Understanding, Avoiding, and Managing Severe Filler Complications

Berthold Rzany, MD, ScM
Claudio DeLorenzi, MD
Berlin, Germany, and Kitchener, Ontario, Canada

Summary: Any injectable filler may elicit moderate-to-severe adverse events, ranging from nodules to abscesses to vascular occlusion. Fortunately, severe adverse events are uncommon for the majority of fillers currently on the market. Because these are rare events, it is difficult to identify the relevant risk factors and to design the most efficacious treatment strategies. Poor aesthetic outcomes are far more common than severe adverse events. These in contrast should be easily avoidable by ensuring that colleagues receive proper training and follow best practices. (Plast. Reconstr. Surg. 136: 196S, 2015.)

Severe filler complications are fortunately rare. However, all injectors need to be aware of them, be able to recognize them when they occur, and know how to manage them properly.

METHODS

The overview is based on an unsystematic review of the literature. It benefits from the practical experience of Rzany and coworkers from running for nearly 10 years the so far most successful registry on adverse filler injections and the extensive practical experience with filler complications of DeLorenzi. Furthermore, it is inspired from the discussions during a meeting on adverse events to fillers and botulinum toxin A, which was held in Moscow on March 20 and 21 from Expert2Expert (http://www.expert2expert.co.uk/ organized by Dr. Patrick Trevidic). Common adverse events such as hematoma and swelling (which can be easily detected by a clinical trial) are not the subject of this review.

EPIDEMIOLOGY OF FILLER COMPLICATIONS

Filler complications need to be separated from unwanted aesthetic effects due to inappropriate use of fillers. The latter are much more common. Adverse events to injectable fillers are rare and often delayed events. Therefore, they will be undetected in a time- and resource-constrained clinical trial. Even hospital- or clinic-based registries will only be able to detect not so rare events. Besides the Germany registry data (a unique disease-based registry), most available data are based on small case series and case reports. Case series and case reports can point out possible products with an increased risk; however, they are usually unable to estimate the size of risk. In this case, a proper epidemiological study is required, which would then serve as a base to calculate numbers needed to harm. We need to keep the lack of evidence in mind specifically when we focus on possible risk factors, their avoidance, and the treatment of filler reactions.

Furthermore, outside the registries, many physicians seem to be reluctant to report serious adverse events, either perhaps they have the feeling that they will not change anything or perhaps fearing that others might consider that faulty technique is at fault. Therefore, it must be clarified that extremely rare events may occur to even the most talented injectors, even when they are practicing all known risk reduction strategies.

INAPPROPRIATE USE

Much more common than severe adverse events after the injection of a filler is overcorrection and/or erroneous placement of filler. Overcorrections are usually due to either a very

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superficial injection of a filler that is intended for deeper injections or the injection of too much volume in an area with very thin skin11 (Table 1). For poly-l-lactic acid, it could also mean skin-colored papules after injecting too superficially, especially if the product is insufficiently diluted, or injecting a sufficiently diluted product with insufficient hydration time, or poorly mixed (which has precipitated in the syringe).2,12 The most common indication for all kinds of overcorrection is “sunken eyes” or subocular lines where either too much filler is injected or it is injected in the wrong place, for example, above the infraorbital rim (within the confines of the orbitomalar ligament) or even too deep, that is, retroseptal. Expert knowledge of the detailed anatomy of the periorbital area is essential to prevent these common errors.6 Physicians must be aware of the surface anatomy of the regions that they are intending to treat with fillers and know how to judge the accurate position of the tip of the application cannula or needle, respectively, in relation to tissue planes from superficial too deep as well as medial to lateral. Even a very small amount of filler placed into the periorbital space will cause severe persistent “eye bags” that has repeatedly been observed to clinically last for much longer than the usual duration of dermal fillers, often extending into several years. This may be due to the reduced breakdown or metabolism of hyaluronic acid (HA) filler products within this anatomical space, where the human vitreous lays, which is primarily HA (however, no references have been found to support this hypothesis).

**Prevention**

How can overcorrection be prevented? Basically by 2 things: (1) good initial training and (2) continuous ongoing training. Detailed experience with the anatomy of these areas is highly recommended, and cadaver dissection courses are now frequently available during most congresses in that field to update knowledge for injectors.

**Outlook**

With the increase of filler injections and inexperienced injectors joining the workforce, overcorrections will continue to occur. For all involved, it is important that through good education and training, the incidence of overcorrection will be curtailed. Teaching on filler and other aesthetic interventions should therefore start as early as possible, for example, during medical school.14

**VASCULAR OCCLUSION**

Vascular occlusion is a (except for blindness) not so rare event, with an incidence of up to 3 in 1000.9 Vascular occlusion occurs in areas, which are supplied by only a single artery, such as the glabellar area (the most commonly affected area according to some reviews), the alae nasi, and the upper lip. If the main blood vessel supplying an area of skin is obstructed by a filler agent, the associated vascular territory will suffer from ischemia and necrosis. In the facial area, the arteria angularis (and its branches) is one of the most commonly affected arteries.9

From a recent smaller retrospective study comes some evidence that vascular occlusions seem to be more common and more severe in non-HA filler. Beleznay et al9 estimated the incidence of vascular occlusion after filler injections approximately 3 to 1000 for calcium hydroxylapatite compared with 3–9 per 10,000 for HA preparations (although no comparative statistics were done). What is clear is that the reactions

<table>
<thead>
<tr>
<th>Table 1. Reasons for Overcorrection*</th>
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<tbody>
<tr>
<td><strong>Product</strong></td>
</tr>
<tr>
<td>Hyaluronic acid</td>
</tr>
<tr>
<td>Calcium hydroxylapatite and other non-HA fillers</td>
</tr>
<tr>
<td>Poly-l-lactic acid</td>
</tr>
</tbody>
</table>

*Overcorrection can occur after injection of any kind of filler. This table gives just a brief overview on the 3 most commonly used biodegradable products.
†Hyaluronidase does not distinguish between good or bad placed hyaluronic acid. It will dissolve all artificial hyaluronidase in the area where injected.
and sequelae seem to be more severe with non-HA fillers such as calcium hydroxylapatite and polymethylmethacrylate.

**Blindness**

The most feared complication is the occlusion of the ophthalmic and/or retinal artery as blindness will invariably result. Blindness after filler injections is an extremely rare event. Most reports on blindness come from Asia, probably because of the prevalence of filler treatment in high-risk areas, for example, areas close to the artery angularis and its intracerebral anastomoses, due to the quest for beautification (eg, a more convex forehead, a more European-looking nose). The mechanism of action of embolic blindness seems to involve the retrograde flow of filler through the blood vessels exiting the supraorbital area, which normally flows outward from the internal carotid artery. The dense anastomotic network between the internal and external carotid vessels occurs in the territory around the nose, where ascending blood from the external carotid meets descending blood from the internal carotid territory. Under conditions of high pressure injection, filler product may be driven upward in the ascending vessels and forced retrograde down the vessels exiting the orbit. Once the pressure is released, the filler product is once again carried by the central retinal artery (as well as the adjacent arteries that exit the periorbital area), which might result in blindness that is rarely, if ever, reversible (Table 2).

**Prevention**

Good evidence confirming strategies for prevention is lacking at the time of this writing. Vascular occlusions are rare events. Blindness after filler occlusions are rare events. Blindness after filler injection is even rarer. Therefore, the present recommendations are almost exclusively based on expert opinion. Using cannulas for deep injection may reduce the risk of vascular occlusion, but no clinical or animal studies have yet been done to show a benefit. Nevertheless, it seems reasonable to assume that a not too small blunt cannula is less likely to penetrate a small artery than a sharp fine needle, and so it seems a priori a good practice to use it in areas of risk. Avoiding high injection pressure and large-volume single-point injection is also advisable because of the consequences of a large bolus within the vascular system. When a needle becomes slightly clogged, for example, physicians should avoid increasing the injection pressure and change the needle instead (to avoid sudden release of the clog and an accidental large bolus injection of filler).

The risk reduction strategies should be applied universally because human facial vascular anatomy is variable, and the smaller arterial vessels could be present just about anywhere filler treatments are done. Extra caution is warranted specifically in the higher risk areas such as the glabella, nose, or injection near to the probable location of named vessels. As a concept, the areas of the face should be considered higher or lower risk accordingly, and it must be understood that there are no areas that are zero risk. Even when following all known risk reduction strategies, and being conscious of the surface anatomy of the face and the known pathways of the named arteries of the face, it is still possible to accidentally inject filler material into the arterial system. Although the authors believe

<table>
<thead>
<tr>
<th>Proposed Action</th>
<th>Assumed Result</th>
<th>Possible Downside Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannula use</td>
<td>Less risk of accidental penetration of arteries</td>
<td>Small-gauge cannulas may still be sharp enough to enter arteries, especially in scar tissues</td>
</tr>
<tr>
<td>Low-pressure techniques</td>
<td>Reduces risk of retrograde blood flow</td>
<td>Even with low pressure, arteries will fill, but only more slowly</td>
</tr>
<tr>
<td>Small bolus (less than 0.1 ml in any one region)</td>
<td>If the needle tip happens to be inside an arterial lumen, the smaller bolus will cause less vascular obstruction</td>
<td>Depends on the size of the artery involved. A tiny artery will fill extensively even with a small bolus</td>
</tr>
<tr>
<td>Aspiration before injection</td>
<td>Arterial flash back is a sign of arterial penetration</td>
<td>Thick fillers with thin injection tubes may not reveal any flash back, even if the lumen is inside an artery</td>
</tr>
<tr>
<td>Detailed anatomical awareness of the likely position and depth of named vessels in the treatment areas</td>
<td>Avoiding the main named vessels is good clinical practice</td>
<td>There is quite a lot of normal variation of blood vessels, even from the left to right sides of the same individual</td>
</tr>
<tr>
<td>Use of local anesthesia with epinephrine before filler treatment</td>
<td>Epinephrine causes vascular constriction and thus reduces the overall cross-sectional area of the arterial lumen</td>
<td>Epinephrine will cause blanching of the skin, which may be misinterpreted as acute vascular occlusion</td>
</tr>
</tbody>
</table>
that we can lower the risk, we do not believe that we can completely eliminate it. By using fillers that have known “antidotes,” such as HA fillers and hyaluronidase, we can decrease the risk of permanent sequelae (since hyaluronidase might be used to dissolve the occlusion if discovered in time\textsuperscript{21}).

**Treatment**

The first clinical sign of vascular obstruction is skin blanching that occurs simultaneously with the injection. The duration of the blanching event is typically only on the order of minutes, and this rapidly changes to a blotchy livedo pattern due to changes in the skin’s venous drainage.\textsuperscript{6,7} The blotchy livedo pattern is gradually replaced with a deep bluish discoloration, and upon clinical examination, capillary refill is found to be much slower than normal.

In the case of a vascular occlusion, a patient may paradoxically not report any pain if the filler is compounded with a local anesthetic or if extensive pretreatment local anesthesia or nerve block has been used. The onset of pain may be delayed in presentation by a few hours. Vascular occlusion occurs contemporaneously with the filler injection, but of course the patients’ symptoms will depend on the size and location of the vascular obstruction, and the nature of the filler material. If the filler material sticks to itself, it may cause complete obstruction of a larger vessel, possibly allowing for some collateral blood flow, whereas if the material disperses into, say, 40- or 50-μm particles that separate, they are carried by the blood flow down the various sized vessels to eventually reach the size that they can no longer pass through (the capillary bed). It may take some time to see the extent of obstruction because of the different pathophysiology of different filler materials.

The first action must be to cease all injections immediately. If an HA filler was used, hyaluronidase should be injected into the area where the filler was injected and in any areas where the signs of ischemia are evident. Remember that blood vessels may transport filler materials distally or even proximally (depending on injection pressure), anatomic ally away from the original injection site, and sometimes even to the contralateral side of the face. Hyaluronidase injections need to be repeated hourly until blood circulation has been again established (DeLorenzi C, personal communication, 2015). In case of visual loss, the injection of hyaluronidase has to be done immediately\textsuperscript{16} in case of other areas as fast as possible. From animal studies,\textsuperscript{26} it is known that occlusion after HA injection and its effects can be reversed when the hyaluronidase is injected within 4 hours after the occlusion.

Later injection might, however, be beneficial to as the affected area might be decompressed and probably healing accelerated in case the vessel can be made penetrable again. In contrast to human skin, the retina, the brain, and muscle tissues are highly sensitive to hypoxia and begin to show serious degradation within moments after the onset of ischemia. Therefore, as mentioned before, in case of acute blindness, hyaluronidase needs to be injected immediately intraorbicularly.

In case of occlusion by a non-HA filler, the therapeutic situation is much more difficult. Several interventions as topical nitroglycerin ointment have been proposed, however, with little evidence. A recent study\textsuperscript{25} was not able to show a significant benefit of topical nitroglycerin ointment in an animal model. For the use of hyperbaric oxygen, we just have a single case report where the postintervention photographs still depict scarring.\textsuperscript{20}

**Outlook**

Will there be an increase of vascular occlusions with an increase of filler use? Probably yes. However, the increased awareness of the risk of vascular occlusion and potential risk factors hopefully will not mirror the increase of filler use. Furthermore, with the increased awareness of the benefits of hyaluronidase, the sequelae after an HA-filler embolus should decrease, too. To have this risk further reduced, in our opinion, any new filler entering the market targeted for high-risk areas should be accompanied by an antidote.

**IMMUNOLOGICAL REACTIONS**

All injected fillers have the potential to elicit an adverse event. These reactions can be grouped depending on the time from injection to onset as acute, subacute, and delayed. “Subacute” is somewhat vaguely defined; it generally encompasses reactions that occur weeks following injection. Reactions can also be grouped according to the clinical diagnosis ranging from abscesses to nodule formation.\textsuperscript{26}

Abscesses usually are acute or subacute although cases occurring after several months or years have been reported. Usually, these late abscesses are not a sign of bacterial infection. If the abscess is fluctuant, it must be drained and its content (even when a noninfectious origin is likely) sent for bacterial microscopy and culture. In case of accompanying cellulitis, an appropriate antibiotic should be added immediately. Hyaluronidase according to the labeling should not be used in the presence of active infection (cellulitis) because it
may facilitate the spread of infection into adjacent tissues (n.b. hyaluronidase has been used in abscess reactions after HA-fillers without signs of worsening the accompanying inflammation).

Nodule formation, not as depot of the product but as a sign of an exaggerated immune response, is the most common adverse event to all fillers. Some colleagues advocate that biofilm, a low-grade bacterial colonization, may play a significant role in nodule formation by triggering an immunological reaction. When antibiotics or 5-fluorouracil seems to be beneficial, it is uncertain if this is due to bactericidal, anti-inflammatory, or immunomodulatory effects or a combination of these (Table 3).

However, before any intervention is considered, it is important to identify the relevant filler. Dadzie et al showed that injected filler families can be distinguished by histopathology, that is, a HA filler can be distinguished from a methylmethacrylate filler.

### Risk Factors/Prevention

If we knew the exact constellations triggering an immunological adverse event, it would be much easier to avoid such reactions. However, because of the limited available evidence on the pathophysiology, the potential risk factors, and the benefit of avoidance, we do not know much.

### Products

HA filler products dominate the filler market, with estimates of 85–95% of the entire filler market over the entire world. However, not all HA products are similar. Some products seem to have a higher risk of an adverse event. This has even happened with well-known products. At the end of the last century, it became apparent that Restylane in the original form elicited inflammatory reactions and led to changes in the manufacturing process. Friedman et al reviewed the data of all unwanted effects of the Restylane range of products (HA) reported globally (Europe, Australia, South America, Asia) to the manufacturer (Q-Med now a Galderma company, Uppsala, Sweden) between 1999 and 2000. In 1999, based on 144,000 treatments, the incidence was calculated as 0.15%; in 2000, based on approximately 262,000 treatments, the incidence was calculated as 0.06%. The differences between these incidences were explained through changes made in the manufacturing process (which involved sourcing a better quality raw HA product with a much lower protein content).

More recent examples are HyaCorp HS and H1000, products from a smaller manufacturer (Bioscience, now Dümmer, Germany). When it became apparent that there were several cases of adverse events with these 2 products, with an estimated risk of adverse event of 1.4% (Skipr. Tot nu toe 25 klachten over rimpelfiller. Online in the internet: http://www.skipr.nl/actueel/id12523-tot-nu-toe-25-klachten-over-rimpelfiller.html (2012-10-25)], the product in 2012 underwent investigation by the Dutch authorities. (Please note that here a risk of less than 2:100 was thought to warrant further investigation.) Finally, the company opted to withdraw HyaCorp H-S 500, H1000, and HyaCorp L from the European market in August 2013.

Permanent products pose several challenges when it comes to nodule formation. As they remain in the body, the lifetime risk increases specifically, especially in products with an increased risk. Here is an example: hydroxyethylmethacrylate and ethylmethacrylate microspheres suspended

### Table 3. Treatment Approach in Case of Filler-Induced Nodular Immunological Reactions

<table>
<thead>
<tr>
<th>Step 1</th>
<th>In case of an HA filler</th>
<th>Inject hyaluronidase around the nodule (in the nodule if possible)</th>
</tr>
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<tbody>
<tr>
<td>Step 2</td>
<td>Start an immunomodulatory treatment</td>
<td>Inject steroids* and/or 5-fluorouracil†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Or start an oral steroid treatment as pulse (eg, methylprednisolone)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>And/or doxycycline</td>
</tr>
<tr>
<td>Step 3</td>
<td>Surgical treatment</td>
<td>Excision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Laser</td>
</tr>
</tbody>
</table>

*Usually 10 mg triamcinolonaacetone diluited with, for example, lidocaine (either 1:4 or 1:5 (DeLorenzi C, personal communication; see Moscow meeting in Methods section)).

†5-Fluorouracil diluted 1:1 with lidocaine.
in HA were available in Europe as DermaLive (Dermatech, Paris, France) from the end of the 1990s until 2007. This product consisted of 40% bacterial HA and 60% acrylic hydrogel particles (diameter of 45–65 µm). A similar formulation with larger-sized particles (about 85–110 µm) and a somewhat higher HA content was marketed as DermaDeep (Dermatech) and was intended to be injected deeper. Early after the introduction to the market, there were case reports of nodule formation due to hydroxyethylmethacrylate. Other adverse events included abscesses and ulceration, which occurred sometimes years and even decades after the initial injection. In 2001, the overall incidence of late side effects and complications (nodules, swelling, and erythema, on average 6 months after injection) based on data from the manufacturer was given as <1.2 per 1000 patients. As the observation period was limited in this early article, the real risk might even have been higher. Although this product is no longer manufactured, however, as it is a permanent product, it is highly likely that adverse events to this permanent product will continue to present years after its use. With a permanent product, the second challenge is the treatment in case of nodule formation. Here, the treatment is much more challenging when compared with biodegradable products.

These examples show that some products might have higher risks, which might lead to modifications in the production process or a withdrawal of the filler from the market. These products were put on the market without preceding good clinical trials. With this in mind, some advice would be to avoid fillers that enter the market without good clinical trials. In our opinion, permanent products should be avoided because of the increased lifetime risk of adverse events unless very compelling evidence of safety and efficacy is provided.

**Patients**

When it comes to patients, risk factors become less clear. Even when analyzing the cases of the Berlin Registry, it became apparent that there is nothing like “THE” risk factor. Based on single cases and case reports in the literature, it seems likely that acute autoimmune diseases and interferon therapy might be risk factors for foreign body or sarcoid-like reactions after filler injections. In a patient with previous permanent filler injections in the same area that is to be treated anew, this constellation might be considered a risk factor for an adverse event (eg, might introduce contamination into a permanent implant). It should be remembered that the number of organisms required to cause clinical infection is drastically reduced from 100,000 to 100 per gram of tissue in the presence of a foreign body, such as permanent filler. Dermal fillers are approved by the Food and Drug Administration as implants (even though they are injected as medications). When an implant is contaminated with bacteria, it is impossible to sterilize it or to “uninfect” it in any way. Hence, any treatment given over top of a permanent implant risks contamination of the existing implant and might lead to pronounced inflammation or even abscesses. Therefore, even without good evidence of an increased risk, it is not recommended to routinely treat over the top of permanent fillers. In certain circumstances, it might, however, be necessary to improve the overall aesthetic appearance of the patient by adding small superficial amounts of an HA filler over a permanent filler to decrease the signs of aging or complications. This need to be done with caution and only after extensive education of the patient (Rzany B, personal communication, 2015) and using considerable care in the use of appropriate skin prep and drape of the treatment site. In other words, the injector should use the same precautions as might be expected when dealing with other permanent implants (ie, consider using Centers for Disease Control and Prevention–recommended chlorhexidine skin prep and sterile technique).

**Outlook**

The treatment of these reactions still presents a lot of questions. Ideally, we would have liked clinical trials comparing immunomodulatory versus

**Table 4. Safety Kit**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Others</th>
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<tbody>
<tr>
<td>In case of overcorrection</td>
<td>Hyaluronidase*, †</td>
</tr>
<tr>
<td>In case of a vascular occlusion</td>
<td>Hyaluronidase*, ‡</td>
</tr>
<tr>
<td>Drugs or interventions that increase the blood flow</td>
<td>Ophthalmologist and/or eye clinic in case of acute blindness after filler injection §</td>
</tr>
</tbody>
</table>

*Several vials should be available (in case of large affected areas or the need of repeated injections).
†Usually 1 ml of hyaluronidase should dilute 1 ml of misplaced hyaluronic acid.
‡In case of vascular occlusion, the hyaluronidase should be injected not only in the treated areas but also in the area where the emboli most likely went.
§In case of acute blindness, the injections need to be done immediately intraorbicular.
antibiotic treatment (for those advocating the biofilm theory) in immunologically mediated nodule formation. But these trials do not exist and would be very difficult to do so. Therefore, we need to collect and analyze data from cases and case series and draw the best possible evidence out of these.

SAFETY KIT

Every physician who works with injectable fillers needs to have a safety kit. The safety kit should contain numbers of specialists as well as drugs as antidotes. So far hyaluronidase is the only available antidote for HA injections. In case of vascular occlusion after a non-HA filler, hyaluronidase may be beneficial by increasing the local perfusion pressure of collateral vessels that may reduce the zone of necrosis. As said before, this recommendation is based on expert opinion. However, it is an intervention that will not cause significant harm (Table 4).

SUMMARY

Adverse events, both vascular and nonvascular, after filler injections do occur and will continue to occur, and this may increase as the number of filler injections continues to climb. True adverse events need to be separated from unwanted aesthetic effects due to the inappropriate use of fillers. In both cases, prevention is the best medicine and experience and education are our best tools. Predictable results are obtained by using predictable products, with a predictable methodology, in a predictable patient. Outside the United States make sure any new product you consider using is backed by good controlled clinical trials.

Berthold Rzany, MD, ScM
RZANY & HUND
Privatpraxis für Dermatologie und Ästhetische Medizin
Kurfürstendamm No. 183
Berlin D-10707, Germany
rzany@kudamm183.de

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REFERENCES


