, the tip of the needle was placed on top of the periosteum. Ultrasound was performed during the entire injection to ensure the material was injected on the periosteum. After injection, correct placement was seen, and the distance between the skin and the bone was measured again directly after treatment.

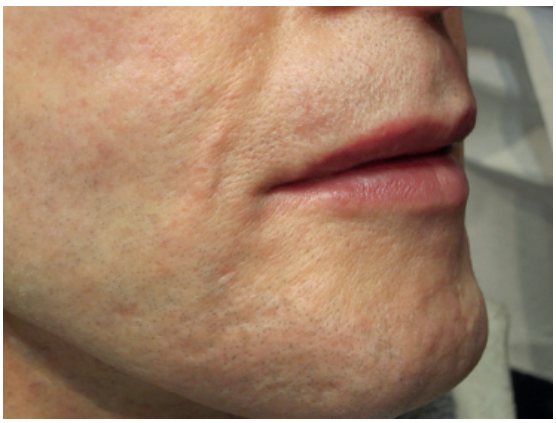

Figure 9. Visible fibrotic tissue reaction after polymethylmethacrylate injection in the nasolabial fold.

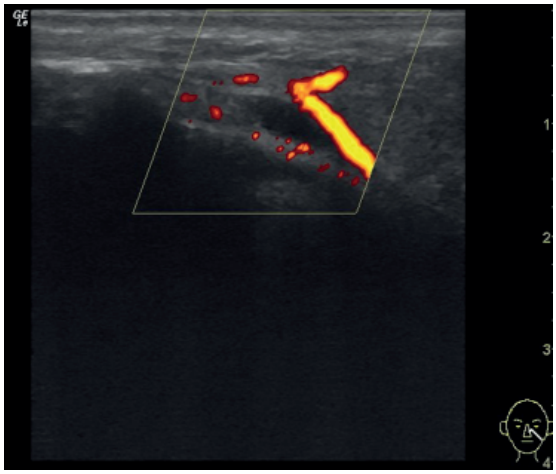

Figure 10. High vessel pressure caused by a depot of injected hyaluronic acid (black lesion).

During a control visit 3 months after treatment, a follow-up ultrasound was performed in both patients, and the location of the product over time and longevity was assessed by measurement of the distance between the skin and the bone (Figure 12).

Discussion

Current knowledge of fillers is mainly based on product information, clinical examination,[12,13] and some histological findings. The latter is limited

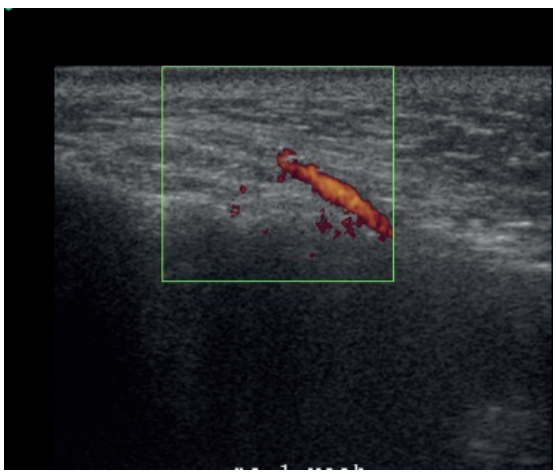

Figure 11. Same vessel as in Figure 10. Normal pressure after hyaluronidase injection in the hyaluronic acid (now almost disappeared).

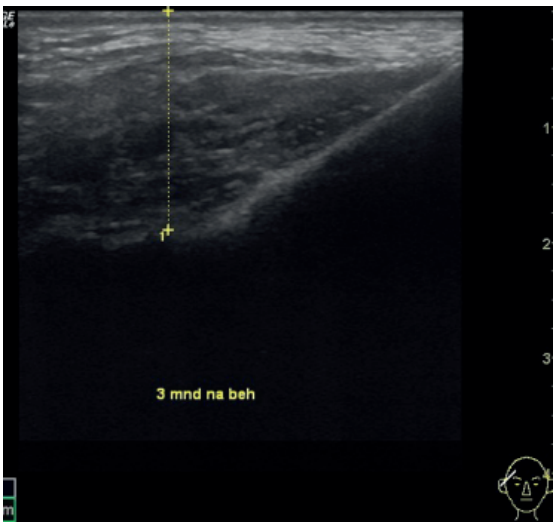

Figure 12. Hyaluronic acid (hypoechogenic black lesions) placed 3 months before just above the periosteal level of the temple.

because most patients are reluctant to have a biopsy taken from their facial skin, and even if a biopsy is obtained, the information is limited to the area from where the piece of skin was taken.[14]

Adding the use of ultrasound to our clinical findings may broaden our knowledge of fillers.

We realize that, in this study, the majority of ultrasounds performed were regarding polyalkylimide and that most patients had ultrasounds because of complications with regard to fillers.

We need more data to confirm different filler echo densities in correlation to their characteristics. If these are consistent, ultrasound examination may add useful information such as degradation, the location of fillers over time, and complications such as migration. Used in clinical research, it may lead to a better understanding of the product and increase safety. For tissue-generating fillers, it would be interesting to investigate whether ultrasound may add useful information by measuring the volume increase due to collagen production. Whether ultrasound may add value in the treatment of complications needs to be evaluated.

Good understanding of, and skills in, ultrasound are necessary. Some structures in the tissue may have the same echo visibility as fillers. By adding Doppler ultrasound (which can detect and measure blood flow) or looking at a different plane or angle, differentiation between vessels, muscles, and fillers was established. Ultrasound information can be interpreted only in conjunction with adequate history taking, clinical examination of the face, and product knowledge.

We used the 13 MHz ultrasound. We may investigate which resolutions between 13 and 20 MHz are even more accurate to explore fillers in the different layers of the skin and tissue underneath, because skin examination using ultrasound with a higher resolution (20 MHz) has recently been described.[9]

Acknowledgments We would like to thank Mr. F.J. Rietema, MD, radiologist (X-ray and Ultrasound Department, Academic Hospital Rotterdam, the Netherlands) for his careful reading.

References

1. Donofrio L, Weinkle S. The third dimension in facial rejuvenation: a review. J Cosmet Dermatol 2006;5:277–83.
2. Bucky LP, Kanchwala SK. The role of autologous fat and alternative fillers in the aging skin. Plast Reconstr Surg 2007;120(6 Suppl):89S–97S.
3. Brandt FS, Cazzaniga A. Hyaluronic acid gel fillers in the management of facial aging. Clin Interv Aging 2008;3:153–9.
4. Vleggaar D, Fitzgerald R. Dermatological implications of skeletal aging: a focus on supraperiosteal volumization for perioral rejuvenation. J Drugs Dermatol 2008;7:209–20.
5. Tezel A, Fredrickson GH. The science of hyaluronic acid dermal fillers. J Cosmet Laser Ther 2008;10:35–42.
6. Kablik J, Monheit GD, Yu L, et al. Comparative physical properties of hyaluronic acid dermal fillers. Dermatol Surg 2009;35(Suppl 1):302–12.
7. Nicolau PJ. Long-lasting and permanent fillers: biomaterial influence over host tissue response. Plast Reconstr Surg 2007;119:2271–86.
8. Falcone SJ, Berg RA. Temporary polysaccharide dermal fillers: a model for persistence based on physical properties. Dermatol Surg 2009;35:1238–43.

9. Schmid-Wendtner MH, Dill-Müller D. Ultrasound technology in dermatology. Semin Cutan Med Surg 2008;27:44–51.

10. Grima PF, Chiavaroli R, Grima P. Ultrasonic assessment of lipodystrophy in HIV-1-infected patients. Radiol Med 2009;114: 114–51.

11. Young SR, Bolton PA, Downie J. Use of high-frequency ultrasound in the assessment of injectable dermal fillers. Skin Res Technol 2008;14:320–3.

12. Pinsky MA, Thomas JAJuverderm vs Zyplast Nasolabial Fold Study Group, et al. Juvéderm injectable gel: a multicentre, double-blind, randomized study of safety and effectiveness. Aesthet Surg J 2008;28:17–23.

13. Smith S, Busso M, McClaren M, Bass LS. A randomized, bilateral, prospective comparison of calcium hydroxyapatite microspheres versus human-based collagen for the correction of nasolabial folds. Dermatol Surg 2007;33(Suppl2):S112–21, discussion S121.

14. Dadzie OE, Mahalingam M, Parada M, et al. Adverse cutaneous reactions to soft tissue fillers-a review of the histological features. J Cutan Pathol 2008;35:536–48.

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Chapter 5.2

Ultrasound to improve the safety of hyaluronic acid filler treatments

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Ultrasound to improve the safety of hyaluronic acid filler treatments

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Summary

Background: Hyaluronic acid fillers are known for a reliable safety profile, but complications do occur, even serious vascular adverse events.

Objective: To improve the safety of hyaluronic acid filler treatments.

Methods: Ultrasound is used to image hyaluronic acid fillers.

Results: Before a filler treatment is performed with ultrasound, previous filler treatments can be brought in to sight and vascular mapping can be performed. In case of adverse events, the filler and the surrounding tissues are visible. Dislocation, abscesses, and vascular adverse events can be seen. Under ultrasound guidance, hyaluronidase can be injected directly into the filler deposit.

Conclusion: Ultrasound examination can be an important tool to improve the safety of hyaluronic acid filler treatments.

KEYWORDS

complications, cosmetic dermatology, filler, hyaluronic acid, safety, ultrasound

1 | INTRODUCTION

Cosmetic medicine is a continuously growing field, including minimally invasive treatments with resorbable dermal fillers. Hyaluronic acid fillers are the most commonly used products. According to the American Society of Aesthetic Plastic Surgery, over 2.4 million treatments were performed with hyaluronic acid fillers in 2016.[1]

As most patients treated are healthy people looking for a cosmetic improvement, the treatments performed should be as safe as possible. Although these fillers are known for a reliable safety profile, adverse events do occur.[2,3] Complications can be caused by the product itself (too strong cross-linking of the product), the product-host interaction (allergic reactions, inflammatory responses), or the injection technique performed (accumulation or dislocation of the product due to muscle movement, intravascular injection, or vascular compression of filler material).[3,4] In its most serious form, intravascular injection or vascular compression of filler material can lead to skin necrosis or, in rare cases, blindness.[5,6] It has been suggested that the minor signs of vascular compression may be misinterpreted as injection-related bruising, pain, and swelling.[7]

Guidelines and other articles focused on hyaluronic acid fillers are published in order to minimize potential damage to skin and underlying tissue.[8–11]

Hyaluronic acid fillers come with the advantage of being dissolvable with hyaluronidase in case of complications.[12] If this is necessary, identifying the location of the filler in the skin is important as hyaluronidase should be injected into the filler mass. However, when the filler is placed deep dermally, detection can be very difficult.

Doppler ultrasound (duplex) is commonly used in dermatology to evaluate dermatological conditions of the skin and vascular structures,[13,14] specifically in the diagnosis of venous disease of the lower leg. Yet, it can also help to improve the safety of hyaluronic acid filler

injections in two distinct ways. First, it is possible to identify the filler in case of a complication.[15,16] Second, prevention of complications will be improved by locating the important vascular structures and earlier filler treatments in the projected area before a new treatment is performed.

2 | ULTRASOUND FOR FILLERS

An ultrasound device consists of a probe and a processor. The probe will generate a sound wave that penetrates body tissue. Sound waves interact with the tissue and become progressively weaker in strength as the waves are absorbed or scattered. Part of the sound waves is being reflected. The reflected sound waves, picked up by the probe and directed to the processor, are transformed into a digital image. Based on echogenicity Table 1, a filler, or its reaction in tissue, will be imaged as hyperechoic (white on the screen), hypoechoic (gray on the screen), and anechoic (black on the screen). Tissues are isoechogenic if they show the same echogenicity as the neighboring tissue, which makes these two tissues indistinguishable.[17]

When a Doppler system is integrated with the ultrasound, the device is named duplex. With a duplex machine, blood flow is made visible on the screen in red and blue colors. Herewith, blood vessels can be identified in conjunction with other dermal structures.

Fillers come in different formulae, but they have hydrophilic or hydrophobic characteristics.

All hyaluronic acid fillers are able to bind water and are thus hydrophilic. As water content does not reflect the sound waves, hyaluronic acid appears black (an echogenic) or light gray hypoechoic) on ultrasound Figure 1.[18] The ubiquitously used hyaluronic acid fillers come in different particle sizes, meant for different applications, and are placed in different layers of the skin and subdermis. Depending on the technique, a treading line of multiple dark deposits can be seen, specifically when a cannula is used Figure 1 or a large dark deposit bolus injections for volume replacement) may be visible Figure 2.

3 | ULTRASOUND TO IMPROVE THE SAFETY OF HYALURONIC ACID FILLER TREATMENTS

At our ambulant cosmetic university hospital clinic, we routinely use ultrasound examination to minimize risks, but also to locate and identify fillers in patients with side effects who are referred to us. With ultrasound/duplex examination, skin, the underlying tissue including muscles, veins, and arteries can be made visible. At the same time, any filler can be brought into sight, measured in pocket size, and the plane of injection can be seen. We experience that the use of duplex provides an important improvement in the safety of dermal filler treatments.

TABLE 1 Grayscale of echogenicity

Echogenicity	The ability of a tissue or substance to reflect sound waves and produce echoes
Anechoic	No echoes, appears black on ultrasound
Hypoechoic	Less reflective and lower amount of echoes, appears as varying shades of dark gray
Hyperechoic	Highly reflective and echo-rich when compared to neighboring structures, appears as varying shades of light gray
Isoechoic	Having similar echogenicity to a neighboring structure

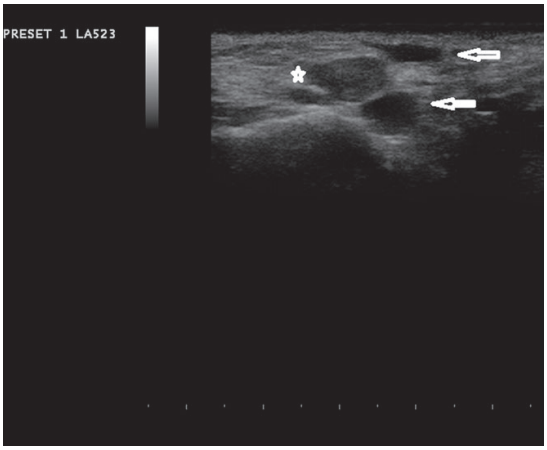

FIGURE 1 Multiple deposits of hyaluronic acid filler, two anechoic deposits (black)and one hypoechoic deposit*

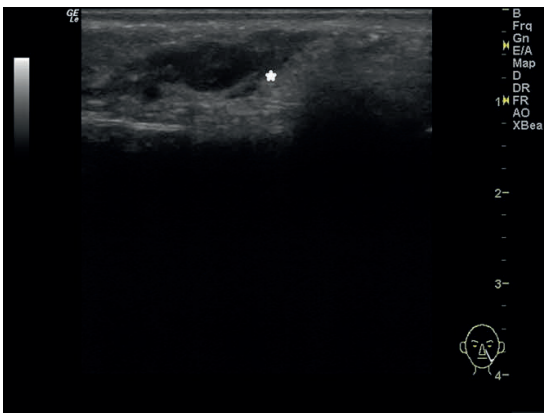

FIGURE 2 Oval-shaped hypoechoic single deposit of hyaluronic acid

3.1 | Previous filler treatments

Not only hyaluronic acid but also all fillers are visible with ultrasound.[15,19] Patients who had previous filler treatments may not always remember the type of filler and the place and plane of injection. Yet, different filler substances may give unwanted side effects,

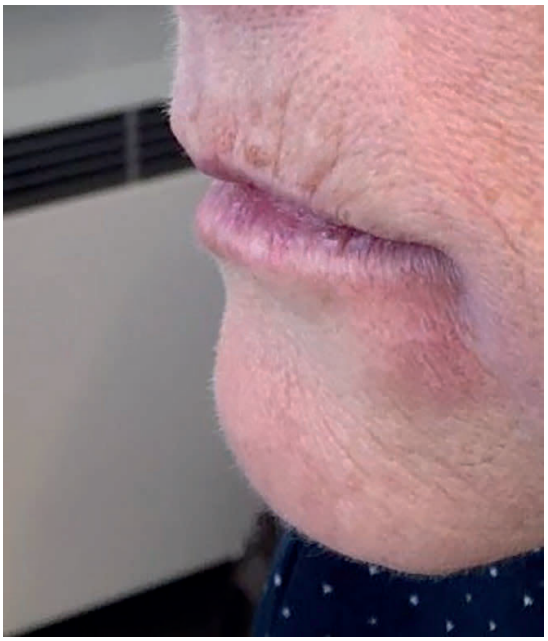

FIGURE 3 Inflammatory response of polymethylmethacrylate after hyaluronic acid filler is injected in the corners of the mouth. Note: the upper lip and chin are also responding

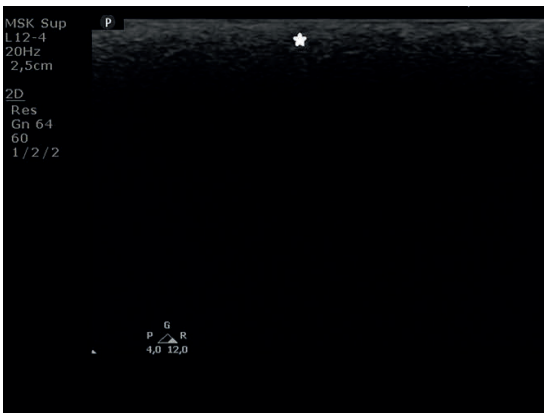

FIGURE 4 Polymethylmethacrylate visible with ultrasound

when mixed. Figure 3 shows the lower face of a 61-year-old woman. She was previously injected with polymethylmethacrylate (PMMA). After a hyaluronic acid filler was injected in the corners of the mouth, she developed an inflammatory response of polymethylmethacrylate (PMMA). The upper lip and chin were also responding with an inflammatory response, although not treated with hyaluronic acid. Using ultrasound before a filler treatment can help to distinguish between the different types of fillers used previously and thus to avoid complications Figure 4.

FIGURE 5 Locating artery with duplex

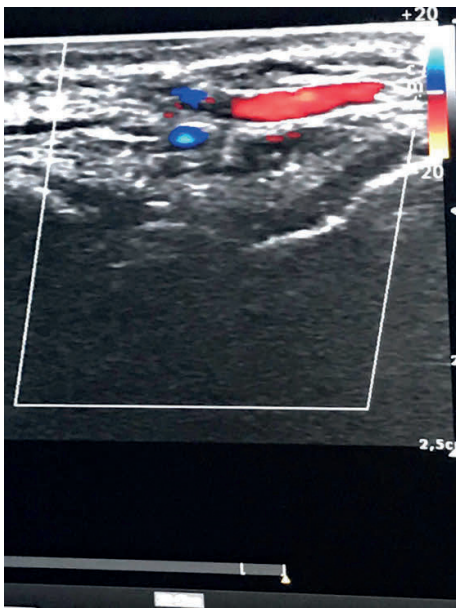

FIGURE 6 Longitudinal view of corresponding artery

3.2 | Anatomical mapping

Serious complications of filler treatments are intravascular injection or vascular compression of filler material leading to skin necrosis or, in rare cases, blindness. As these vessels are not visible clinically, prevention is extremely important. Guidelines advise to use an

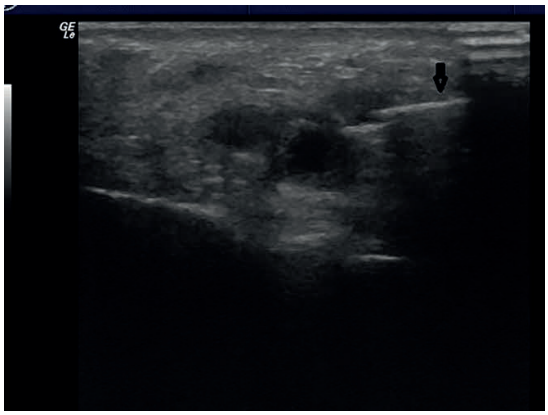

FIGURE 7 Under ultrasound guidance the needle is inserted in the filler deposit top right

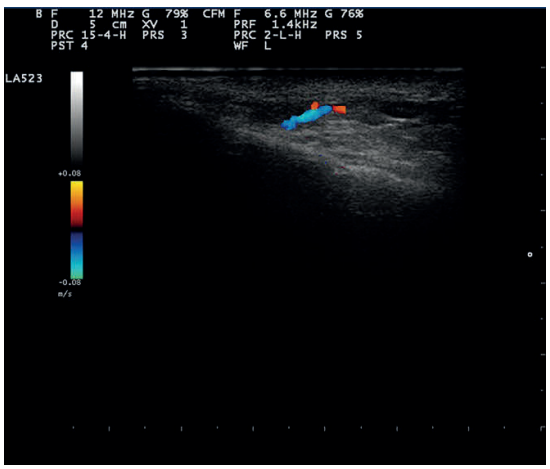

FIGURE 8 Vascular adverse event, hyaluronic acid filler deposit compromises vessel

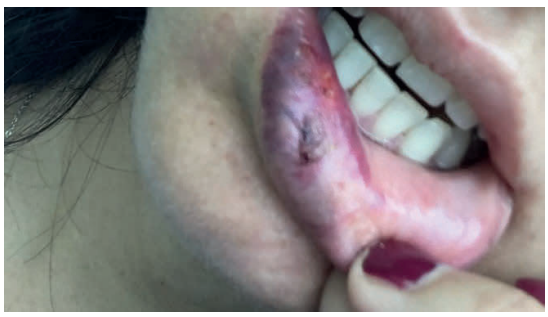

FIGURE 9 Crusting on under lip

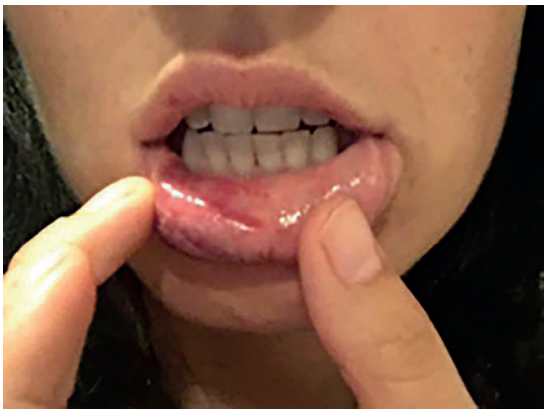

FIGURE 10 Healing of the under lip, no scarring

adequate injection technique such as cannulas and to inject slowly.[11,20,21] Most of all, anatomical knowledge of the face and the course of veins and arteries is crucial. Unfortunately, individual variations in facial artery anatomy may exist.[22,23] Ultrasound allows visualization of the facial arteries and veins of the proposed treatment area and is a noninvasive imaging tool for vascular mapping before the treatment is started.

Vascular structures appear anechoic black, containing liquid) and linear when the transducer is in the same line as the vessel, or circular when the transducer is placed on a section of the vessel. Duplex sonography B-scan ultrasound combined with color Doppler ultrasound) helps to distinguish structures with movement, for example blood moving within vessels. Color Doppler blue vs red) can also be used to determine the direction of the blood flow when needed Figures 5 and 6.

3.3 | Treatment of adverse events with ultrasound

Recently publicized protocols and guidelines describe how to treat unwanted adverse events.[24] In our experience, dissolving the filler will terminate most of the adverse events. As mentioned above, hyaluronic acid fillers are easily seen with ultrasound. The pocket size and the location of the filler can be brought into sight. Under ultrasound guidance, hyaluronidase can be injected directly into the filler pocket causing the adverse event Figure 7.

Dislocation, overcorrection of product, and vascular adverse events can be treated in this way to eliminate the cause of the problem. In case of an inflammatory response, temporary medication as antibiotic treatment may be needed as adjuvant treatment. Special attention is given to vascular adverse events as intravascular injection of filler material or vascular compression Figure 8 may lead to severe complications as necrosis. The use of ultrasound is very helpful in the treatment of these complications and in the treatment outcome. In Figure 9, the beginning of crusting as a result of a vascular adverse event is seen. This was due to a hyaluronic acid filler treatment in the right lower lip to obtain a lip augmentation. The

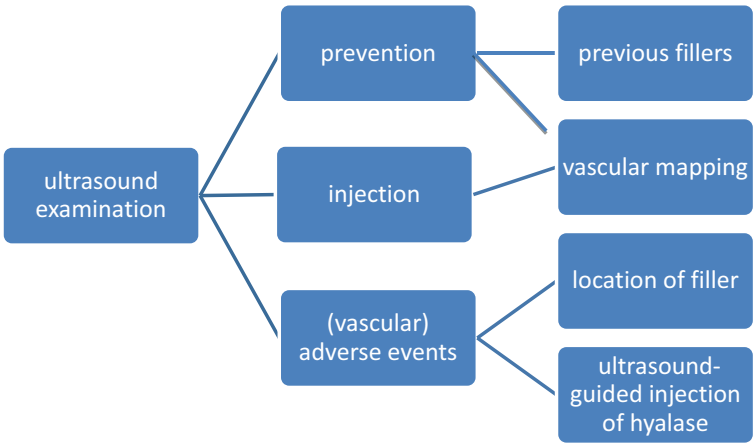

FIGURE 11 Ultrasound examination for filler treatment

referring physician described pain and blanching during injection. Hyaluronidase (150U) was injected once under ultrasound guidance in the hypoechogenic deposit. Immediate improvement was noted by the patient, continuing throughout the day, with complete recovery of her lip Figure 10.

4 | CONCLUSION

Ultrasound examination can be an important tool to improve the safety of hyaluronic acid filler treatments. The amount, location, and depth of the injected hyaluronic acid fillers can be identified. With some practice, it makes a precise intralesional delivery of hyaluronidase possible. As prevention, duplex ultrasound can be used to identify vascular structures in the proposed treatment areas Figure 11.

The learning curve to use and interpret duplex ultrasound pictures is, in our experience, not too steep. Small probes with direct connections to tablets are becoming more and more available for reasonable prices. We feel that these devices should be available in any office of a doctor using hyaluronic acid-based fillers.

CONFLICT OF INTEREST

No conflict of interest disclosures.

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REFERENCES

1. American Society for Aesthetic Plastic Surgery (ASAPS). *Cosmetic Surgery National Data Bank Statistics*; 2016. https://www.surgery.org/sites/default/files/ASAPS-Stats2016.pdf.
2. Artzi O, Loizides C, Verner I, Landau M. Resistant and recurrent late reaction to hyaluronic acid-based gel. *Dermatol Surg*. 2016;42(1):31-37.
3. Vanaman M, Fabi SG, Carruthers J. Complications in the cosmetic dermatology patient: a review and our experience (part 1). *Dermatol Surg*. 2016;42(1):1-11.
4. de Vries CG, Geertsma RE. Clinical data on injectable tissue fillers: a review. *Expert Rev Med Devices*. 2013;10(6):835-853.
5. Lazzeri D, Agostini T, Figus M, et al. Blindness following cosmetic injections of the face. *Plast Reconstr Surg*. 2012;129:995-1012.
6. Kassir R, Kolluru A, Kassir M. Extensive necrosis after injection of hyaluronic acid filler: case report and review of the literature. *J Cos Derm*. 2011;10(3):224–3112.
7. Gilbert E, Hui A, Meehan S, Waldorf HA. The basic science of dermal fillers: past and present part II: adverse effects. *J. Drugs Dermatol*. 2012;11(9):1069-1077.
8. Philipp-Dormston WG, Bergfeld D, Sommer BM, GI S, et al. Consensus statement on prevention and management of adverse effects following rejuvenation procedures with hyaluronic acid-based fillers. *J Eur Acad Dermatol Venereol*. 2017;31(7):1088-1095.
9. Signorini M, Liew S, Sundaram H et al. Global aesthetics consensus: avoidance and management of complications from hyaluronic acid fillers-evidence- and opinion-based review and consensus recommendations. *Plast Reconstr Surg*. 2016;137(6):961e–971e.
10. Carruthers J, Fagien S, Dolman P. Retro or PeriBulbar injection techniques to reverse visual loss after filler injections. *Dermatol Surg*. 2015;41(suppl 1):S354-S357.
11. Beleznay K, Carruthers JD, Humphrey S, Jones D. Avoiding and treating blindness from fillers: a review of the world literature. *Dermatol Surg*. 2015;41(10):1097-1117.
12. Cavallini M, Gazzola R, Metalla M, Vaienti L. The role of hyaluronidase in the treatment of complications from hyaluronic acid dermal fillers. *Aesthet Surg J*. 2013;33(8):1167-1174.
13. Wortsman X, Alfageme F, Roustan G et al. Guidelines for performing dermatologic ultrasound examinations by the DERMUS Group. *J Ultrasound Med*. 2016;35(3):577-580.
14. Wortsman X. Sonography of dermatologic emergencies. *J Ultrasound Med*. 2017;36:1905-1914.
15. Wortsman X, Wortsman J, Orlandi C, Cardenas G, Sazunic I, Jemec GB. Ultrasound detection and identification of cosmetic fillers in the skin. *J Eur Acad Dermatol Venereol*. 2012;26(3):292-301.

16. Grippaudo FR, Di Girolamo M, Mattei M, Pucci E, Grippaudo C. Diagnosis and management of dermal filler complications in the perioral region. *J Cosmet Laser Ther*. 2014;16(5):246-252.
17. Rallan D, Harland CC. Ultrasound in dermatology – basic principles and applications. *Clin Exp Dermatol*. 2003;28:632-638.
18. Kohn JC, Goh AS, Lin JL, Goldberg RA. Dynamic high resolution ultrasound in vivo imaging of hyaluronic acid filler injection. *Dermatol Surg*. 2013;39:1630-1636.
19. Schelke LW, DenElzen HJ, Erkamp PP, Neumann HA. Use of ultrasound to provide overall information on facial fillers and surrounding tissue. *Dermatol Surg*. 2010;36(suppl 3):1843-1851.
20. Casabona G. Blood aspiration test for cosmetic fillers to prevent accidental intravascular injection in the face. *Dermatol Surg*. 2015;41:841-847.
21. Coleman SR. Avoidance of arterial occlusion from injection of soft tissue fillers. *Aesthet Surg J*. 2002;22:555-557.
22. Lee SH, Gil YC, Choi YJ, Tansatit T, Kim HJ, Hu KS. Topographic anatomy of the superior labial artery for dermal filler injection. *Plast Reconstr Surg*. 2015;135(2):445-450.
23. Furukawa M, Mathes DW, Anzai Y. Evaluation of the facial artery on computed tomographic angiography using 64-slice multidetector computed tomography: implications for facial reconstruction in plastic surgery. *Plast Reconstr Surg*. 2013;131(3):526-535.
24. DeLorenzi C. New high dose pulsed hyaluronidase protocol for hyaluronic acid filler vascular adverse events. *Aesthet Surg J*. 2017;37:1–12.

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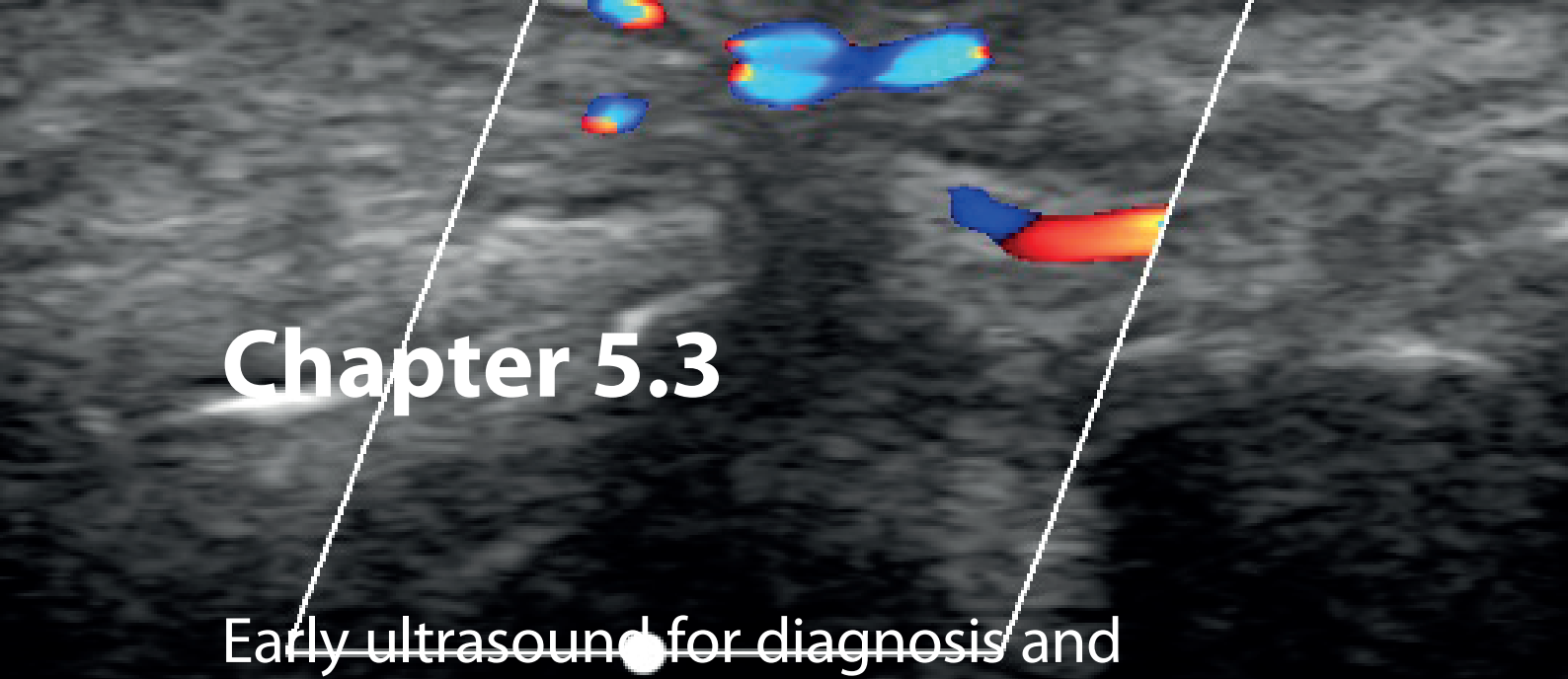

Chapter 5.3

Early ultrasound for diagnosis and treatment of vascular adverse events with hyaluronic acid fillers

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Abstract

Background: Hyaluronic acid fillers are known for a reliable safety profile, but complications do occur, even serious vascular adverse events .

Objective: To improve the treatment outcome after an vascular adverse event safety of hyaluronic acid filler treatments

Methods: Duplex / ultrasound is used to detect the hyaluronic acid filler causing the intra-arterial obstruction

Results: If treated in time, one single treatment of ultrasound guided injections of hyaluronidase into the filler deposit will prevent skin necrosis.

Conclusion: As the use of duplex / ultrasound adds extra essential information, its use may become an integral part of the prevention and treatment of injection adverse events.

Capsule summary

• Vascular adverse events caused by hyaluronic acid fillers may lead to skin necrosis. To prevent necrosis, the use of hyaluronidase to dissolve the filler remains the first treatment option • The use of duplex / ultrasound adds essential information and should be a priority in the treatment of vascular adverse events

Introduction

The popularity of robust hyaluronic acid (HA) fillers for facial contouring has seen a dramatic rise in the past years leading to their dominance in the aesthetic marketplace[1]. The hyaluronic acid molecule itself is a high–molecular weight polysaccharide, which, at physiologic pH, binds water extensively, is completely resorbable., and therefore biochemically considered to be a safe compound[2,3]. However, even with safe degradable products, the techniques and treatment protocols employed by physicians must portend a low rate of adverse events. The Department of Dermatology, Erasmus Medical Centre, Rotterdam has established an out-patient clinic for filler complications that treats patients referred for both product related (inflammatory responses and allergic reactions) and injector related adverse events which include overcorrection, injector nodules, malar edema, dislocation and accumulation of product (due to underlying muscle movement), and vascular events [4,5,6,7]. The frequency seen at the clinic of intravascular complications leading to skin necrosis or blindness is as of this publication (April 2019) noted to be twice monthly . An increasing number of articles and guidelines have recently been published regarding these disastrous complications, including a safety warning of the FDA on its website in 2015 [,4,,7,8,9,10,11].

One of the advantages of HA fillers is their dissolvability with hyaluronidase in the event of post-injection complications. Commercially available hyaluronidases serve as endoglycosidases that cleave the glycosidic bonds inducing depolymerization[12,13] and a reduction of the normal high viscosity and lubricating action associated with the various HA roles in tissues . The clinical safety record in humans for hyaluronidase is well established, dating back more than 50 years, with an allergic reaction as the most serious complication occurring at an incidence of 1:2000[14].

For a vascular adverse event leading to skin necrosis, the use of hyaluronidase (HAse) remains the first line of treatment[9,11,13]. Hyaluronidase has been shown to penetrate through thin vessel walls, but from a mechanical perspective will be limited in reaching the distal part of the HA filler obstruction in the blocked vessel [16,17,18]. Therefore, the current leading guideline involves the use of pulsed high-dose hyaluronidase in one hour intervals in order to bathe the obstructed vessels in a concentration sufficient enough to diffuse across the arterial wall and then break

down the HA filler particles to metabolic products small enough to pass through the capillary system. For each ischemic area measuring 3 x 3 cms, a minimum of 500 iu of hyaluronidase is advised. It has also been recommended to keep the patient in the clinic for observation between pulses for anywhere from three to eight treatment sessions until normal skin color returns[18].

The outcome from this high dose protocol has shown to be very effective, as the majority of patients treated did not develop necrosis nor was there any residual scar tissue. However, there are several important drawbacks that should be noted with this therapeutic approach. The treating physician must rely purely on clinical observation, therefore the precise location of the vessel obstruction within the zone of ischemia as well as the amount of filler is neither detectable nor appreciated. The hourly, multiple pulsed injections of high dose hyaluronidase over the ensuing hours has intendant skin trauma, is arduous, and often leads to exhaustion of both the patient and the physician abandoning the treatment until the subsequent day[18,19]. Finally, the high dose of hyaluronidase required to penetrate the vessel wall increases the risk of possible retinal toxicity in the event of inadvertent intravascular deployment, especially in the periorbital region.

It is with this understanding, that the use of a duplex/ultrasound (DUS) device was investigated for vascular mapping in high risk zones pre-injection, as well as to determine both quantity and location of the HA to guide treatment in those cases of vascular compromise[20]. A comparison of current hyaluronidase protocols and ultrasound-guided therapy is listed in Table 1.

Table 1. Comparison of Current HAse Protocols and Ultrasound-Guided HAse Injections for Intravascular HA Events

	High dose protocol	**Ultrasound guided**
Prior avoidance of vessels in high risk areas by vascular mapping	No	Yes
Amount/extent of filler determined	No	Yes
Treatment timing	Immediate	Immediate
Dose interval	Hourly for 3-8 hours	Once
Hyaluronidase Dose	High (>500iu)	Low (35-50iu)
Ancillary Tx	None	None
Treatment Outcome	Very Good (partial to full resolution)	Excellent (full resolution if performed early)
Special equipment necessary	No	High frequency Doppler US

In our referral centre specialized in filler complications, the nine year plus experience with ultrasound in detecting fillers and their complications has evolved to its implementation for the emergency treatment of vascular adverse events. With high frequency ultrasound, the depth, location and injectate size of all soft tissue fillers including hyaluronic acid fillers are visible and can be differentiated as to their composition[21,22,23,24].

HA fillers are extremely hydrophilic (water binding) and thus are visualized by DUS as anechoic to hypoechoic lesions[21,24,26]. The injected hyaluronic acid depots are well defined. During breakdown, the characteristics of fillers may change as does the appearance of fillers with ultrasound[19]. HA fillers have an anechoic appearance immediate post-injection which gradually changes to a more hypoechoic lesion over the ensuing months as the filler tends to integrate into the surrounding tissue over time. It may then only by perceptible as a hypo to isoechoic structure which is recognizable as it disturbs the normal architecture of its surroundings.

Material and methods

Twenty one patients from July 2018 to May 2019 were enrolled in this retrospective study. All were referred to the out-patients clinic of the Erasmus University Medical Centre for vascular occlusion after hyaluronic acid injections in the face. Eligible patients were 18 years or older. Exclusion criteria included earlier use of permanent facial fillers, a vascular occlusion caused by a non-HA filler, pregnancy or intent for pregnancy or the presence of an inflammatory condition of the face. Informed consent was obtained from all patients.

The location of intravascular injection, the time between onset of vascular adverse event and treatment, the amount of HAse units of treatment were recorded. Furthermore, complete recovery was labeled as positive when no obvious scarring was left after skin healing.

Upon arrival at our out-patient clinic, all patients underwent physical and DUS examination of the affected area. After this the treating physician would attempt to inject 35-50 units of hyaluronidase into the obstructing intravascular bolus of filler under ultrasound guidance. Ancillary therapy instituted to increase blood flow were aspirin (ASA) and the application of warm compresses. In those cases of delayed referrals where disruption of skin integrity was visible or the presence of necrosis was evident, oral antibiotics were prescribed to prevent superinfection.

Immediately after an intravascular deposition, the freshly injected hyaluronic acid is detectable as a black (anechoic) well defined lesion. With the DUS in duplex mode, blood vessels can be distinguished from the surrounding tissues as the blood flow is visible on the screen in pulsating red and blue colors. In normal vessels, laminar flow as seen with duplex ultrasound relates to successively higher velocities (a gradient) from zero at the walls to a maximum along the centerline of the vessel. Most filler obstructions are not truly 100% obstructive, varying from stenosis to near complete blockage. Both of these situations lead to disrupted laminar flow with marked turbulence. This turbulence is depicted as a combination of red and blue colours on the duplex ultrasound. Laminar flow recovers at some distance from the stenosis. (figure 1).

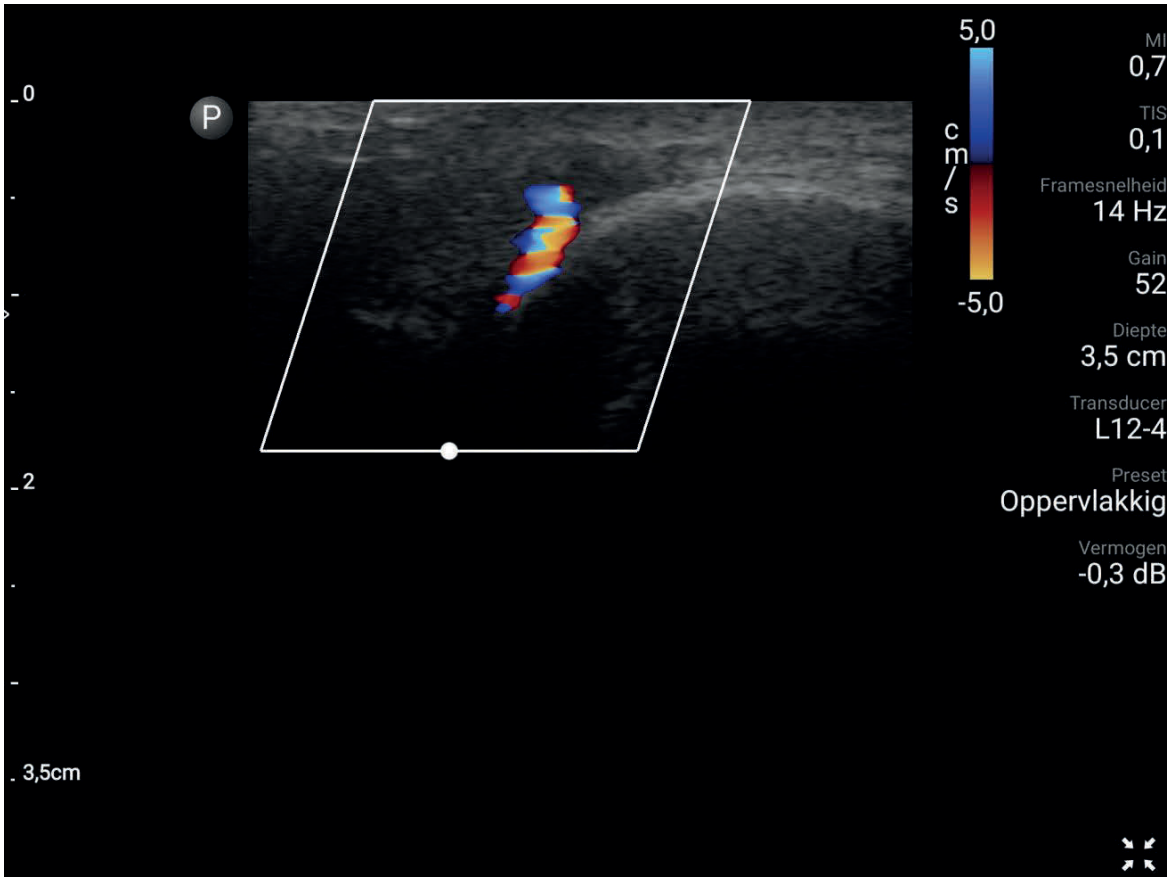


Fig 1 Hyper vascular artery with hypoechoic pocket of hyaluronic acid filler

Results

Twenty one patients referred with a vascular adverse event due to hyaluronic acid fillers were treated with ultrasound-guided hyaluronidase injections (Table 2). Vascular occlusions were located at the lips (n=8), the nose (n=4), the forehead (n=3) and the chin (n=4), the cheek (n=2) and . The involved arteries were the angular artery (n=3), the superior labial artery (n=9), the submental artery (n=2), the inferior labial artery (n=2), the columellar artery (n=2) the transverse facial artery (n=1), the superficial temporal artery (n=1), the supratrochlear artery (n=3) and the facial artery (n=1).

Under ultrasound guidance, typically 35-50 units of hyaluronidase (Hyalase, 125 units per 1 ml) were injected (minimum of 35 units and a maximum of 150 units).into the hyaluronic acid deposits responsible for the occlusion (Table 2), resulting in immediate restoration of blood flow (figure 3 c, 3d). Clinical improvement of the livedo reticularis aspect of the skin was noted after restoring the blood flow.

Table 2. Patients and Outcomes

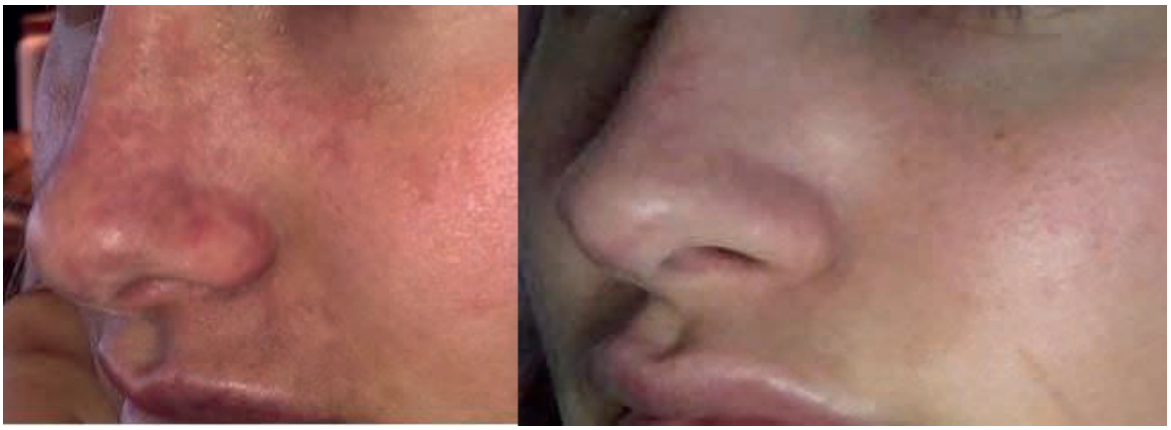
	Location	Artery	Units of HAse	Delay in treatment time	Number of treatments	Complete recovery
1	Nose	Angular artery	35	1 day	1	Yes
2	Nose	Angular artery	65	4 hours	1	Yes
3	Nose	Angular artery	35	1.5 days	2	Yes
4	Nose	Facial artery, superior labial artery	60 / 60	1 day	2	Yes
5	Lip	Superior labial artery, columellar artery	45 /45	12 hours	1	Yes
6	Lip	Superior labial artery, columellar artery	40/40	3 hours	1	Yes
7	Lip	Superior labial artery	40	4 hours	1	Yes
8	Lip	Superior labial artery	50	3 days	1	Yes
9	Lip	Superior labial artery	40	1 day	2	Yes
10	lip	Superior labial artery	40	1 day		

11	Forehead	Supratrochlear artery	35	4 hours	1	Yes
12	Forehead	Supratrochlear artery	35	8 hours	1	Yes
13	Forehead	Supratrochlear artery	150	2.5 days	1	Yes
14	Chin	Submental artery	50	4 days	1	Yes
15	Chin	Submental artery	75	1 day	1	Yes
16	Chin	Inferior labial artery	60	1.5 days	1	Yes
17	Chin	Inferior labial artery	50	8 weeks	1	No
18	Parietal area	Superficial temporal artery	75/50	3 weeks	2	
19	Lip	Superior labial artery, columellar artery	45 /45	3 days	2	Yes
20	Mandibula	Transverse facial artery,	80/50	3 days	2	Yes
21	Lip	Superior labial artery, columellar artery	40/40	3 days	2	Yes

In seven patients (3,4, 9, 18-21), a second treatment session was performed within 24 hours of the initial treatment. The blood flow had been restored with the first treatment however the second treatment was scheduled as an DUS checkup to clear some more defragmented hyaluronic acid pockets known to stimulate angiogenesis [27]. Two patients (3 and 9) with signs of developing necrosis before DUS guided filler removal were advised to get hyperbaric oxygen therapy as well. In these cases, we are not sure whether restoring the blood flow alone would have been sufficient as a standalone treatment. Patient 4 with a vascular injection leading to necrosis in the glabella area and the dorsum of the nose, had restored flow of the glabella area after initial hyaluronidase treatment. The following day she developed some pustules over the dorsum of her nose; ultrasound application at this time revealed another (sidetracked) pocket of HA which was treated with HAse with resultant clearing of the ischemic area of the nasal dorsum.

The remaining vascular adverse events (except for patient 17) were resolved with one DUS-guided hyaluronidase injection (figure 2,3). Patient 17 was referred for treatment with a delay of 8 weeks. She described pain during injection in her chin followed by pustules and necrosis. She had been treated with one injection of hyaluronidase directly after filler treatment and had recovered slowly with some scarring of her skin, but there was still a livedo aspect to the skin of

her chin. With ultrasound, a hypervascular aspect to the inferior labial artery was visualized, still surrounded by a hypoechoic well-defined homogeneous deposit of hyaluronic acid and decreased distal flow. Multiple collaterals were visible as well. Ultrasound guided injection of hyaluronidase cleared the persistent livedo aspect.



Patient No. 4 before (figure 2) treatment and one day following (figure 3) single treatment with ultrasound-guided HAse injection.

Discussion

Multiple hypotheses on the pathogenesis of filler-induced necrosis have been proposed, but the exact mechanism for tissue ischemia is not fully understood. Current theories include arterial or venous compression and intra-arterial injection leading to ischemia[29].

The vascular compression theory holds that a large volume of filler injected into a tight space or scarred region, or as a consequence of intradermal bleeding or edema, may result in occlusion of the vasculature and in subsequent ischemia[30,31,32]. However, clinical and histopathologic observations support the fact that the embolic consequence of intra-arterial filler injection is the culprit in causing tissue ischemia and necrosis[31-,34] . The exact etiology of the ischemia being due to embolization of filler particles into the end arterioles none-the-less has been disputed based on the fact that crosslinked HA gels exhibit high bio stability [35, 36,37]. A further participant in the occurrence of ischemia may be the phenomenon of arterial spasm.

The face has a very extensive vascularity with numerous communicating branches between both direct and indirect linking vessels in the coronal, sagittal, and transverse planes[38,39]. These communicating branches consist of two quite distinct and different types of arteries. The first type of interconnections is less frequent and consists of vessels that are constant in caliber: the true anastomoses. The second and most common interconnections are formed by means of so-called choke vessels[,40,42]. These anastomotic vessels have the functional ability to go into spasm, reducing their vessel caliber and by this, controlling blood flow. It is thought that this additional protective mechanism will ensure vascular flow to the skin if needed, but on the other hand will minimize flow to restrict necrosis in the event of damage. What triggers these vessels to go into spasm, whether it is critical perfusion pressure, oxygen tension, reaction to a toxin, or anything else, is unknown[41,42]. Although well tolerated in skin, intravascular hyaluronic acid has shown to be strongly irritant and to be very potent in inducing a strong inflammatory response within the wall of blood vessels[40]. Thus, it is not improbable that an embolus of hyaluronic acid injected into an artery will lead to inflammation of the vessel wall. This has been postulated to induce spasm of the anastomotic connections around its anatomical perimeter in order to restrict necrosis, provided that these vessels are reduced-caliber choke anastomoses[42].

The observations with DUS examination supports this intra-arterial choke hypothesis. The

arteries before the obstruction are hypervascular with an absence of flow in the ischemic area and most important, there is an immediate recovery of arterial flow after ultrasound guided hyaluronidase injection into the HA filler deposit. In our cases studied above, only the filler deposit causing the intravascular event was dissolved, followed in each case by a clinical improvement of the livedo aspect. This may imply that the compromising perfusion at the level of the capillary bed is the result of a filler deposit at the root of the bigger artery, leading to protective spasm of the choke anastomoses rather than arteriolar occlusion due to filler particles pushed through the capillary system. This would also explain the almost direct clearing of livedo aspect once the filler deposit causing the vascular event is dissolved, as the spasm will be neutralized.

However, if the connection by which the filler material is transported is a true anastomosis, without the possibility of reduction of caliber, the filler may get sidetracked into other branches of the vessel leading to a second ischemic area[42]. Indeed, with DUS examination these sidetracked filler depots can be visualized (No 4,5,6 table 2). For example, during a vascular adverse event, filler material was found both in the superior labial artery and further away in the columellar artery.. Undoubtedly, the use of DUS is a valuable source of critical information on vascular adverse events, however, more extensive research in this area, as in the case of ocular vascular events[44], is definitely warranted.

The chemical composition and physical properties of HA fillers differ by HA concentration, amount of cross-linking, particle size, extrusion force, and elastic modulus. Thus, the available hyaluronidases have variable interactions in a time and dose dependent manner[40]. Differences in sensitivity of specific fillers to enzymatic degradation seem to affect tissue residence time and the speed at which the product is dissolved[45,46] . To overcome this issue in urgent cases of intravascular occlusion, higher doses of hyaluronidase are recommended to compensate for possible relative resistance of the gel to degradation [45 - 49]. However, with ultrasound-guided injection of hyaluronidase, an average injected dose of 35-60 units per deposit was sufficient in most cases, independent of the type of HA filler used. A possible explanation may be the precise

injection into the targeted HA deposit requiring a lower amount of units.

As in all fields of therapeutic medicine, the development of initiatives to ensure safety in the aesthetic arena is paramount for optimal patient outcomes. The use of DUS for facial arterial mapping, safe deployment of hyaluronic acid and directed low-dose hyaluronidase reversal of impending intravascular adverse events is a welcome technological advancement. Although training in the use of ultrasound and its interpretation is required, the learning curve is rapid and ongoing practice is necessary. As the use of DUS adds essential information, it is the authors' opinion that this modality will inevitably become mainstream as an integral part of the prevention and treatment of injection adverse events.

References

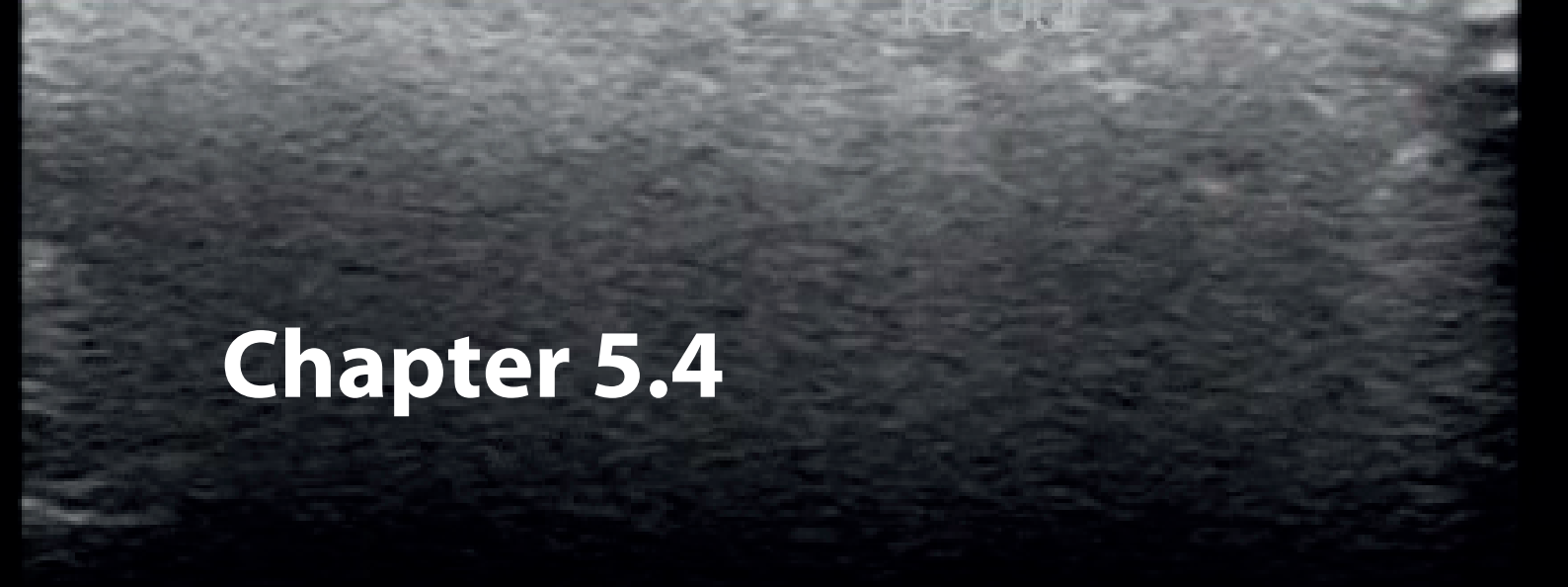
1. American Society for Aesthetic Plastic Surgery (ASAPS). 2018 Cosmetic Surgery National Data Bank Statistics. Available at: https://www.surgery.org/sites/default/files/ASAPS-Stats2018.pdf
2. Maytin EV. Hyaluronan: More than just a wrinkle filler. Glycobiology, 2016, vol. 26, no. 6, 553–559
3. Flynn TC, Sarazin D, Bezzola A, Terrani C, Micheels P. Comparative Histology of Intradermal Implantation of Mono and Biphasic Hyaluronic Acid Fillers. Dermatol Surg 2011;37:637–643
4. W.G. Philipp-Dormston WG, Bergfeld D, Sommer BM,Sattler G, Cotofana S, Snozzi P et all. Consensus statement on prevention and management of adverse effects following rejuvenation procedures with hyaluronic acid-based fillers. JEADV 2017, 31, 1088–1095
5. Artzi O, Loizides C, Verner I, Landau M. Resistant and Recurrent Late Reaction to Hyaluronic Acid–Based Gel. Dermatol Surg 2016;42:31–37
6. Bhojani-Lynch T. Late-Onset Inflammatory Response to Hyaluronic acid Dermal Fillers. Plast Reconstr Surg Glob Open 2017;5:e1532;
7. Signorini M1, Liew S, Sundaram H, De Boulle KL, Goodman GJ, Monheit G, Wu Y, Trindade de Almeida AR, Swift A, Vieira Braz A; Global Aesthetics Consensus Group. Global Aesthetics Consensus: Avoidance and Management of Complications from Hyaluronic Acid Fillers-Evidence- and Opinion-Based Review and Consensus Recommendations. Plast Reconstr Surg. 2016 Jun;137(6):961e-71e
8. Beleznay 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
9. Lazzeri D, Agostini T, Figus M, et al. Blindness following cosmetic injections of the face. Plast Reconstr Surg. 2012;129:995–1012
10. Carruthers J, Fagien S, Dolman P. Retro or PeriBulbar Injection Techniques to Reverse Visual Loss After Filler Injections. Dermatol Surg. 2015 Dec;41 Suppl 1:S354-7

11. Lohman ME, Ghobadi CW, Xu S. Device Safety Implications of the Clinical Data Leading to US Food and Drug Administration Approval of Soft-Tissue Fillers: A Systematic Review. JAMA Facial Plast Surg. 2017;19(5):421-9.
12. Cavallini M, Gazzola R, Metalla M, Vaienti L. The role of hyaluronidase in the treatment of complications from hyaluronic acid dermal fillers. Aesthet Surg J. 2013 Nov 1;33(8):1167-74
13. 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):1053-1056.
14. Landau M. Hyaluronidase Caveats in Treating Filler Complications. Dermatol Surg 2015;41:S347–S353
15. Delaere L, Zeyen T, Foets B, Van Calster J, Stalmans I.Allergic reaction to hyaluronidase after retrobulbar anaesthesia: a case series and review. Int Ophthalmol. 2009 Dec;29(6):521-8
16. Wang M, Li W, Zhang Y, Tian W, Wang H. Comparison of Intra-arterial and Subcutaneous Testicular Hyaluronidase Injection Treatments and the Vascular Complications of Hyaluronic Acid Filler. Dermatol Surg. 2017 Feb;43(2):246-254
17. DeLorenzi C. Transarterial Degradation of Hyaluronic Acid Filler by Hyaluronidase. Dermatol Surg 2014;40:832–841
18. DeLorenzi C. New High Dose Pulsed Hyaluronidase Protocol for Hyaluronic Acid Filler Vascular Adverse Events. Aesthet Surg J. 2017 Mar 17; 1-12
19. Sykes JM. Commentary on: New High Dose Pulsed Hyaluronidase Protocol for Hyaluronic Acid Filler Vascular Adverse Events. Aesthetic Surgery Journal 2017, Vol 37(7) 826–827
20. Kwon HJ, Kim BJ, Ko EJ, Choi SY. The Utility of Color Doppler Ultrasound to Explore Vascular Complications After Filler Injection. Dermatol Surg. 2017 Dec;43(12):1508-1510
21. Schelke LW, Van Den Elzen HJ, Erkamp PP, Neumann HA. Use of ultrasound to provide overall information on facial fillers and surrounding tissue. Dermatol Surg. 2010 Nov;36 Suppl 3:1843-51

22. Wortsman X1, Wortsman J, Orlandi C, Cardenas G, Sazunic I, Jemec GB. Ultrasound detection and identification of cosmetic fillers in the skin. J Eur Acad Dermatol Venereol. 2012 Mar;26(3):292-301.
23. Schelke LW, Van Den Elzen HJ, Erkamp PP, Neumann HA. Use of ultrasound to provide overall information on facial fillers and surrounding tissue.Dermatol Surg. 2010 NSov;36 Suppl 3:1843-51
24. Grippaudo FR, Di Girolamo M, Mattei M, Pucci E, Grippaudo C. Diagnosis and management of dermal filler complications in the perioral region. J Cosmet Laser Ther. 2014 Oct;16(5):246-52.
25. Kohn J.C., Goh A.S., Lin J.L.,Goldberg R.A. Dynamic high resolution ultrasound in vivo imaging of hyaluronic acid filler injection. Dermatol Surg 2013;39:1630–1636
26. D. Rallan and C. C. Harland. Ultrasound in dermatology – basic principles and applications. Clinical and Experimental Dermatology, 2003: 28, 632–638
27. Scotto di Santolo M, Massimo C, Tortora G, Romeo V, Amitrano M, Brunetti A, Imbriaco M. Clinical value of high-resolution (5-17 MHz) echo-color Doppler (ECD) for identifying filling materials and assessment of damage or complications in aesthetic medicine/surgery. Radiol Med. 2019 Jan 5
28. Kim HJ, Kwon SB, Whang KU, Lee JS, Park YL, Lee SY. The duration of hyaluronidase and optimal timing of hyaluronic acid (HA) filler reinjection after hyaluronidase injection. J Cosm Laser Therapy, 20:1, 52-57
29. Chang SH,YousefiS, Qin J, Tarbet K, Dziennis S et all.External Compression Versus Intravascular Injection: A Mechanistic Animal Model of Filler-Induced Tissue Ischemia. Ophthal Plast Reconstr Surg 2016;32:261–266)
30. Lima VGF, Regattieri NAT, Pompeu MF, Costa IMC. External vascular compression by hyaluronic acid filler documented with high-frequency ultrasound. J Cosmet Dermatol. 2019;00:1–3.Ganary Dabiri G, Damstetter E, Chang Y, Ebot EB, Gloeckner Powers J et all. Coagulation disorders and their cutaneous presentations: Diagnostic work-up and treatment J Am Acad Dermatol 2016;74:795-804.)

31. Narins RS, Jewell M, Rubin M, et al. Clinical conference: management of rare events following dermal fillers–focal necrosis and angry red bumps. Dermatol Surg 2006;32:426–34.
32. Inoue K, Sato K, Matsumoto D, et al. Arterial embolization and skin necrosis of the nasal ala following injection of dermal fillers. Plast Reconstr Surg 2008;121:127e–8e
33. Kassir R, Kolluru A, Kassir M. Extensive necrosis after injection of hyaluronic acid filler: case report and review of the literature. J Cosmet Dermatol 2011;10:224–31.17,18
34. Bruce AC, Kelly-Goss MR, Heuslein JL, Meisner JK, Price Rj et all. Monocytes are Recruited from Venules during Arteriogenesis in the Murine Spinotrapezius Ligation Model. Arterioscler Thromb Vasc Biol. 2014; 34(9): 2012–2022
35. Pluda S, Pavan M, Galesso D, Guarise C. Hyaluronic acid auto-crosslinked polymer (ACP): Reaction monitoring, process investigation and hyaluronidase stability. Carbohydr Res. 2016 Oct 4;433:47-53.
36. De Boulle K, Glogau R, Kono T, Nathan M, Tezel A et all. A review of the metabolism of 1,4-butanediol diglycidyl ether-crosslinked hyaluronic acid dermal fillers. Dermatol Surg. 2013 Dec;39(12):1758-66.
37. Prasetyo AD, Prager W, Rubin MG, Moretti EA, Nikolis A. Hyaluronic acid fillers with cohesive polydensified matrix for soft-tissue augmentation and rejuvenation: a literature review. Clin Cosmet Investig Dermatol. 2016 Sep 8;9:257-80
38. Pilsl U, Anderhuber F, Neugebauer S. The Facial Artery-The Main Blood Vessel for the Anterior Face? Dermatol Surg. 2016 Feb;42(2):203-8
39. Lee HJ, Won SY, O J, Hu KS, Mun SY, Yang HM, Kim HJ. The facial artery: A Comprehensive Anatomical Review. Clin Anat. 2018 Jan;31(1):99-108.
40. Taylor GI, Corlett RJ, Ashton MW. The functional angiosomes clinical implications of the anatomical concept. Plast Reconstr Surg. 2017 Oct;140(4):721-733
41. Saint-Cyr M, Wong C, Schaverien M, Mojallal A, Rohrich RJ.The perforasome theory: vascular anatomy and clinical implications. Plast Reconstr Surg. 2009 Nov;124(5):1529-44

42. Ashton MW, Taylor GI, Corlett RJ.The Role of Anastomotic Vessels in Controlling Tissue Viability and Defining Tissue Necrosis with Special Reference to Complications following Injection of Hyaluronic Acid Fillers. Plast Reconstr Surg. 2018 Jun;141(6):818e-830e.
43. Zhuang Y, Yang M, Liu C. An islanded rabbit auricular skin flap model of hyaluronic acid injections-induced embolism. Aesthetic Plast Surg. 2016.40:421–427.
44. Huang P1, Liu A2, Ren H2, Xue K2. Color Doppler Flow Imaging of Retrobulbar Ocular Blood Flow Changes in Retinal Artery Occlusions Caused by Cosmetic Facial Filler Injections. Ophthalmic Plast Reconstr Surg. 2018 Sep 4
45. Sundaram H. Going with the Flow: An Overview of Soft Tissue Filler Rheology and Its Potential Clinical Applications (2 of 3) cosmetic Dermatoloy June 2011
46. Flynn TC1, Thompson DH, Hyun SH. Molecular Weight Analyses and Enzymatic Degradation Profiles of the Soft-Tissue Fillers Belotero Balance, Restylane, and Juvéderm Ultra. Plast Reconstr Surg. 2013 Oct;132(4 Suppl 2):22S-32S.
47. Alam M, Hughart R, Geisler A, Paghdal K, Maisel A. Effectiveness of Low Doses of Hyaluronidase to Remove Hyaluronic Acid Filler Nodules A Randomized Clinical Trial. JAMA Dermatol. 2018;154(7):765-772
48. Hwang E, Song YS. Quantitative Correlation Between Hyaluronic Acid Filler and Hyaluronidase Craniofac Surg 2017;28: 838–841
49. Park KY, Kim HK, Kim BJ. Comparative study of hyaluronic acid fillers by in vitro and in vivo testing. JEADV 2014, 28, 565–568



Chapter 5.4

Nomenclature proposal for the sonographic description and reporting of soft tissue fillers

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Nomenclature proposal for the sonographic description and reporting of soft tissue fillers

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Abstract

Background: There is a steady increase in publications about the use of ultrasound and filler treatments, written by physicians from different specialties. The terminology used to describe the ultrasound images of fillers is not uniform, making the different articles difficult to compare. Standardization of the descriptions based on their basic sonographic parameters is recommendable.

Aims: The purpose of this study is to propose a nomenclature for the sonographic description and reporting of cosmetic fillers.

Methods: An assessment of articles indexed for MEDLINE/PubMed and Embed electronic database was conducted; in total of 39 articles could be included.

Results: All articles were investigated for their sonographic descriptions of soft tissue fillers. Ten parameters used for describing and monitoring soft tissue fillers were distinguished.

Conclusion: The proposed sonographic descriptions for cosmetic fillers may contribute to a better standardization and understanding fillers ultrasound images in the reports or literature.

KEYWORDS
fillers, nomenclature, review, ultrasound

1 | INTRODUCTION

Modern era ultrasound devices are small, portable, practical, and increasingly affordable. Probes connectable to tablets or smartphones including software are available worldwide. The technique allows direct interaction with the patient. We feel that in the near future ultrasound will be an indispensable diagnostic tool in any dermatologists office.

The use of ultrasound for imaging soft tissue fillers, has been reported and recommended in a growing number of publications during the last decade.[1-7] The use of ultrasound is being promoted as it is a noninvasive imaging modality that provides a good definition for studying the skin and deeper layers in real time, including blood flow.[8-12]

Currently, ultrasound is considered the first-imaging technique for dealing with fillers and managing their potential complications,[13-15] because it can detect and identify the most common types of cosmetic fillers,[15-17] including their anatomical location, size, and depth.[12,18] In cases where filler treatments have been performed previously, it can be helpful in patients without a clear history of fillers.[13-15,19] In the clinical practice setting, ultrasound examination can support the diagnosis and treatment of early and late complications.[16,17,19-22] In the case of hyaluronic acid fillers, hyaluronidase can be placed with ultrasound-guided injections exactly into the filler deposit.[11,23]

The use of color Doppler, as in other indications of ultrasound, has been strongly suggested.[9,15,21] This allows observation of the anatomical variants of the main facial arteries before treatment is performed.[21]

For research purposes, ultrasound examination provides valuable information on the behavior, longevity, and interaction of the filler within the tissues.[24-29]

All articles published describe the good visibility of different fillers and consider ultrasound as an asset for cosmetic medicine as it improves the safety of filler treatments. These papers have been published by physicians from different specialties and backgrounds; therefore, there is a wide range of terminology in the ultrasound description of the same type of filler. Interpreting these different descriptions may be confusing. For new applications, nomenclature should be unequivocal. Standardization of the descriptions based on basic sonographic parameters may lead to a better mutual understanding and interpretation. This paper examines ultrasound glossary for soft tissue fillers.

2 | METHODS

An assessment of articles indexed for MEDLINE/PubMed and Embed electronic database was conducted according to the PRISMA guidelines (Jan 2000–May 2018), which was restricted to papers published in English, using the relevant keywords: ultrasound [or] sonographic [and] dermal fillers, soft tissue filler, injectable filler, tissue augmentation, hyaluronic acid, collagen, poly-L-lactic acid, polycaprolactone, calcium hydroxyapatite, polyalkylimide, polyacrylamide, silicon oil, dimethylsiloxanes, polymethylmethacrylate, hydroxyethyl methacrylate lipofilling, complications, and adverse events.

As this topic is an innovative, developing area of cosmetic medicine, all studies excluding case reports were selected.

3 | RESULTS

In this assessment, a total of 39 articles (19 published in a journal for dermatology, 11 for plastic surgery, 9 for radiology) published between 2009 and 2018 could be included. Of these 39 articles, 12 described the ultrasound as a tool for research purposes, 10 to detect fillers and 17 articles mention the follow-up and treatment of complications.

All of these articles were investigated for their sonographic descriptions of soft tissue fillers and described in Table 1.

Furthermore, the main parameters used for describing and monitoring soft tissue fillers were grouped. In total, ten parameters were distinguished. Among these, echogenicity was the most common parameter reported. Echogenicity is the characteristic reflection of sound waves generated by a tissue expressed in the gray scale. Four scales are being used as follows:

- Anechoic when there are no echoes and the structure appears black on screen.
- Hypoechoic when there are low reflectiveness and density of echoes; a structure will appear as varying shades of gray.
- Hyperechoic when there is highly reflectiveness and an echo rich structure when compared to neighboring structures; it appears as varying tones of white.
- Isoechoic when the structure appears with similar echogenicity to a neighboring structure.

The other nine parameters extracted from the articles were texture, border, shape, quantity, diameter, artifacts, internal characteristics, anatomical location, and evolution. However, the descriptions of these parameters differed widely in the reports.

For example, the sonographic glossary will use the term “homogenous” or “heterogeneous” to describe the texture of a structure. However, some articles mention “regular” instead of homogeneous. Furthermore, sharp regular borders or distinct walls were re-defined as “well-defined”. Inner spots or an irregular inner pattern were categorized as “internal echoes”.

All articles mention the anatomical location of the soft tissue filler identified with ultrasound and most of them describe the filler changes over time. The ten parameters and their subtypes were extracted from literature and shown in Table 2.

3.1 | Sonographic parameters for identifying and reporting fillers

As mentioned above, the following sonographic parameters were commonly reported in the articles and may be relevant for identifying, monitoring, and reporting fillers:

3.1.1 | Echogenicity

Soft tissue fillers present distinctive sonographic patterns of echogenicity.[15] For example, water-based (hydrophilic) fillers will give a different ultrasound image compared with hydrophobic fillers. All hydrophilic fillers are able to bind water and are usually injected as a gel; therefore, the sound waves will easily pass through and they appear as anechoic (black) on screen. Most hydrophobic fillers are made from synthetic materials and do not degrade in tissue. Examples of these fillers are silicon oil and polymethylmethacrylate (PMMA).[29] These type of fillers contain microspheres that provoke variable degrees of intense reflection of the sound waves; therefore, they appear as hyperechoic (white) on the screen.[30] Some fillers may change in echogenicity over time as their water-soluble gel vehicle may be reabsorbed.

3.1.2 | Texture

The texture within the deposits may be homogeneous or heterogeneous.

Homogeneous: the filler deposit is uniform in echogenicity. Heterogeneous: the filler deposit is not uniform in echogenicity. For example, silicone oil tends to appear as homogeneously hyperechoic.[3,4,30-32] In contrast, polycaprolactone shows a mixed echogenicity with a hypoechoic matrix that contains hyperechoic spots.[31]

TABLE 1 Ultrasound descriptions of cosmetic fillers reported in the medical literature

Hyaluronic acid
Scattered anechoic round structures pseudocysts,[2] fairly distinct hypoechogenic (black) lesion with some hyperechogenic (linear) reflections,[3] anechoic or hypoechoic round or oval pseudocystic structures,[9] well-defined regular hypoechoic mass without any signs of internal echoes,[11,23] oblong, homogeneous papule, with an isoechogenic aspect,[39] mixture of iso- and hypoechogenic pools,[39] dark nonechogenic zone,[15] oval-shaped anechoic pseudocystic structures,[17] cross linked: heterogeneous echogeneous appearance of papulae,[19] monophasic: homogenous papule that was as dense as the surrounding tissue,[19] small anechoic pseudocystic structures,[22] hyaluronic acid depots,[27] anechoic pearls,[28] anechoic bubble with diffuse margins,[28] largely anechoic with internal echoes called "the sparkly lake sign",[29] a well-defined regular hypoechoic mass or band,[30] well-defined, hypoechoic subcutaneous lesions without any signs of internal echoes,[32] hypoechoic pseudocyst [33] anechoic (black) and hypoechoic deposit [34]
Calcium hydroxyapatite
Hyperechogenic tissue (shadowing),[3] hyperechoic deposits with variable degrees of acoustic shadowing due to calcium,[2,8] hyperechoic deposits with posterior acoustic shadowing artifact,[7,22] hypoechoic but with denser areas inside [24]
Polycaprolactone
Bright hyperechoic spots with a mini-comet-tail artifact within a hypoechoic matrix [18]
Polyalkylimide (PAIG)
Anechoic with water-like aspect in recent implants and corpusculated in older ones,[10] hyperechoic mass with a distinct edge from surrounding tissues, with small echoes inside,[11] anechoic oval pseudo cystic structures,[20] hyperechoic mass with inner spots,[21] oval-shaped anechoic pseudocystic structures,[22,26] hyperechoic pattern surrounded by a wall [24]
Polyacrylamide (PAAG)
Anechoic to hypoechoic lesions with distinct echogenic walls,[3] hyperechoic mass with inner spots,[11,21] anechoic round or oval-shaped pseudocystic structures,[17] hyperechoic mass and containing a spot of linear diffusion of the material[21] increased hypodermal echogenicity in the vicinity of the deposits,[22] hyperechoic pattern surrounded by a wall[24]
Silicon oil
Hyperechoic deposits (snow storm) with high degree of sound scattering,[2] shadowing due to tight fibrotic tissue,[3] snowstorm pattern,[11,24] hyperechoic deposits with a posterior reverberance that produces a "snowstorm" artifact [7] hyperechoic, with a posterior reverberation artifact,[17] strong acoustic shadow[21]
Pure silicon
Anechoic[2] Anechoic round or oval-shaped pseudocystic structures,[17] oval anechoic lacunar areas[22]
Polymethylmethacrylate (PMMA)
Multiple bright hyperechoic dots producing mini-comet tail artifact,[2,17] hyperechoic dots producing mini-comet tail shaped artifact,[22] shadowing due to tight fibrotic tissue,[3] large and old deposits may show reverberance) after 6 mo: posterior acoustic shadowing artifact[17]
Hydroxyethyl methacrylate (HEMA)
Diffusely hyperechoic appearance[20]
Lipofilling
A well-defined, compact, finely textured area and are isoechogenic to slightly hyperechogenic,[3] lobulated hypoechoic deposits with some hyperechoic linear septa,[17] area of hyperechogenicity with regular margins[31]

3.1.3 | Border

Hydrophilic fillers have a well-defined border whereas hydrophobic fillers tend to be ill-defined.[30,31] Resorbable polymeric fillers such as polycaprolactone may change in contour over time, as the hydrophilic gel carrier is being reabsorbed, the polyesters alone may remain visible as bright hyperechoic spots.[32]

3.1.4 | Shape

Hydrophilic fillers tend to have an oval or round shape. Some synthetic fillers that come in a gel such as polyacrylamide tend to maintain their oval or rounded shape, echogenicity, and size during extended periods of time, usually years.[2,31,33] In contrast, pure hyaluronic acid (noncross-linked) deposits tend to modify their shape over months.[34,35] Other filler may have a different appearance as band- or mass-like.

3.1.5 | Diameter

The most widely used hydrophilic filler is hyaluronic acid. This filler are meant for different treatment applications and duration and are injected in different depot sizes.[36] The diameter can be measured during ultrasound examination, and changes in size may be followed up.[26,31]

3.1.6 | Quantity

Depending on the technique, one large dark bolus injected for volume or a line of multiple deposits may be visible in the path of the injection.[2,28]

3.1.7 | Internal characteristics

Some hydrophilic fillers such as hyaluronic acid present variations in their echogenicity over time due to the loss of the gel vehicle that contains the deposits and may become more hypoechoic and/or may show inner echoes.[32,37,38] Examples of this situation are the long-lasting or cross-linking types of hyaluronic acid and polymeric fillers with gel vehicles.[31]

3.1.8 | Artifacts

Most hydrophobic fillers are made from synthetic materials and do not degrade in tissue. On sonography, they show different patterns of posterior acoustic artifacts which can allow their

TABLE 2 Description of parameters of sonographic fillers

Parameter	Description	Description	Description	Description
Echogenicity	Anechoic	Hypoechoic	Isoechoic	Hyperechoic
Texture	Homogeneous: the filler deposit is uniform in echogenicity	Heterogeneous: The filler deposit is not uniform in echogenicity		
Border	Well-defined	Ill-defined		
Shape	Oval	Round	Band-like	Mass-like
Quantity: when the deposits can be delimited or separated into units	Single	Multiple		
Diameter: measurements in mm or cm	Small deposits: a representative sample of the size of the deposits can be taken	Wide or diffuse dispersion of the deposits		
Artifacts	Posterior Reverberance "snow storm"	Mini-comet tail	Posterior acoustic shadowing	
Internal characteristics	Internal echoes	Septa	Hyperechoic calcifications	
Anatomical location				
Evolution	Shape	Size	Echogenicity	Content

TABLE 3 Sonographic descriptions for cosmetic fillers

Hyaluronic acid	Well-defined oval- or round-shaped anechoic homogeneous deposits without any signs of internal echoes.
Calcium hydroxyapatite	Well-defined band-like hyperechoic deposit with posterior acoustic shadowing artifact
Polycaprolactone	Ill-defined hypoechoic matrix that contain bright hyperechoic spots with a mini-comet tail artifact
Polyalkylimide	Hypoechoic mass, hyperechoic pseudocapsule, containing a spot of linear, sometimes an irregular patter of hyperechoic material within the mass
Polyacrylamide	Well-defined, oval-shaped anechoic homogeneous deposits that produce posterior acoustic
Silicon oil	Ill-defined, hyperechoic mass-like deposits that produce diffuse posterior reverberation ("snow storm pattern").
Polymethylmethacrylate	Ill-defined, hyperechoic mass-like deposits that produce mini-comet tail artifacts
Hydroxyethylmethacrylate	Ill-defined, hyperechoic mass-like deposits
Lipofilling	Hypoechoic, heterogeneous well-defined oval-shaped mass-like deposit (marker 2) with some hyperechoic linear septa

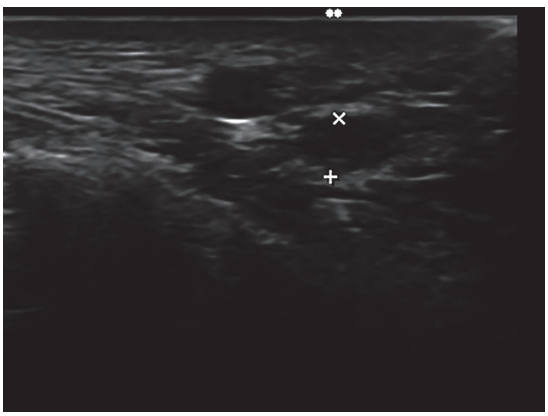

FIGURE 1 hyaluronic acid; two anechoic, homogeneous, well-defined oval-shaped deposits, one of them between markers

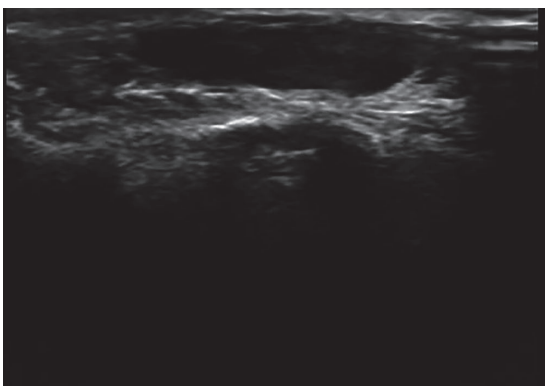

FIGURE 2 Polyalkylimide: an anechoic, homogeneous, well-defined, oval-shaped single oval deposit (without internal echoes)

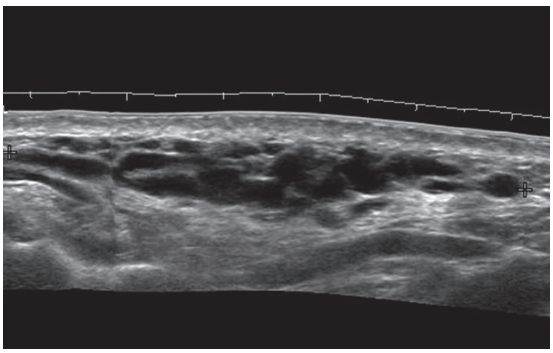

FIGURE 3 Polyacrylamide: anechoic, homogeneous, and well-defined, multiple deposits with a slight posterior reinforcement artifact

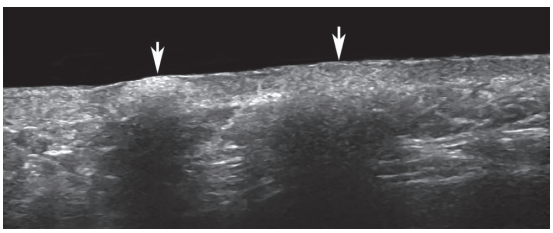

FIGURE 4 Calcium hydroxyapatite: two hyperechoic, well-defined band-like deposits (arrows) with posterior acoustic shadowing artifact

FIGURE 5 Silicon oil: hyperechoic, heterogeneous, ill-defined, mass-like deposits that produce diffuse posterior reverberation artifact ("snow storm pattern")

identification.[11] Silicone oil produces a high reflection and a diffuse posterior reverberance artifact called "snow storm." Other fillers such as polymethylmethacrylate generate a strong and tiny posterior reverberance of the sound waves which is called mini-comet tail artifact. Additionally, these fillers may generate a dense fibrotic reaction around the particles of the material

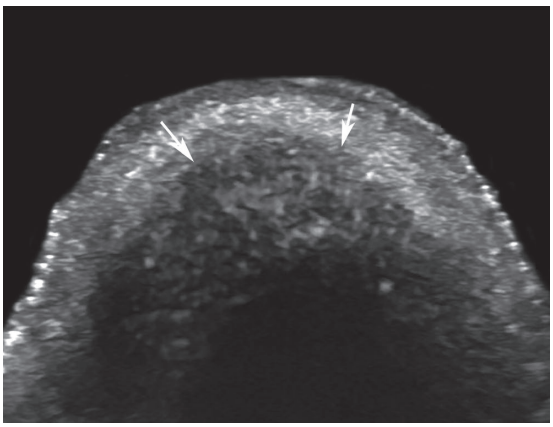

FIGURE 6 Polycaprolactone: hypoechoic, heterogeneous and ill-defined matrix (arrows) that contains multiple bright hyperechoic spots that present a posterior mini-comet tail artifact

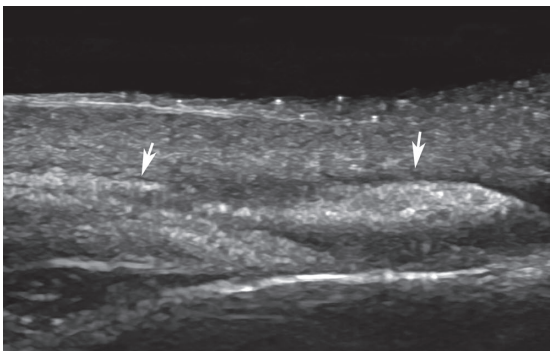

FIGURE 7 Polymethylmethacrylate (PMMA): hyperechoic, heterogeneous, ill-defined, mass-like deposits (arrows) that produce mini-comet tail artifacts

that can produce areas with posterior acoustic shadowing artifact.[3,25]

3.1.9 | Anatomical location

Another important point to bear in mind is that fillers used for increasing the volume will be injected on a deeper plane, usually close to the bony margin. In contrast, fillers for treating wrinkles are injected more superficially,[31,32]

3.1.10 | Evolution

The intrinsic characteristics of each filler will generate variations in their ultrasound appearance. For example, hyaluronic acid deposits tend to modify their shape, decrease in size and become more hypoechoic over time.[37,38]

In Table 3 and the Figures 1-8 underneath, these parameters are applied to the most commonly fillers used.

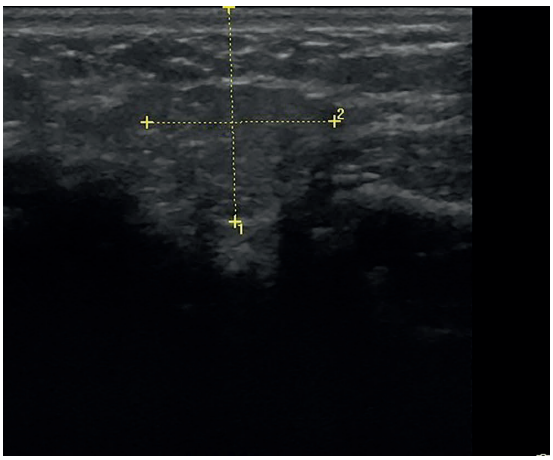

FIGURE 8 Lipofilling: hypoechoic, heterogeneous well-defined oval-shaped mass-like deposit (marker 2) with some hyperechoic linear septa that disrupt the architecture of the neighboring fatty tissue of the subcutis. Marker 1 is showing the distance from the epidermal surface to the bottom of the fatty graft

4 | CONCLUSION

In this article, we examined the terminology and parameters used to describe soft tissue fillers. One of the current shortcomings is that data and patient numbers described in the existing publications are limited. More extensive data and prospective series are necessary to evaluate and if necessary adjust the proposed parameters in the future.

Although sometimes lacking sonographic glossary, most articles focus on the same parameters.

A proposal considering ten sonographic parameters for identifying, monitoring, and reporting these deposits on ultrasound is herewith provided. We notice that incorporating these parameters improves an accurate and uniform terminology. It may serve as a guideline for dermatologists using ultrasonography in their offices. Furthermore, it may contribute to standardize future literature and reports and facilitate the comparison of research.

CONFLICTS OF INTEREST

None declared.

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REFERENCES

1. Cassuto D, Sundaram H. A problem-oriented approach to nodular complications from hyaluronic acid and calcium hydroxylapatite fillers: classification and recommendations for treatment. *Plast Reconstr Surg*. 2013;132(4 suppl 2):48S-58S.
2. Cassuto D. Management of complications caused by permanent fillers in the face: a treatment algorithm. *Plast. Reconstr. Surg*. 2016;138:215e.
3. Wortsman X, Wortsman J, Orlandi C, Cardenas G, Sazunic I, Jemec GB. Ultrasound detection and identification of cosmetic fillers in the skin. *J Eur Acad Dermatol Venereol*. 2012;26(3):292-301.
4. Schelke LW, Van Den Elzen HJ, Erkamp PP, Neumann HA. Use of ultrasound to provide overall information on facial fillers and surrounding tissue. *Dermatol Surg*. 2010;36(suppl 3):1843-1851.
5. Young SR, Bolto PA, Downie J. Use of high frequency ultrasound in the assessment of injectable dermal fillers. *Skin Res Technol*. 2008;14:320-323.
6. Scotto di Santolo M, Sagnelli M, Tortora G, et al. The utility of the high-resolution ultrasound technique in the evaluation of autologous adipose tissue lipofilling, used for the correction of post-surgical, post-traumatic and post-burn scars. *Radiol Med*. 2016;121(6):521-527.
7. Fiaschetti V, Pistolese CA, Fornari M, et al. Magnetic resonance imaging and ultrasound evaluation after breast autologous fat grafting combined with platelet-rich plasma. *Plast Reconstr Surg*. 2013;132(4):498e-509e.
8. Wortsman X, Alfageme F, Roustan G, et al. Guidelines for performing dermatologic ultrasound examinations by the DERMUS group. *J Ultrasound Med*. 2016;35(3):577-580.
9. Rallan D, Harland CC. Ultrasound in dermatology – basic principles and applications. *Clin Exp Dermatol*. 2003;28:632-638.
10. Barcaui EO, Carvalho ACP, Lopes FPPL, Piñeiro-Maceira J, Barcaui CB. High frequency ultrasound with color doppler in dermatology. *An Bras Dermatol*. 2016;91(3):262-273.
11. Iwayama T, Hashikawa K, Osaki T, Yamashiro K, Horita N, Fukumoto T. Ultrasonography-guided cannula method for hyaluronic acid filler injection with evaluation using laser speckle flowgraphy. *Plast Reconstr Surg Glob Open*. 2018;6(4):e1776.
12. Kwon HJ, Kim BJ, Ko EJ, Choi SY. The utility of color Doppler ultrasound to explore vascular complications after filler injection. *Dermatol Surg*. 2017;12(43):1508-1510.
13. Skrzypek E, Górnicka B, Skrzypek DM, Krzysztof MR. Granuloma as a complication of polycaprolactone-based dermal filler injection: ultrasound and histopathology studies. *J Cosmet Laser Ther*. 2018;14:1-4.
14. Seok J, Kim JM, Kwon TR, Kim JH, Li K, Kim BJ. Ultrasonography-guided curettage of poly-DL-lactic acid filler granulomas. *J Am Acad Dermatol*. 2018;78(1):e5-e6.
15. Pérez-Pérez L, García-Gavín J, Wortsman X, Santos-Briz Á. Delayed adverse subcutaneous reaction to a new family of hyaluronic acid dermal fillers with clinical, ultrasound and histologic correlation. *Dermatol Surg*. 2017;43(4):605-608.
16. Wortsman X. Sonography of dermatologic emergencies. *J Ultrasound Med*. 2017;36(9):1905-1914.
17. Indrizzi E, Moricca LM, Pellacchia V, Leonardi A, Buonaccorsi S, Fini G. Biomaterial implantation in facial esthetic diseases: ultrasonography monitor follow-up: follow up after bio alcamid. *J Craniofac Surg*. 2008;19(4):1098-1103.
18. Schelke LW, Decates TS, Van der Lugt C, Pelzer L, de Mey G, Velthuis PJ. Intralesional laser treatment for dermal fillers complications. *Plast. Reconstr. Surg*. 2018;141(6):1361-1369.
19. Grippaudo FR, Mattei M. The utility of high-frequency ultrasound in dermal filler evaluation. *Ann Plast Surg*. 2011;67(5):469-473.
20. Grippaudo FR, Mattei M. High frequency sonography of temporary and permanent dermal fillers. *Skin Res Technol*. 2010;16:265-269.
21. Wortsman X, Wortsman J. Polyacrylamide fillers on skin ultrasound. *J Eur Acad Dermatol Venereol*. 2012;26(5):660-661.

22. Faundez E, Vega N, Vera E, Vega P, Sepulveda D, Wortsman X. Clinical and color Doppler ultrasound evaluation of polyacrylamide injection in HIV patients with severe facial lipoatrophy secondary to antiretroviral therapy. *Skin Res Technol*. 2017;23:243-248.
23. Schelke LW, Decates TS, Velthuis PJ. Ultrasound to improve the safety of hyaluronic acid filler treatments. *J Cosmet Dermatol*. 2018;17(6):1019-1024.
24. Micheels P, Besse S, Sarazin D, Vincent AG, Portnova N, Diana MS. Quantifying depth of injection of hyaluronic acid in the dermis: data from clinical, laboratory, and ultrasound settings. *J Drugs Dermatol*. 2016;15(4):483-490.
25. Micheels P, Besse S, Sarazin D. Two crosslinking technologies for superficial reticular dermis injection: a comparative ultrasound and histologic study. *Clin Aesthet Dermatol*. 2017;10(1):29-36.
26. Tedeschi A, Lacarrubba F, Micali G. Mesotherapy with an intradermal hyaluronic acid formulation for skin rejuvenation: an intrapatient, placebo-controlled, long-term trial using high-frequency ultrasound. *Aesth Plast Surg*. 2015;39:129-133.
27. Turlier V, Rouquier A, Black D, et al. Assessment of the clinical efficacy of a hyaluronic acid-based deep wrinkle filler using new instrumental methods. *J Cosmet Laser Ther*. 2010;12(4):195-202.
28. Micheels P, Besse S, Flynn TC, Sarazin D, Elbaz J. Superficial dermal injection of hyaluronic acid soft tissue fillers: comparative ultrasound study. *Dermatol Surg*. 2012;38:1162-1169.
29. Vent J, Lefarth F, Massing T, Angerstein W. Do you know where your fillers go? An ultrastructural investigation of the lips. *Clin Cosmet Investig Dermatol*. 2014;20(7):191-199.
30. Grippaudo FR, Di Girolamo M, Mattei M, Pucci E, Grippaudo C. Diagnosis and management of dermal filler complications in the perioral region. *J Cosmet Laser Ther*. 2014;16(5):246-252.
31. Wortsman X, Jemec G. *Dermatologic Ultrasound with Clinical and Histologic Correlations*. New York: Springer Science+Business Media; 2013.
32. Wortsman X. Identification and complications of cosmetic fillers: sonography first. *J Ultrasound Med*. 2015;34(7):1163-1172.
33. Wortsman X, Quezada N. Ultrasound morphology of polycaprolactone filler. *J Ultrasound Med*. 2017;13:2611-2615.
34. Scotto di Santolo M, Massimo C, Tortora G, et al. Clinical value of high-resolution (5–17 MHz) echo-color doppler (ECD) for identifying filling materials and assessment of damage or complications in aesthetic medicine/surgery. *Radiol Med*. 2019;124:568-574.
35. Giovagnorio F, Drudi FM, Valentini C, Paonessa A. Ultrasound in follow up of soft tissue augmentation of the face with synthetic materials; a pilot study. *Acta Radiol*. 2004;45:746.
36. De Pasquale A, Russa G, Pulvirenti M, Di Rosa L. Hyaluronic acid filler injections for tear-trough deformity: injection technique and high-frequency ultrasound follow-up evaluation. *Aesthetic Plast Surg*. 2013;37:587-591.
37. Goh AS, Kohn JC, Rootman DB, Lin JL, Goldberg RA. Hyaluronic acid gel distribution pattern in periocular area with high-resolution ultrasound imaging. *Aesthetic Surg J*. 2014;34:510-515.
38. Kohn JC, Goh AS, Lin JL, Goldberg RA. Dynamic high resolution ultrasound in vivo imaging of hyaluronic acid filler injection. *Dermatol Surg*. 2013;39:1630-1636.
39. Mlosek RK, Skrzypek E, Skrzypek DM, Malinowska S. High-frequency ultrasound-based differentiation between nodular dermal filler deposits and foreign body granulomas. *Skin Res Technol*. 2018;24(3):417-422.

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Chapter 6

Discussion

The research described in this thesis is the culmination of a mounting realization that in the past we as physicians have not been fully aware of the potential dangers we may be exposing our patients to when performing filler treatments. What seemed a very simple procedure with biocompatible and hence 'safe' materials, is now known to have a much greater impact on tissue and patients than anticipated when aesthetic treatments began around 20 years ago.

Even now, much research on filler treatments is still in its infancy. Most published papers, including the contents of this thesis, are mainly descriptive. In all new medical fields research begins in this way. In cosmetic medicine it is particularly difficult to proceed because of the nature of the patients involved and their 'problem'. The patient's appearance is paramount and few are willing to participate in any type of medical research.

Filler substances and social behavior

Among the medical community, the first indication that injected filler substances might cause problems became evident when inflammatory reactions were observed with poly-alkylimide (Bio-Alcamid®). In 2009, we published data that this substance was associated with complications in 4.8 % of treated patients, a much higher percentage than that claimed by the manufacturer when the filler entered the market (0.06%). A decade later we believe that this first estimate was too low, and that the complication rate is more likely around 50%.

While it may now seem naïve, it was only then that the realization came that filler chemical composition might alter over time in vivo and thus affect their behavior and effects on human tissue. When first injected, poly-alkylimide does not exert much tissue reaction. In marketing terms it is 'very biocompatible'. However, this changes when the product remains in the tissue for a longer time. Specifically, once surrounded by subcutaneous tissue, the poly-alkyl-imide gel dehydrates and attracts inflammatory cells. Since 2015, the use of all non-resorbable fillers has been banned in the Netherlands, but HA fillers, the most popular resorbable fillers, are also gel-based and could potentially succumb to dehydration. At the present time, no data have been published on HA filler biochemistry after injection.

A number of other factors aside from dehydration have also been implicated in filler complications. For example, it is known that the degradation products of HA fillers can have an inherent biological activity, with low molecular weight chains exerting pro-inflammatory actions[1]. Indeed, delayed inflammatory reactions (developing weeks or even months after injection) have been observed with some HA filler treatments [2,3]. There is also an increasing tendency among patients to begin filler injections at younger ages. The skin tissues of these individuals, sometimes as young as 16, may be constantly exposed to HA substances for many decades. From a scientific point of view, the long-term effects of such an exposure cannot yet be assessed in terms of risks and safety and much research is required in this area.

On the positive side, out of a total of almost 140,000 yearly filler treatments in the Netherlands [4], the number of new filler complications seen at the Erasmus Medical Center is relatively low, particularly for the HA fillers. In a retrospective study, 10% of all referred patients was about HA related complications. However, this probably represents only a minority of the total number of complications [5].

Qualifications and competence

Among the HA filler complications that are referred to Erasmus MC, we estimate that approximately 50% are technique related. Physician training would therefore seem an obvious way of increasing safety. Many doctors begin to treat patients after receiving only a 1- or 2-day course hosted by the supplying company. Although it may appear quite simple to inject small amounts of HA filler in the cutis and subcutis, for optimal efficacy and safety outcomes physician knowledge and expertise is essential. Some of the problems observed after treatments performed by inexperienced doctors are described in table 1.

More training would also be valuable to raise the threshold of doctors entering the field. The latter has been recognized by the Dutch Authorities, who have subsidized the development of a training program for doctors in cosmetic medicine. Initiated by the Minister of Health, the Dutch Society for Cosmetic Medicine (Nederlandse Vereniging voor Cosmetische Geneeskunde, NVCG) has receive a certified status in 2019 for a 2-year educational program to educate and train physicians from different backgrounds in cosmetic treatments. Potential barriers to this program include the high costs and the lack of available patients willing to undergo procedures by inexperienced residents [6,7,8]. The term, Cosmetic Physician (in Dutch: Cosmetisch Arts), has become a protected title that is only awarded to doctors who successfully complete the program. This is a major step forward as it allows consumers to immediately recognize doctors with specific and thorough training in cosmetic medicine. While doctors can refer to themselves by other titles, e.g. 'aesthetic physician', all healthcare professionals, by law, must register in the Individual Healthcare Professions Act (BIG-register), which is available for public consultation. The BIG-register provides clarity about the care provider's qualifications and entitlement to practice.

Location	**Technical error suspected**	**Complication**
Lower face	Filler injected in muscle	Nodules due to accumulation of product
Mid face	Filler injected in muscle	Nodules due to dislocation of product
Tear trough	Incorrect indication	Malar edema
Whole face	Filler placed too superficial or in excessive amounts	Nodules, Tyndall effect

Table 1. Complications seen at Erasmus Medical Center as a result of incorrect injection technique

Ultrasound imaging

Most of the patients referred to the out-patient clinic at Erasmus Medical Center present with visible and palpable facial nodules. Ultrasound has proved indispensable for the examination of these lesions. This technology enables us to perform a real time assessment of the structures. Features of the nodule such as volume, depth, internal structure, subcutaneous interconnections, and reactive inflammation of the surrounding tissues can all be visualized[9,10]. This information allows us to identify the type of filler

injected.

In cases of vascular complication, the exact location of the causative blocking agent can be determined and targeted with precise ultrasound guided hyaluronidase injections (in patients treated with an HA filler), leading to an immediate restoration of blood flow.

High variable-frequency ultrasound (HVFUS) ranging from 6 to 25 MHz combined with color doppler at a frequency of 7 to 4 MHz has become available in the past several years. It is capable of clearly defining skin layers and deeper structures as well as vascularization patterns in real time. Ultrasound with frequencies of 15 MHz or higher penetrates only a few centimeter into the tissue. It renders very good resolutions of superficial structures[11]. Skin layer morphology including changes in epidermal thickness, subcutaneous tissue and deep structures (muscles, tendons, bone margins and regional lymph nodes) can be clearly defined. A basic knowledge of the principles of ultrasound is essential for correct image interpretation. The ultrasound waves travel through the skin and diffuse in fluid and surrounding tissue. The resultant echoes (back waves) reflected by these structures will return to the screen and produce an image. The intensity of the echoes in the image is known as echogenicity. Images with high intensity echoes are referred to as echogenic or hyperechoic, those with low intensity as hypoechoic, and those with no echo as anechoic or echo lucent. What determines the echogenicity of each tissue is the speed at which the sound wave passes through it, and the quantity and intensity of the echoes returned to the device. Like all body structures, fillers have their own echogenicity[12,13,14].

Doppler is based on the principle that sound waves emitted by the transducer and by the reflector move in relation to each other. Thus, Doppler can be used to visualize moving structures, such as blood flow. On color Doppler, blood flow is differentiated by colors, while power Doppler illustrates the flow volume[10,11]. At present, the clinical efficacy of ultrasound use remains to be proven, i.e. validation of the echogenicity of the different fillers needs to be confirmed.

A methodological framework to guide innovative research and to protect patients from the potential harms of any novel procedures has been proposed by the Balliol collaboration, a collection of methodologists and clinicians who held a series of conferences at Balliol College Oxford in 2007-2009 (published in the Lancet as a series of three papers on surgical innovation and evaluation) [14,15,16]. This proposal is based on five stages: Idea, Development, Exploration, Assessment and Long-term study (IDEAL, table 2).

	Stages 0–1 Innovation	Stage 2a Development	Stage 2b Exploration	Stage 3 Assessment	Stage 4 Long term
Number and types of patients	Single digit, highly selected	Few, selected	Many, mixed but not all	Many, variable	Almost all
Number of surgeons	Very few	Few, Innovators	Many	Many, early majority	Most, late Majority
Ethics	Sometimes	Yes	Yes	Yes	No
Learning curve in human beings	No	Yes	Yes	Maybe	No

Table 2: Stages of surgical innovation (IDEAL paradigm)

In terms of the IDEAL recommendations, the use of ultrasound for filler examination is currently at the end of stage 2b, facing stage 3. One of the first publications reporting on the visibility of dermal fillers was published in 2008 (stage 1), followed by other articles describing the use of ultrasound as a research tool and in the management of filler complications (stage 2a). To elevate the use of ultrasound into stage 3, the device has to be integrated into the day-to-day practice of physicians performing filler treatments. For this to occur, clinicians need to be trained in Doppler-ultrasound techniques and their interpretation [9]. In the Erasmus Medical Center Department of Dermatology, dermatologists and residents with an interest in soft tissue filler procedures are educated in ultrasound examination. Experience indicates that the learning curve is not steep. To reach a larger audience, an educational project has been developed in collaboration with a group of radiologists (Cutaneous). The devices used range from 4-12 MHz and are suitable for filler ultrasound examinations in daily practice.

Stage 4 is concerned with long-term implementation and monitoring. As the value of long-term monitoring also depends on the uniformity of data entry, nomenclature should be unequivocal. The use of ultrasound for imaging soft tissue fillers has been reported in a growing number of publications during the past decade. However, the data from these papers with their various terminologies are hard to compare (and sometimes to understand). In the future, standardization of the sonographic description of filler images will improve the ability to compare data. Our attempt to construct a descriptive terminology will hopefully be adopted by others.

At the Erasmus Medical Center, doctors treating filler complications perform ultrasound analysis of the face in every patient and recognize the importance of working with this technology. It is our hope that in the near future every physician performing injectable filler treatments (and lipofilling for that matter) will be able to precede patient treatment with mapping of important blood vessels in the target areas, and have the ultrasound ready in case of a filler emergency.

Legal aspects

Medical devices do not achieve their principal intended action in or on the human body by pharmacological, immunological or metabolic means. Fillers are classified as medical devices because their primary intended action is mechanical ("filling effect") [17]. The European Legislation governing this process is the Medical Devices Directive (MDD), established in 1970. It is principally based on “Good Manufacturing Practice” and not pre-market approval. One of the reasons for this is that out of the more than 500,000 different medical devices, the majority are low risk, and safety and quality are guaranteed by a safe production process. A pre-market approval requires additional investments and is thought to slow down innovation [18,19]. Notified Bodies are responsible for reviewing CE Marking applications and issuing the CE certificates required for entry into the European market. However, this notification process is limited and only requires copies of labelling and approval certificates (CE and Declaration of Conformity) [17,20] As a result, new fillers have a relatively low threshold to enter the market, and companies can launch new products without much, if any, scientific supporting data[20,21,22].

A similar situation is observed with other medical devices. For example, the Björk-Shiley prosthesis was

a second-generation mechanical cardiac valve that was implanted in a large patient population worldwide from 1979. Subsequent reports of strut stresses and disc escape caused widespread concern about the soundness and safety of the disc valve. The material component of the disc was later changed to pyrolytic carbon, but the Björk-Shiley mechanical valve was eventually taken off the market in 1985[23]. In another example, Poly Implant Protheses (PIP) used as breast implants were withdrawn from the market in March 2010 after it was found that they had been fraudulently manufactured with unapproved silicone gel, and were far more prone to rupturing (2 to 6 times) than other breast implants. It has been estimated that around 47,000 women had PIP implants fitted, most of whom are still living with them[24,25].

The low threshold for approval of medical devices also made it possible for an inferior product in the form of the HA filler Hyacorp M2000 to gain a CE certificate and become available on the Dutch market in 2011[26]. It was withdrawn in 2014 after a series of complications. Bio-Alcamid was launched in 2001 with hardly any published papers about its biocompatibility.

New European requirements (Medical device Regulations, MDR) have been implemented in the Netherlands by 26 May 2020 . With these medical devices classified as high risk, including fillers, need stricter admissions procedures with more clinical evaluation [29]. Post-marketing clinical follow-up (PMCF) will also be required, instead of the current post-market surveillance. A new European Database on Medical Devices (Eudamed) listing all complications for each filler agent will also come into effect in 2020. This will be accessible by everyone (including consumers, doctors, manufacturers, governments), further increasing transparency and accountability [29]. These measures hopefully lead to earlier identification of unforeseen adverse events. Although, many of the details of these new processes remain to be established, this is a major step forward regarding filler safety.

Host–filler interactions

The pathogenesis of host–filler inflammatory reactions is currently a major research interest in our department. Questions that need to be answered include whether the reactions are related to the filler substance, host immune status or microbiological agents[30-37] In the breast prosthesis field, where capsular contraction is being researched in depth, no clear cause has yet been identified. In implant-based breast reconstruction, the foreign body response results in a certain degree of fibrous encapsulation [38,39]. The capsule is important for maintaining the correct positioning of the implant, but excess fibrosis and capsular contracture can lead to pain, hardening, extrusion, and deformity. It has been shown that, as with soft tissue fillers, surface texture and volume have a linear relation to immune system activation [34]. At the same time, studies have also suggested that bacterial influx increases the chances for capsular contracture[40,41]. Current research suggests the immune system is constantly active, i.e. with activated macrophages that induce a cascade of signaling that eventually results in differentiation of fibroblasts into myofibroblasts [42,43,] However, despite the vast amount of microbial and immunological data available, several important questions remain .

A new indication for laser treatment

The introduction of lasers has profoundly changed therapeutics in dermatology. In particular, the concept of selective photothermolysis (SP) [44], in which a laser beam with a specific wavelength can destroy a target without damaging surrounding tissue, has proved to be a fertile ground for many laser applications [45,46]. SP has been successfully applied to the treatment of pigmented lesions, including exogenous pigment (tattoo ink), where it performs almost exactly as in theory. However, in the other major laser indication in dermatology, i.e. visible facial capillaries, it soon became clear that the SP concept would need some adjustment. The reason for this is that the intended target (blood vessel wall) is different from the laser target (or chromophore), which is hemoglobulin [47]. The extended theory of selected photothermolysis (ESP) was subsequently put forward, which sets out how different objects can be destroyed by heat diffusion [48]. Using this method, vessels can be destroyed through heat transfer via blood [49,50]. In phlebology, diode lasers (800 nm, 810 nm and 1470 nm) have been extensively used for this purpose as their wavelengths can be guided through an optic fiber to deliver high temperatures at the tip (endovascular laser treatment = EVLT). The same diode lasers with optic fibers are also used for laser lipolysis. This technique, first described in 1990, is now widely used throughout Europe and the USA [51,52]. Laser lipolysis is temperature-dependent using temperatures from 43°C up to 70°C to damage fat tissue and trigger tightening of the dermis.

A new indication for diode lasers is the removal of unwanted dermal fillers. This procedure is known as Intralesional Laser Therapy (ILT) and was first described by Cassuto in 2009. The 810 nm and 1470 nm wavelength diode laser (continuous wave) are the most frequently used. As with EVLT and laser lipolysis procedures, when using ILT it is not the wavelength of the device, but the amount of energy and heat delivered to the implanted filler that is thought to be important for successful removal [53,54,55]. ILT is active in the same tissue layers and using the same temperatures as laser lipolysis, but with decreased power (0.5-1 W). There is a thermal therapeutic margin between the lesion melting and the pain threshold elicited by excessive diffusion of heat into the surrounding tissues. Energy delivery is modulated according to patient tolerance; if the patient shows excessive discomfort, power is reduced or the treatment is stopped to prevent heat diffusing into the surrounding tissue.

When applying the IDEAL guidelines to this innovative use of ILT, the first step in the evaluation of innovation (stage 1) was performed and described by Cassuto in 2009 and 2016 (20 and 219 patients, respectively) [53,54] . The technique is currently at stage 2a: the technical details of the laser procedure and equipment have improved, but other details, such as the amount of energy per filler type or location is required, have not been completely validated. Attempts to reliably replicate early results are being published [55]. More studies, with increased numbers of patients are necessary, and randomized trials would be the favored option at this stage. However, randomized trials are generally more difficult to perform with interventional procedures than pharmaceuticals. The assessment of nonpharmacological treatments entails specific challenges, such as difficulties in implementing blinding, procedure standardization and operator dependency. Most patients would probably prefer a laser treatment with less down time and no visible scarring before attempting surgery.
The implementation of standardized data collection for the type and amount of filler, treatment settings and outcomes, and questionnaires would give more insight into the efficacy of ILT for dermal filler removal.

Concluding remarks

Research in cosmetic medicine is very much at a pioneering stage. As such, this thesis presents a largely descriptive overview of research in this area. Nevertheless, important steps forward have been taken both in delineating the problem and in discovering new methods of diagnosing and treating, as well as preventing filler-related complications. Ongoing research and discoveries in this field will be to the perpetual benefit of our patients.

References

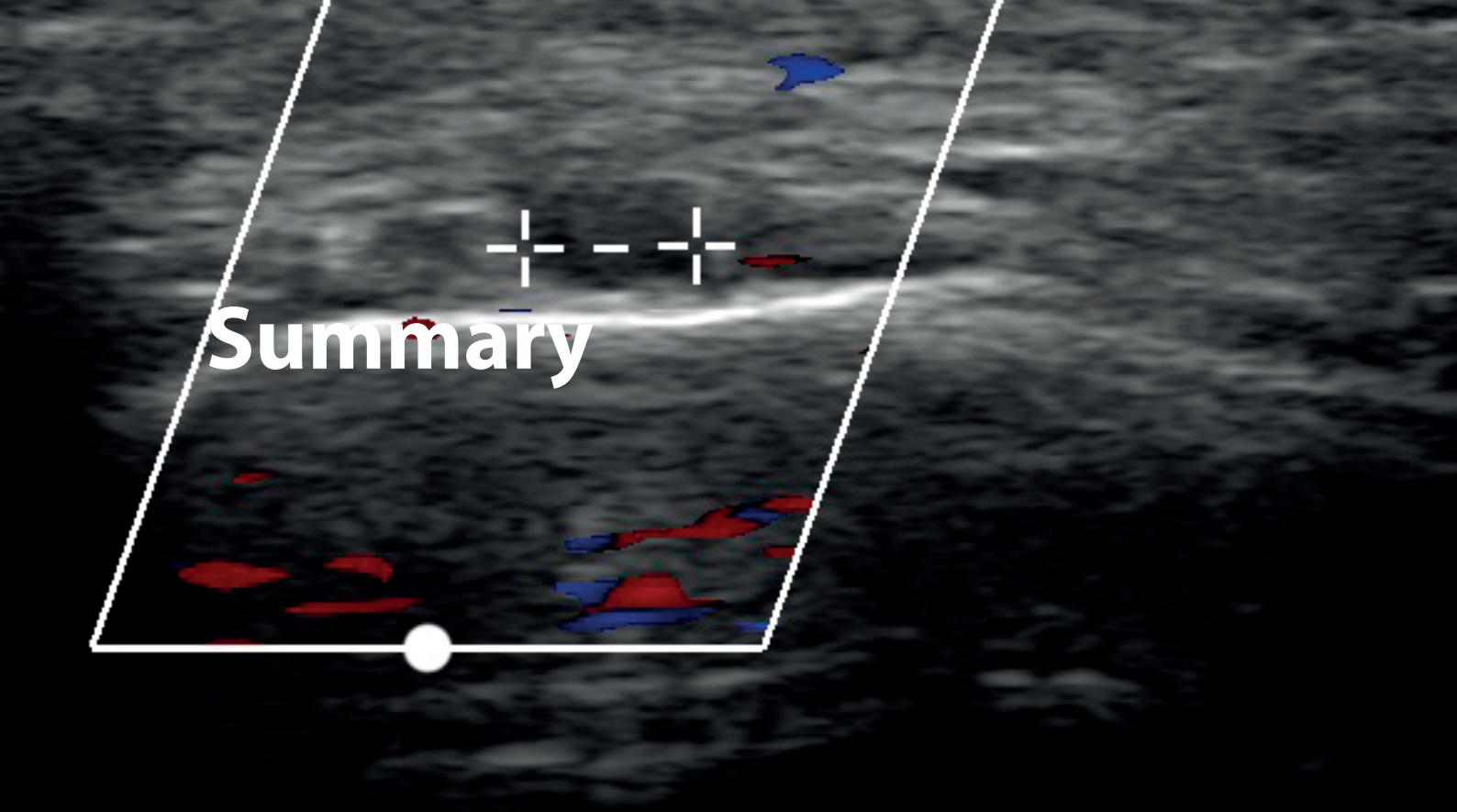
1. Philipp-Dormston WG, Bergfeld D, Sommer BM , Sattler G, Cotofana S et all.Consensus Statement on Prevention and Management of Adverse Effects Following Rejuvenation Procedures With Hyaluronic Acid-Based Fillers. J Eur Acad Dermatol Venereol 2017 Jul;31(7):1088-1095.
2. Artzi O, Loizides C, Verner I, Landau M. Resistant and Recurrent Late Reaction to Hyaluronic Acid-Based Gel. Dermatol Surg 2016 Jan;42(1):31-7.
3. Bhojani-Lynch T. Late-Onset Inflammatory Response to Hyaluronic Acid Dermal Fillers. Plast Reconstr Surg Glob Open 2017 Dec 22;5(12):e1532.
4. Decates T, de Wijs L, Nijsten T, Velthuis P. Numbers on injectable treatments in the Netherlands in 2016. J Eur Acad Dermatol Venereol. 2018 Feb 14. doi:10.1111/jdv.14877
5. Schelke L.W. Decates T. Hu C. Velthuis P. Een poli voor complicaties van fillers Klinische les. Ned Tijdschr Genesskd. 2019;163:D3074 1
6. Alam M, Olson JM, Asgari MM. Needs assessment for cosmetic dermatologic surgery. Dermatol Clin. 2012;30(1):177-187,
7. Bauer B, Williams E, Stratman EJ. Cosmetic Dermatologic Surgical Training in US Dermatology Residency Programs Identifying and Overcoming Barriers. JAMA Dermatol. 2014;150(2):125-129.
8. Todd MM1, Miller JJ, Ammirati CT. Dermatologic surgery training in residency .Dermatol Surg. 2002 Jul;28(7):547-9; discussion 549-50.
9. Wortsman X, Alfageme F, Roustan G, Arias-Santiago S, Martorell A, Catalano O, Scotto di Santolo M, Zarchi K, Bouer M, Gonzalez C, Bard R, Mandava A, Gaitini D. Guidelines for Performing Dermatologic Ultrasound Examinations by the DERMUS Group. J Ultrasound Med. 2016 Mar;35(3):577-80. doi: 10.7863/ultra.15.06046
10. Wortsman X. Sonography of Dermatologic Emergencies. J Ultrasound Med 2017;00:00-00
11. D. Rallan and C. C. Harland. Ultrasound in dermatology – basic principles and applications. Clinical and Experimental Dermatology, 2003: 28, 632–638
12. de Oliveira Barcaui E, Pires Carvalho A C, Paiva Proença Lobo Lopes F, Piñeiro-Maceira J ,Baptista Barcaui C. High frequency ultrasound with color Doppler in dermatology. An Bras Dermatol. 2016 May-Jun; 91(3): 262–273.
13. Wortsman X, Jemec GBE. Dermatologic Ultrasound with Clinical and Histologic Correlations. New York, Springer Science+Business Media 2013
14. Barkun, JS, Aronson JK, Feldman LS, Maddern GJ, Strasberg SM , for the Balliol Collaboration. Surgical Innovation and Evaluation 1. Evaluation and stages of surgical innovations. Lancet 2009; 374: 1089–96
15. Ergina PL, Cook JA, Blazeby JM, Boutron I, Clavien PA, Reeves BC, Seiler CM, for the Balliol Collaboration. Surgical Innovation and Evaluation 2. Challenges in evaluating surgical innovation. Lancet 2009; 374: 1097–104
16. McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, Nicholl J, for the Balliol Collaboration. Surgical Innovation and Evaluation 3 No surgical innovation without evaluation: the IDEAL recommendations. Lancet 2009; 374: 1105–12
17. COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning medical devices. EUR-Lex Access to European Union law
18. Wetgeving medische hulpmiddelen: een stand van zaken. Sluijters B, Frank S. Tijdschrift voor

Gezondheidsrecht (2001) 25:57–66
19. European Commission DG Health & Consumers Directorate B -Consumer Affairs Unit B2 – Health technology and Cosmetics MEDICAL DEVICES: Guidance document MEDDEV 2.5/10 January 2012 Guideline for authorized representatives
20. Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007. Official Journal of the European Union
21. Ministerie van Volksgezondheid, Welzijn en Sport. Handreiking medische hulpmiddelen. 12-12-2017
22. Verordening 2017/745 van het Europees Parlement en de Raad van 5 april 2017 betreffende medische hulpmiddelen, tot wijziging van Richtlijn 2001/83/EG, Verordening (EG) nr. 178/2002 en Verordening (EG) nr. 1223/2009, en tot intrekking van Richtlijnen 90/385/EEG en 93/42/EEG van de Raad. Publicatieblad van de Europese Unie
23. Sansone F, Zingarelli E, Actis Dato GM, Punta G, Flocco R et all. The 37-Year Durability of a Björk-Shiley Delrin-Disc Aortic Valve Prosthesis. Tex Heart Inst J. 2012;39(2):284-5.
24. Martindale V, MenacheA. The PIP scandal: an analysis of the process of quality control that failed to safeguard women from the health risks. J R Soc Med 2013: 106: 173–177
25. Berry MG, Stanek JJ. The PIP mammary prosthesis: a product recall study. J Plast Reconstr Aesthet Surg. 2012 Jun;65(6):697-704.
26. Inspectie Gezondheidszorg en Jeugd. Ministerie van Volksgezondheid, Welzijn en Sport. Meer producten van fabrikant van Hyacorp filler verboden. Nieuwsbericht 19-04-2016.
27. Geertsma RE, de Bruijn ACP, van Drongelen AW, Hollestelle ML, de Jong WH et all. Mate van voorkomen en ernst van complicaties bij het gebruik van permanente vullers bij rimpelbehandelingen. RIVM-briefrapport 078/2006 VGC/AH/RG/ccc
28. Inspectie Gezondheidszorg en Jeugd. Ministerie van Volksgezondheid, Welzijn en Sport. Inspectie voor de Gezondheidszorg waarschuwt voor rimpelvulmiddelen. 18 Mei 2006
29. Ministerie van Volksgezondheid, Welzijn en Sport. Verdiepende sessie Klinisch onderzoek MHM. Opbrengsten en actiepunten. Woensdag 14 februari 2018
30. Alijotas-Reig J, Garcia-Gimenez V. Delayed immune-mediated adverse effects related to hyaluronic acid and acrylic hydrogel dermal fillers: clinical findings, longterm follow-up and review of the literature. JEADV, 2008;22:, 150–161
31. Kastellorizios M, Tipnis N, Burgess DJ. Foreign Body Reaction to Subcutaneous Implants. Chapter 6. Springer International Publishing Switzerland 2015 93 J.D. Lambris et al. (eds.), Immune Responses to Biosurfaces, Advances in Experimental Medicine and Biology 865,
32. Rostam HM, Singh S, Salazar F, Magennis P, Hook A, et all. The impact of surface chemistry modification on macrophage polarisation. Immunobiology. 2016 Nov;221(11):1237-46.
33. Christo SN, Diener KR, Bachhuka A, Vasilev K, Hayball JD. Innate Immunity and Biomaterials at the Nexus: Friends or Foes. BioMed Research International Volume 2015
34. Sáncheza O, Rodríguez-Suredaa V, Domíngueza C, Fernández-Figuerasc T, Vilchesa A, Llurbaa E, Alijotas-Reiga J. Study of biomaterial-induced macrophage activation, cell-mediated immune response and molecular oxidative damage in patients with dermal bioimplants Immunobiology 217 (2012) 44– 53
35. Anderson JM, Rodriguez A, Chang DT. Foreign body reaction to biomaterials. Semin Immunol.

2008 April ; 20(2): 86–100.
36. Alijotas-Reig J, Fernández-Figueras, MT, Puig L. Inflammatory, immune-mediated adverse reactions related to soft tissue dermal fillers. Sem Arth Rheum 43(2013)241–258
37. Browne S, Pandit A. Biomaterial-mediated modification of the local inflammatory environment. Front Bioeng Biotechnol. 2015 May 15;3:67
38. Cappellano G, Ploner C, Lobenwein S, Sopper S, Hoertnagl P et al. Immunophenotypic characterization of human T cells after in vitro exposure to different silicone breast implant surfaces. PLoS One. 2018 Feb 8;13(2)
39. Bachour Y, Verweij SP, Gibbs S, Ket JCF, Ritt MJPF et all. The aetiopathogenesis of capsular contracture: A systematic review of the literature. J Plast Reconstr Aesthet Surg. 2018 Mar;71(3):307-317.
40. Bachour Y, Bargon CA, de Blok CJM, Ket JCF, Ritt MJPF, Niessen FB.. Risk factors for developing capsular contracture in women after breast implant surgery: A systematic review of the literature. J Plast Reconstr Aesthet Surg. 2018 Sep;71(9):e29-e48
41. Major MR, Wong VW, Nelson ER, Longaker MT, Gurtner GC. The foreign body response: at the interface of surgery and bioengineering. Plast Reconstr Surg. 2015 May;135(5):1489-98
42. Danino MA, Nizard N, Paek LS, Govshievich A, Giot JP. Do Bacteria and Biofilm Play a Role in Double-Capsule Formation around Macrotextured Implants? Plast Reconstr Surg. 2017 Nov;140(5):878-883
43. Tang L, Hu W. Molecular determinants of biocompatibility. Expert Rev Med Devices. 2005 Jul;2(4):493-500.
44. Houk LD, Humphreys T. Masers to magic bullets: an updated history of lasers in dermatology. Clinics in Dermatology 2007; 25:434–442
45. Yun SH, Kwok SJJ. Light in diagnosis, therapy and surgery. Nat Biomed Eng. 2017;1
46. Adamic M, Troilius A, Adatto M, Drosner M, Dahmane R. Vascular lasers and IPLS: guidelines for care from the European Society for Laser Dermatology (ESLD). J Cosmet Laser Ther. 2007 Jun;9(2):113-24.
47. Altshuler GB, Anderson RR, Manstein D, Zenzie HH, Smirnov MZ. Extended theory of selective photothermolysis. Lasers Surg Med 2001; 29:416–432
48. Palm MD, Goldman MP. Laser lipolysis: current practices. Semin Cutan Med Surg 2009; 28:212–219
49. Reynaud JP, Skibinski M, Wassmer B, Rochon P, Mordon S. Lipolysis using a 980-nm diode laser: a retrospective analysis of 534 procedures. Aesthetic Plast Surg 2009; 33:28–36
50. Malskat W. S. J., Stokbroekx M. A. L., Geld van der C. W. M., Nijsten T. E. C. Bos van den R. R. Temperature profiles of 980- and 1,470-nm endovenous laser ablation, endovenous radiofrequency ablation and endovenous steam ablation. Lasers Med Sci (2014) 29:423–429
51. Weiss RA, Weiss M.A., MD, Eimpunth S, Wheeler S, Udompunturak S., MSc, Beasley KL. Comparative Outcomes of Different Endovenous Thermal Ablation Systems on Great and Small Saphenous Vein Insufficiency: Long-Term Results Lasers in Surgery and Medicine 47:156–160 (2015)
52. Boersma D, Smulders D.L.J, Bakker O.J., Haak van den R.F.F., Verhoeven B.A.N., Koning O.H.J.

Endovenous laser ablation of insufficient perforating veins: Energy is key to success. Vascular 2016, Vol. 24(2) 144–149

53. Cassuto D.,Marangoni O., De Santis G., Christensen L. Advanced Laser Techniques for Filler-Induced Complications. Dermatol Surg 2009;35:1689–1695
54. Cassuto D., Pignatti M., Pacchioni L. , Boscaini G. , Spaggiari A., De Santis G. Management of complications caused by permanent fillers in the face: A treatment algorithm. Plast. Reconstr. Surg. 138: 215e, 2016
55. Goldman, A., & Wollina, U. Intralesional Neodymium YAG laser to Treat Complications of Polymethylmethacrylate. Open access Macedonian journal of medical sciences,2018: 6(9), 1636-1641


Summary

Cosmetic medicine is a continuously growing field, including minimally invasive treatments with dermal fillers. As most patients treated are healthy people looking for a cosmetic improvement, the treatments performed should be as safe as possible. This requires safe products and an adequate performed injection technique. This thesis describes my work to improve filler safety over the past ten years.

The first part of this thesis focuses on the safety of the filler substances and their possible complications. Under the current system, Notified Bodies are responsible to grant approval for dermal fillers to enter the European market. Despite additional requirements throughout the years, regulations are still not considered to be strict enough. New European legislation to improve the admission procedure will be implemented this year. This includes enhanced clinical evaluation and a more transparent post-marketing surveillance. The procedures did not require long term clinical data. This has led to the situation that dermal fillers, especially the permanent ones, gave rise to more late onset adverse events than anticipated

Chapter one is an introduction to the thesis. A description of the different types of dermal fillers (permanent and resorbable) is given. The known direct and late onset adverse events and the current treatment options are discussed.

Chapter two is about the long term adverse events of a hydrogel (poly-alkylimide). The first publications about this permanent filler were very promising and reassuring. High biocompatibility of the product after three months was shown. The only complication described (with a 0,06% chance) was an inflammatory response, directly after treatment. This would be easy to treat with antibiotics. If desired or needed, the product could be removed by puncturing into the gel and squeeze the product out. However, long term clinical studies were lacking and years after injection a high percentages of late onset adverse events as inflammation, dislocation and accumulation of the product leading to nodules was noted. This led to the advice of the The Dutch Society of Cosmetic Medicine against the use of poly-alkylimide.

In chapter three, we tried to find an explanation for the causes of the late onset complications due to the permanent hydrogel poly-alkylimide. Clinically we observed that in most patienta with complications a whitish-yellow could be squeezed out. Whereas the hydrogel was transparent at the time of injection. Histological examination revealed dehydration and degeneration of the material in all patients. An influx of neutrophilic cells was noted. In case of inflammation, giant cell invasion was seen. We conclude that a dermal filler should not be judged solely on its biocompatible characteristics direct after production but also after a degradation process in the human body over time.

In chapter four, an overview is given of the different types of filler complications seen at our policlinic. The current treatment options (systemic drugs and surgical removal of the material) are being described. The main interest of this article was a new treatment option for removal of filler material, named intralesional laser treatment. Retrospectively data from 242 patients with complications caused by fillers were reviewed, all treated with this intralesional laser treatment. In 92% an improvement was achieved. The satisfaction rate was much lower. We concluded that intralesional laser treatment may be considered as a treatment option before surgery

The second part of this thesis is concerned with adequate diagnosis of filler complications and the safety to perform filler treatments. Aesthetic medicine is more and more recognized as a medical specialty. Physicians performing these treatments should be competent in their field. In the Netherlands, the

Dutch Society for Cosmetic Medicine (Nederlandse Vereniging voor Cosmetische Geneeskunde, NVCG) has received in 2019 a certified status for a two-year educational program to train and educate physicians from different backgrounds in cosmetic treatments. This is a big leap forward.

Additionally, safety can be enhanced with the use of duplex ultrasound prior to treatments. In chapter 5.1 we describe all the different fillers that can be visualized with ultrasound. Follow-up on filler characteristics such as longevity and in situ behavior is possible. Filler complications such as migration and inflammatory responses can be visualized. By this, the use of ultrasound may provide information to broaden our knowledge of facial fillers. In future times this may improve the performance and safety of filler treatments.

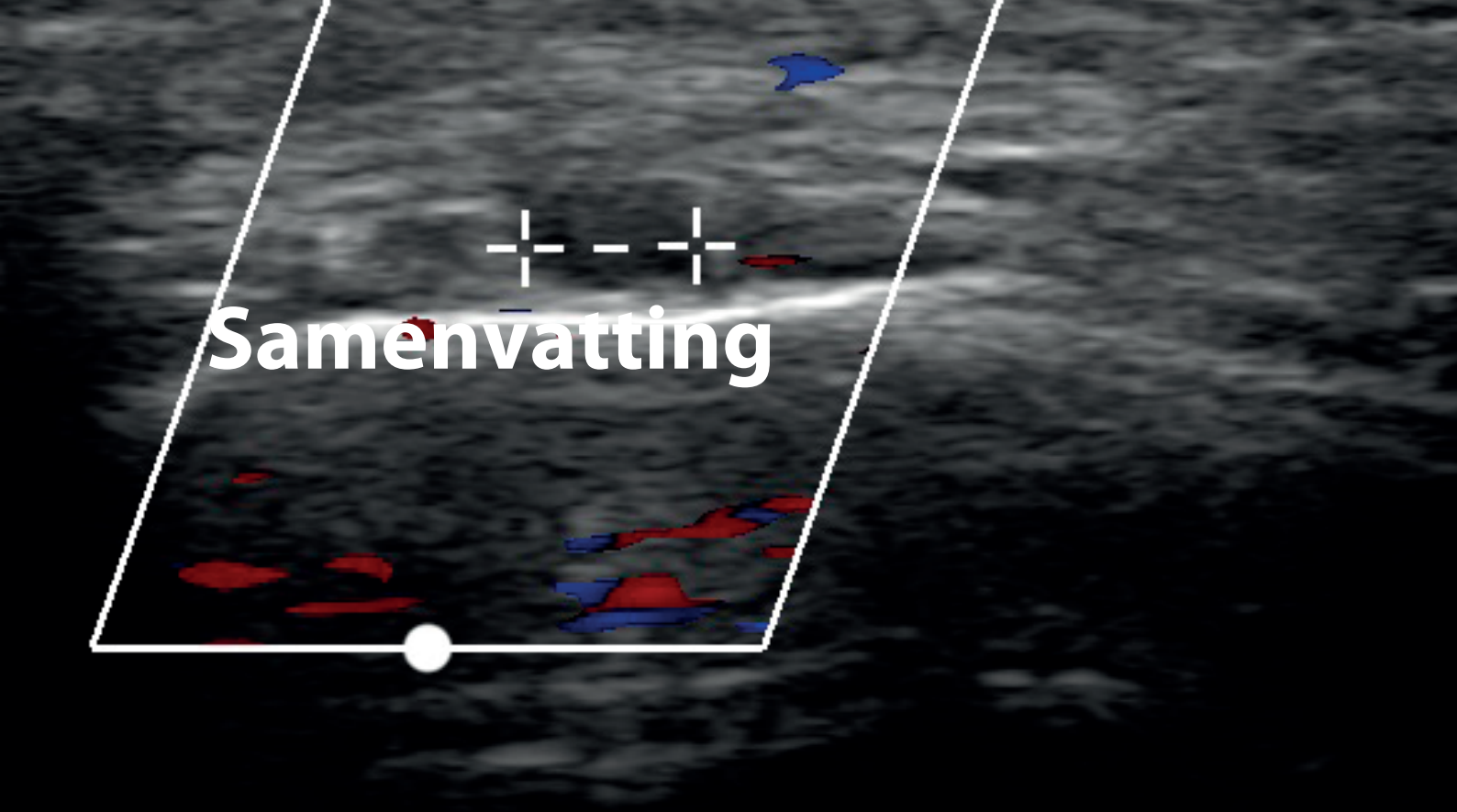
In chapter 5.2 specific notion is pointed towards hyaluronic acid fillers. Hyaluronic acid is the most used fillers product worldwide. It is resorbable and known for its reliable safety profile. But complications, even serious vascular adverse events, do occur. Hyaluronic acid deposits are easy to recognize with ultrasound. Examination of the face with duplex ultrasound prior to filler treatment can bring previous filler treatments into sight. Vascular mapping to identify individual variation in the course of arteries can be performed. In case of adverse events, the filler and the surrounding tissues can be visualized. Dislocation, abscess formation and vascular adverse events can be seen. Under ultrasound guidance, hyaluronidase can be injected very precisely into the filler deposit to the product. Duplex ultrasound examination is an important tool to improve the safety of hyaluronic acid filler treatments.

Chapter 5.3 focuses on one of the most serious adverse events of hyaluronic acid filler treatments, vascular occlusion. This can lead to skin necrosis or very seldom, to blindness. Hyaluronic acid fillers come with the big advantage that they can be dissolved with hyaluronidase. The current protocol to treat vascular adverse events advises to flood the area with 1500 units every hour. However, using duplex/ultrasound to detect the hyaluronic acid filler causing the intra-arterial obstruction and subsequently ultrasound guided injections of hyaluronidase into the filler deposit proves to be an excellent way to prevent skin necrosis. As this method is very precise, a low dose of hyaluronidase is required and often one or two treatments are sufficient. Instant recurrence of blood flow is observed and scarring is prevented. As the use of duplex ultrasound adds essential extra information, we conclude that its use should become an integral part of the prevention and treatment of vascular adverse events

Chapter 5.4 is a proposal for a nomenclature for the sonographic description of dermal fillers and their complications. As duplex ultrasound becomes a more integral part of daily practice around the world, there is an increased number of publications about its use in combination with filler treatments. The terminology used to describe the ultrasound images of fillers proves to be not uniform, making the different articles difficult to compare. Standardization of the descriptions based on their basic sonographic parameters is recommended. Hopefully this will contribute to a better standardization and understanding fillers ultrasound images in the literature and in communication between physicians.

In Chapter 6 the overall results are discussed and recommendations for future research and development of the medical cosmetic field are given. The start of the out-patient clinic for filler complications at ErasmusMC in 2011 was an indirect result of our initial nativity as doctors regarding filler products and the lack of clinical data before these products entered the market. With this clinic our group became the referral center for the Netherlands. The numbers of patients we have seen throughout the years have given us insight in how to recognize and manage all the diverse types of complications caused by different types of fillers. As more awareness is growing globally about adverse

events caused by fillers, our clinic now serves as an educational center for physicians from all over the world. More important, it rises awareness that a lot of these complications could have been prevented if a better insight in the patients anatomy and previous filler treatments would have been possible. With new, good quality but affordable portable duplex ultrasound devices entering the market, we hope we will be able to reach out for more physicians to start using these devices in their practices, make filler treatments safer and improve the quality of their work.



Samenvatting

De cosmetische geneeskunde, inclusief de minimaal invasieve filler behandelingen, laat jaarlijks een toenemende groei in het aantal behandelingen zien. Aangezien de meeste patiënten die een behandeling wensen gezond zijn, dienen de behandelingen zo veilig mogelijk en zoveel mogelijk gespeend te zijn van bijwerkingen en complicaties. Dit vereist veilige producten en een adequaat uitgevoerde injectie techniek. Dit proefschrift beschrijft mijn werk van de afgelopen tien jaar om de veiligheid van fillers behandelingen zoveel mogelijk te verbeteren

Het eerste gedeelte van dit proefschrift focust op de veiligheid van het filler materiaal en de mogelijke complicaties. In het huidige system beoordelen de Aangemelde Instanties (Notified Bodies) of filler producten voldoen aan de regelgeving om toegelaten te worden op de Europese markt. Ondanks diverse aanpassingen in die regelgeving afgelopen jaren, is deze nog steeds niet voldoende om de veiligheid van fillers te waarborgen. Nieuwe Europese wetgeving die de toelatingseisen tot de markt aanscherpen worden dit jaar ingevoerd. De vereisten zijn onder andere uitvoeren van langere termijn studies en een transparant post-marketing surveillance systeem. Onder de huidige richtlijnen is dit niet verplicht. Dit heeft geleid tot veel meer verlate en ernstige complicaties dan verwacht.

Hoofdstuk één is een introductie van dit proefschrift. De verschillende typen van dermale fillers (zowel permanent als afbreekbaar) worden beschreven. De directe en late complicaties en de huidige behandel opties worden besproken

Hoofdstuk twee gaat over de langere termijn complicaties van een hydrogel (poly-alkylimide). De eerste publicaties die over deze permanente filler verschenen waren veelbelovend en geruststellend. De aangetoonde bio compatibiliteit na drie maanden was goed. De enige complicatie was een inflammatoire reactie (0,06% kans) aansluitend aan de behandeling. Deze kon goed behandeld worden met antibiotica. Indien gewenst of nodig kon de gel worden verwijderd middels punctie en uitdrukken van het product. Echter, lange termijn studies ontbraken. Pas jaren na behandeling werd een hoog percentage aan late complicaties bekend zoals inflammatoire reacties, opeenhoping en migratie van het materiaal. Dit leidde tot een negatief advies van de Nederlandse vereniging van Cosmetische Geneeskunde ten aanzien van het gebruik van dit product.

In hoofdstuk drie proberen we een verklaring te vinden voor het ontstaan van deze late complicaties veroorzaakt door de permanente hydrogel poly-alkylimide. Klinisch opvallend was het wit-gele aspect van de gel bij verwijdering, terwijl ten tijde van injectie de gel transparant is. Histologisch onderzoek liet bij alle patiënten degeneratie en dehydratie van het materiaal zien met een influx van neutrofiele cellen. Indien er sprake was een inflammatoire reactie, waren reuscellen aantoonbaar. Conclusie was dat een dermale filler niet allen beoordeeld dient te worden op de bio comptabiliteit direct na injectie maar ook het degradatie proces over tijd beoordeeld moet worden.

In hoofdstuk vier wordt een overzicht gegeven van de verschillende soorten complicaties van fillers die we op onze polikliniek behandelen. De huidige behandel opties (systemische behandeling en chirurgische verwijdering van het materiaal) worden besproken. Het belangrijkste aandachtspunt van dit hoofdstuk is echter een nieuwe behandelmethode om fillers te verwijderen; de intralesionale laser behandeling. Retrospectieve data van 242 patiënten met filler complicaties en behandeld met de intralesionale laser werden beoordeeld. In 92% was er sprake van een verbetering. De mate van tevredenheid was een stuk lager. We concludeerden dat de intralesionale laser behandeling een goede behandel methode is alvorens chirurgie te overwegen.

Het tweede gedeelte van dit proefschrift richt zich op de adequate diagnose stelling van filler complicaties en de veiligheid bij het uitvoeren van een filler behandeling. Esthetische geneeskunde wordt steeds meer gezien als een aparte medische specialisatie. Artsen die deze behandelingen uitvoeren dienen competent te zijn in de uitoefening van dit vak. In 2019 is de Nederlandse Vereniging voor Cosmetische Geneeskunde, (NVCG) met een door de KNMG gecertificeerde 2 jarige opleiding gestart. Artsen met een verschillende medische achtergrond kunnen worden opgeleid en getraind in cosmetische behandelingen. Dit is een grote stap voorwaarts.

Een andere verbetering van de veiligheid van filler behandelingen is de inzet van duplex echo onderzoek. In hoofdstuk 5.1 beschrijven we dat alle verschillende soorten fillers met echo zichtbaar zijn. Filler eigenschappen als levensduur en veranderingen in vivo kunnen in de tijd worden vervolgd. Filler complicaties zoals migratie en inflammatoire reacties kunnen in beeld worden gebracht. Het gebruik van duplex-echo verbreedt de kennis over fillers. In de toekomst zal dit mogelijk ook de veiligheid en uitvoering van filler behandelingen ten goede komen

In hoofdstuk 5.2 wordt met name aandacht besteed aan hyaluronzuur fillers. Hyaluronzuur is het meest gebruikte filler product wereldwijd. Het is een afbreekbaar product met een veilig risico profiel. Desondanks kunnen (ernstige) complicaties voorkomen. Hyaluronzuur filler is makkelijk met de echo te herkennen. Door een echo onderzoek uit te voeren vlak voor een fillerbehandeling, kunnen eerdere (permanente) filler behandelingen in beeld worden gebracht. Vasculaire beeldvorming maakt de individuele variatie van vaten zichtbaar. Bij eventuele complicaties kan zowel de filler, de locatie en de complicatie (migratie, abcessen, vasculaire complicaties) in kaart worden gebracht. Onder echogeleide kan hyaluronidase nauwkeurig in de hyaluronzuur filler worden geïnjecteerd om deze op te lossen. Het gebruik van duplex-echo onderzoek blijkt een belangrijke bijdrage aan de veiligheid van hyaluronzuur filler behandelingen

Hoofdstuk 5.3 focust op één van de meest ernstige complicaties van hyaluronzuur filler behandelingen: de vasculaire occlusie. Dit kan leiden tot huidnecrose en (zelden) tot blindheid. Een groot voordeel van hyaluronzuur fillers is dat ze met hyaluronidase kunnen worden opgelost. Het huidige protocol voor vasculaire occlusies adviseert het aangedane gebied ieder uur met 1500 eenheden te doordrenken. Echter, het gebruik van duplex-echo onderzoek om de pocket hyaluronzuur te lokaliseren die de obstructie veroorzaakt en deze vervolgens echo geleid op telossen met hyaluronidase, blijkt een zeer geode manier om huid necrose te voorkomen. Deze methode is erg nauwkeurig waardoor slechts op één of twee injecties met een lage dosering van hyaluronidase nodig is.

Hoofdstuk 5.4 is een voorstel voor een echografische filler nomenclatuur inclusief de betreffende complicaties. Nu duplex echo wereldwijd steeds vaker bij filler behandelingen wordt ingezet, neemt ook het aantal berichtgevingen en publicaties hier over toe. De gebruikte terminologie is onderling erg verschillend wat onderling vergelijken van studies niet eenvoudig maakt. Standaardisatie van filler omschrijvingen gebaseerd op hun sonografische parameters wordt dan ook aanbevolen. Hopelijk kan dit bijdragen tot een betere onderlinge communicatie.

In Hoofdstuk 6 is een discussie over de resultaten van alle hoofdstukken en worden aanbevelingen gedaan voor verder onderzoek en gewenste ontwikkelingen in de toekomst. Het opstarten van de polikliniek voor filler complicaties kwam deels voort uit onze naïviteit ten aanzien van fillerproducten en

het gebrek aan klinische data als deze producten beschikbaar komen voor gebruik. Door deze polikliniek zijn we nu een de landelijke verwijspoli binnen Nederland geworden. De grote aantallen patiënten die we afgelopen tien jaar hebben gediagnosticeerd en behandeld, hebben onze kennis over de verschillende mogelijke complicaties bij diverse typen van filler producten vergroot. Nu ook wereldwijd er steeds meer aandacht komt voor filler complicaties, is deze polikliek een kennis centrum geworden voor andere artsen, nationaal en internationaal. Tevens wordt de aandacht gevestigd op het feit dat veel complicaties voorkomen hadden kunnen worden als vooraf de individuele variatie en oudere permanente filler behandelingen bekend en zichtbaar waren geweest. Nu kwalitatief goede en tevens betaalbare mobiele echo apparaten beschikbaar komen, hopen we dat steeds meer artsen deze apparaten zullen incorporeren in hun cosmetische praktijk. Dit zal de veiligheid en de kwaliteit van de behandelingen ten goede komen.

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List of publications (2017-2020)

1. Schelke L, Decates T, Kadouch J, Velthuis P. Incidence of Vascular Obstruction After Filler Injections. Aesthetic Surgery Journal 2020 (in press)
2. Velthuis P, Jansen O, Schelke L, Moon H, Ascher B, Cotofana S. A Guide to Doppler Ultrasound Analysis of the Face in Cosmetic Medicine. Part 1: Standard Positions. Aesthetic Surgery Journal 2020 (accepted for publication)
3. Velthuis P, Jansen O, Schelke L, Moon H, Ascher B, Cotofana S. A Guide to Doppler Ultrasound Analysis of the Face in Cosmetic Medicine. Part 2: Vascular mapping. Aesthetic Surgery Journal 2020 (accepted for publication)
4. Habib SM, Schelke LW, Onderdijk AJ, Velthuis PJ. Management of dermal filler (vascular) complications using duplex ultrasound. Dermatologic Therapy 2020 (accepted for publication)
5. Kadouch J, Schelke LW, Swift A. Ultrasound to Improve the Safety and Efficacy of Lipofilling of the Temples. Aesthet Surg J. 2020 Mar 11. sjaa066. doi: 10.1093/asj/sjaa066.
6. Schelke LW, Cassuto D, Velthuis P, Wortsman X. Nomenclature proposal for the sonographic description and reporting of soft tissue fillers. J Cosmet Dermatol. 2020 Feb;19(2):282-288. doi: 10.1111/jocd.13127. Epub 2019 Aug 28. Review.
7. Schelke LW, Velthuis P, Kadouch J, Swift A. Early ultrasound for diagnosis and treatment of vascular adverse events with hyaluronic acid filler. J Am Acad Dermatol. 2019 Jul 17. pii: S0190-9622(19)32392-8. doi: 10.1016/j.jaad.2019.07.032.
8. Schelke L, Decates T, Hu C, Velthuis P. [An out-patient clinic for filler complications].Ned Tijdschr Geneeskd. 2019 Jan 3;163. pii: D3074. Dutch.
9. Schelke LW, Decates TS, Velthuis PJ. Ultrasound to improve the safety of hyaluronic acid filler treatments. J Cosmet Dermatol. 2018 Dec;17(6):1019-1024. doi: 10.1111/jocd.12726. Epub 2018 Aug 6.
10. Schelke LW, Decates TS, van der Lugt CIM, Pelzer L, de Mey G, Velthuis PJ. Intralesional Laser Treatment for Dermal Filler Complications. Plast Reconstr Surg. 2018 Jun;141(6):1361-1369. doi: 10.1097/PRS.0000000000004428.
11. Schelke LW, Velthuis PJ, van Dijk MR. Polyalkylimide: A Nonstable Filler Over Time. Dermatol Surg. 2018 Apr;44(4):563-567. doi: 10.1097/DSS.0000000000001388.

12. Schelke LW, Fick M, van Rijn LJ, Decates T, Velthuis PJ, Niessen F. [Unilateral blindness following a non-surgical rhinoplasty with filler]. Ned Tijdschr Geneeskd. 2017;161:D1246. Dutch.

Curriculum Vitae

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