Complications Associated With Injectable Soft-Tissue Fillers

A 5-Year Retrospective Review

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Importance: Even when administered by experienced hands, injectable soft-tissue fillers can cause various unintended reactions, ranging from minor and self-limited responses to severe complications requiring prompt treatment and close follow-up.

Objectives: To review the complications associated with injectable soft-tissue filler treatments administered in the Williams Rejuva Center during a 5-year period and to discuss their management.

Design and Setting: Retrospective medical record review in a private practice setting.

Participants: Patients receiving injectable soft-tissue fillers and having a treatment-related complication.

Interventions: Injectable soft-tissue filler treatments.

Main Outcome Measures: A retrospective medical record review was conducted of patients undergoing treatment with injectable soft-tissue fillers between January 1, 2007, and December 31, 2011, and identified as having a treatment-related complication.

Results: A total of 2089 injectable soft-tissue filler treatments were performed during the study period, including 1047 with hyaluronic acid, 811 with poly-L-lactic acid, and 231 with calcium hydroxyapatite. Fourteen complications were identified. The most common complication was nodule or granuloma formation. Treatment with calcium hydroxyapatite had the highest complication rate.

Conclusions and Relevance: Complications are rare following treatment with injectable soft-tissue fillers. Nevertheless, it is important to be aware of the spectrum of potential adverse sequelae and to be comfortable with their proper management.

Level of Evidence: 4.


Volume enhancement has long been recognized as a means to achieve facial rejuvenation. Various soft-tissue fillers have gained popularity among aesthetic surgeons and patients alike for their rapid and predictable results, relative ease of delivery, and favorable safety profiles. Over the years, as patients have developed an almost insatiable appetite for soft-tissue augmentation with injectable fillers, the pool of providers has expanded from aesthetic surgeons and dermatologists to include health care practitioners with little or no formal training in aesthetic medicine.

A recent study conducted by the American Society of Plastic Surgeons revealed a 190% increase in the number of soft-tissue filler treatments performed by plastic surgeons between 2000 and 2011. This astounding number does not reflect the explosion in filler treatments administered by non-core physicians and other medical practitioners.

Even when administered by experienced hands, injectable fillers can cause various unintended reactions, ranging from minor and self-limited responses to severe complications requiring prompt treatment and close follow-up. The aesthetic surgeon should not only have a firm understanding of the potential complications caused by injectable fillers but also know when to intervene and be confident in managing the entire spectrum of adverse sequelae.

In this study, we review 5 years of injectable filler treatments administered in the Williams Rejuva Center to determine the number and types of complications that occurred and how they were managed. We also searched the literature to provide treatment options for the more commonly observed adverse reactions.
We queried the billing database to determine the total number of soft-tissue injectable filler treatments administered in the Williams Rejuva Center between January 1, 2007, and December 31, 2011. Neurotoxin injections were not included in our analysis. The treatments were further categorized as hyaluronic acid, poly-L-lactic acid, and calcium hydroxylapatite. In practice, we routinely see all patients treated with hyaluronic acid or calcium hydroxylapatite 2 weeks after treatment for reassessment, whereas patients undergoing treatment with poly-L-lactic acid are seen approximately 8 to 12 weeks after they are treated. Any adverse reactions noted at a follow-up visit or reported at any other time by the patient are documented in their clinic medical record, as well as in a monthly quality assurance report. To determine the total number of complications associated with injectable soft-tissue fillers during this interval, we reviewed the medical records of all the patients identified in the quality assurance reports as having a filler-related complication.

### RESULTS

Between January 1, 2007, and December 31, 2011, a total of 2089 soft-tissue filler injections were performed in the office for volume augmentation. These injectable treatments consisted of the following: 1047 hyaluronic acid, 811 poly-L-lactic acid, and 231 calcium hydroxylapatite. Complications were defined as adverse events not considered expected sequelae of the injection itself (ie, swelling, bruising, pain, and others). During the 5-year period reviewed, 14 complications were identified: 2 involved treatment with hyaluronic acid, 6 with poly-L-lactic acid, and 6 with calcium hydroxylapatite. The filler type and number of complications are summarized in the Table.

Calcium hydroxylapatite was the filler most commonly associated with complications in this series. Three patients developed cellulitis at the treatment site, one of whom developed cellulitis on 2 separate occasions following treatments administered 7 months apart. One patient developed a submucosal nodule visible beneath the buccal mucosa, and another patient experienced partial-thickness necrosis at the alar-facial junction following injection of calcium hydroxylapatite into her melolabial folds.

Patients treated in the office with poly-L-lactic acid experienced 6 total complications, including 5 cases of subcutaneous nodules and 1 case of perioral dermatitis. In a patient with a history of sarcoidosis, the nodules were visible at rest, while in 2 other patients the nodules were barely perceptible with extreme facial animation. The other 2 cases of nodules were palpable but not visible, although the nodules were associated with a generalized induration of the midface in one of these patients.

Hyaluronic acid injections were the least likely to result in a complication in this series. One patient developed an inflammatory granuloma after treatment of her lips with hyaluronic acid. A second patient experienced the Tyndall phenomenon after injection of hyaluronic acid to treat a tear trough deformity.

**Table. Breakdown of Injectable Soft-Tissue Filler Types and Their Associated Complications**

<table>
<thead>
<tr>
<th>Filler Type (Total No. of Treatments)</th>
<th>Cellulitis</th>
<th>Nodule or Granuloma Formation</th>
<th>Skin Necrosis</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaluronic acid (n = 1047)</td>
<td>0</td>
<td>1 (0.1)</td>
<td>0</td>
<td>1 (0.1)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Poly-L-lactic acid (n = 811)</td>
<td>0</td>
<td>5 (0.6)</td>
<td>0</td>
<td>1 (0.1)</td>
<td>6 (0.7)</td>
</tr>
<tr>
<td>Calcium hydroxylapatite (n = 231)</td>
<td>4 (1.7)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>0</td>
<td>6 (2.6)</td>
</tr>
<tr>
<td>All fillers (N = 2089)</td>
<td>4 (0.2)</td>
<td>7 (0.3)</td>
<td>1 (0.05)</td>
<td>2 (0.1)</td>
<td>14 (0.7)</td>
</tr>
</tbody>
</table>

Although rare, skin necrosis is a potentially devastating complication of treatment with injectable fillers. Necrosis is caused by vascular compromise resulting from arterial or venous obstruction. The occlusion of blood flow can be due to trauma to the vessel wall, inadvertent intravascular injection of the product, or a direct pressure effect of the filling agent on the vessel causing obstruction of the vessel lumen. Furthermore, injection-related edema can compromise blood flow by contributing an external force on the vessel wall.

Arterial compromise is typically heralded by immediate-onset blanching and severe pain, whereas venous obstruction frequently manifests with a delayed reticulated, violaceous appearance. If untreated, injection-related vascular compromise (IRVC) will progress to a partial-thickness or full-thickness injury to the skin, leading to necrosis, skin slough, and scarring. Various algorithms have been described to manage IRVC, although none are supported by more than anecdotal evidence. If IRVC is recognized during the treatment session, the injection should immediately be stopped, and an attempt should be made to aspirate the product. Measures should then be implemented to improve blood flow and dissipate the agent. These include aggressive massage, warm compresses, and the application of nitroglycerin to the affected area. When the culprit filler is hyaluronic acid, hyaluronidase can also be administered to digest the offending product. A course of aspirin has also been advocated in these circum-

### METHODS

Injectable soft-tissue fillers offer patients noticeable and immediate results, without the downtime associated with traditional facial rejuvenation surgery. Whereas mild pain, swelling, and bruising at the injection site are common and expected consequences of these treatments, true complications arise less commonly.

### VASCULAR OCCLUSION AND SKIN NECROSIS

Although rare, skin necrosis is a potentially devastating complication of treatment with injectable fillers. Necrosis is caused by vascular compromise resulting from arterial or venous obstruction. The occlusion of blood flow can be due to trauma to the vessel wall, inadvertent intravascular injection of the product, or a direct pressure effect of the filling agent on the vessel causing obstruction of the vessel lumen. Furthermore, injection-related edema can compromise blood flow by contributing an external force on the vessel wall.

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stances because of its anti-inflammatory and antiplatelet effects, and some authors have promoted the use of topical oxygen therapy to facilitate an enhanced rate of epithelialization.

In cases of IRVC, prompt recognition and swift intervention can potentially prevent progression to necrosis. If the IRVC cannot be reversed, local wound care should proceed in the usual fashion, and the resultant mature injury can be dealt with using traditional scar mitigation techniques.

In this series, 1 of 2089 injections (<.05%) was complicated by IRVC. The sole instance occurred in a 43-year-old woman who underwent calcium hydroxyapatite filler injection to the melolabial folds. Three days after treatment, she developed an area of painful swelling and gray to purple discoloration along the ala and superior portion of the nasolabial fold (Figure 1). Initially presumed to be cellulitis, she was treated with multiple courses of antibiotics. The acute presentation ultimately evolved into a small violet-hued patch of skin that eventually resolved with topical hydroquinone, as well as treatment with the pulsed dye laser. In retrospect, what was initially thought to be infectious in nature was likely an instance of IRVC resulting in superficial epithelial necrosis and prolonged postinflammatory hyperpigmentation.

CELLULITIS AND BIOFILMS

Cellulitis can occur following treatment with soft-tissue fillers due to inadvertent inoculation of bacteria into the skin or entry of pathogens following temporary disruption of the skin’s barrier function. The head and neck usually represents an anatomical safe haven against postprocedural soft-tissue infections owing to its excellent blood supply and high rate of metabolism. However, cellulitis, abscess formation, and other infectious complications can be seen following treatment with injectable fillers.

Biofilms are a potential mechanism in injectable filler–related complications and have been implicated in infections involving a diverse array of organ systems, especially in the setting of indwelling prosthetic devices or other foreign bodies. A biofilm typically consists of a living bacterial colony that adheres to a foreign implant and self-encapsulates with a complex extracellular matrix principally consisting of polysaccharides. Biofilms are able to alter gene expression and change their microenvironment to evade the host immune system and become antibiotic resistant. A common denominator for the development of an injectable filler–related biofilm is the need for bacterial or other infectious contamination as an inciting event.

Chronicity and recurrence of infection are hallmarks of biofilms. Implants, especially those that are permanent (silicone), may become contaminated by a biofilm, yet activation may not occur until hematogenous seeding or local trauma introduces a new load of bacteria, leading to an active infection. Although antibiotics and drainage may suppress an active infection, complete resolution is rare (if not impossible) without removal of the implant and its associated biofilm. Some authors propose a 2-week window during which bacterial contamination can occur and lead to biofilm formation. Avoiding additional injections in the region of the implant, as well as dental procedures and facial trauma, will mitigate the risk of biofilm formation. Given the potential for biofilm formation and the significant morbidity that can result, a topic of future investigation should be whether periprocedural prophylactic antibiotics offer an improvement in infection rates.

In this series, 3 patients developed early postprocedural cellulitis, with all cases occurring following treatment with calcium hydroxyapatite in the perioral region or midface. In each instance, oral antibiotics were promptly initiated, and complete resolution of symptoms ensued. Figure 2 shows a female patient who un-
underwent treatment of the prejowl region with a calcium hydroxylapatite filler. One day later, she developed an area of erythema and swelling along the chin and lower cheek that was indurated and warm to the touch. She was diagnosed as having cellulitis and oral antibiotics were started. The affected area blistered and desquamated and was then treated with topical emollients until healing was complete. The cellulitis completely resolved, with no long-term sequelae.

One patient developed 2 distinct episodes of cellulitis of the cheek after treatment sessions with calcium hydroxylapatite separated by 7 months. The second episode was more fulminant, with extensive erythema and numerous small pustules. Given the recrudescence of her infection during such a lengthy interval, the specter of bacterial biofilm formation was considered. Fortunately, both infections resolved with conservative medical management.

**NODULES AND GRANULOMAS**

Subcutaneous nodules are a known complication of injectable fillers. Fibrotic nodules may arise from stimulatory products such as poly-L-lactic acid and calcium hydroxylapatite. They tend to be painless, appear weeks to months following treatment, and can last for years. In most cases, they are palpable but cannot be seen. Although the nodules usually remain localized to the site of treatment, a degree of migration can also occur. In extreme cases, they can become visible and are a source of significant anxiety for the affected patient.14

Subcutaneous nodules have been reported in 0% to 40% of patients receiving poly-L-lactic acid.15,16 Localized accumulations of product are the most common cause of nodules in patients receiving calcium hydroxylapatite or hyaluronic acid, whereas fibrotic nodules are usually seen with stimulatory products, such as poly-L-lactic acid.17 Furthermore, certain anatomical sites are known to present a higher risk for nodule formation, particularly the lower eyelid. Overall, a decrease in nodule formation may be seen with subdermal injection, postinjection massage, a higher reconstitution volume, and a longer latency between reconstitution and injection.18,19

In this series, one instance occurred of an accumulation of calcium hydroxylapatite visible beneath the buccal mucosa due to an inadvertent depot delivery of filler in this region. Five cases of apparent fibrotic nodule formation also occurred in patients receiving poly-L-lactic acid. One patient, a 66-year-old woman with a history of sarcoidosis, underwent a series of 3 treatments during 5 months to the midface, melolabial folds, and prejowl regions. Six months after her final treatment, she was noted to have diffuse beadlike nodules throughout her treatment areas (Figure 3). Unlike the other 4 patients in the series who developed fibrotic nodules that were only apparent on palpation, hers were visible at rest. Although the bumps were not painful and demonstrated no other inflammatory characteristics, we surmised that the sarcoidosis may have had a role in her developing such an extensive distribution of nodules. She was followed expectantly and showed no further nodule progression.

Although the prescribing information provided by the manufacturer of injectable poly-L-lactic acid recommends reconstitution of 1 vial of product with 5 mL of sterile water,20 we prefer an off-label 8:1 dilution. In addition, we reconstitute the product 48 hours before injection and use a laboratory vortex to agitate the mixture before its transfer for injection. We believe that these simple measures in conjunction with meticulous injection technique are responsible for our very low rate of nodule formation (0.6%).

Nodules can also represent an infectious, immune, or inflammatory process resulting in granuloma formation.21 A granuloma can be differentiated from a fibrotic nodule by its later onset, tenderness, swelling, possible erythema, and occasional suppuration. Proposed causes include biofilms, protein impurities, and irregularities of surface microspheres.22 Histologically, these nodules show a foreign-body response with epithelioid granulomas and an inflammatory infiltrate surrounding the inert product.22 With poly-L-lactic acid, it is possible that processes resulting in localized inflammation, such as sunburn, trauma, or treatment of the skin with a laser, could stimulate inflammatory nodule formation.

Hyaluronic acid fillers can also form intradermal granulomas that are characterized by abundant multinucleated giant cells surrounding the basophilic product.23 Hyaluronidase injections are the initial treatment of choice.9 One patient in this series developed an inflammatory granuloma after undergoing augmentation of the upper and lower lips with hyaluronic acid filler. Approxi-
mately 2 months after injection, she noted painful swelling of the lower lip and was found to have nonfluctuant swelling and induration confined to the left side of the lower lip (Figure 4). She was treated with a course of antibiotics and a tapering course of oral corticosteroids, and the swelling completely resolved during the next few weeks. Because of the delayed presentation, this was thought to be an inflammatory granuloma, with biofilm formation a possible culprit.

During the 5-year study period, a patient with chronic inflammatory granulomas was managed who had undergone perioral silicone injections in another city. She was seen in the office intermittently reporting pain, redness, and swelling around her mouth and chin (Figure 5) and was treated on each occasion with oral and intralesional corticosteroids. This chronic waxing-and-waning inflammatory response is a hallmark of granulomas resulting from soft-tissue injection of silicone. Because of the potentially devastating consequences associated with injectable silicone, we strongly recommend against its use for volume augmentation.

CONCLUSIONS

A significant shortcoming of this study was the retrospective nature of its design. Furthermore, despite a policy to see all patients treated with injectable soft-tissue fillers for scheduled follow-up visits and to document all complications in the quality assurance reports, it is possible that we were unable to capture every adverse event that occurred during the study period. Some patients may have failed to recognize an adverse event, did not return for their follow-up visits, or sought care for a complication with another physician.

Volume loss, an integral component of the facial aging process, is responsible for some of the telltale signs of senescence. Therefore, volume restoration, alone or in conjunction with other procedures, has become an important focus of most facial rejuvenation strategies. Soft-tissue injectable fillers have been and will continue to be popular because of their minimal downtime, favorable safety profile, and rapid and reproducible results. Nevertheless, injectables are not without risk. Today’s expanding population of patients seeking injectable soft-tissue fillers may be vulnerable to complications that go unrecognized and undertreated due to physician shopping, limited follow-up care, and the lack of training among many practitioners performing filler treatments. Infection, fibrotic nodules, granuloma formation, and vascular compromise are possible sequelae that must be recognized and managed properly to prevent potentially permanent disfigurement.

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