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ORIGINAL ARTICLE

# Adverse reactions caused by consecutive injections of different fillers in the same facial region: risk assessment based on the results from the Injectable Filler Safety study

F Bachmann,[†,*] R Erdmann,[†] V Hartmann,[†] P Becker-Wegerich,[‡] L Wiest,[§] B Rzany[†]

[†]Division of Evidence Based Medicine, Department of Dermatology, Charité-Universitätsmedizin Berlin, Charité, Charitéplatz 1, Berlin, Germany

[‡]Aesthetik- und Laserzentrum Zürichsee, Dorfstrasse 94, Meilen, Switzerland

[§]Über der Klause 1, München, Germany

*Correspondence: F Bachmann. E-mail: frank.bachmann@charite.de

## Abstract

**Background** The combination of different injectable fillers in one area is considered to increase the risk of adverse reactions.

**Objectives** To characterize adverse reactions in patients who received more than one filler in the same facial region.

**Methods** Data (up to July 2009) of the Injectable Filler Safety Study, a German-based registry for adverse filler reactions, was analysed descriptively. All cases were discussed individually.

**Results** In 22 of the 161 patients (13.7%), two or more different fillers were injected consecutively into the same facial region. All patients were female with an average age of 50.6 (SD 13.6) years. In 12 of the 22 patients (54.5%), a specific filler could be attributed to the adverse reactions whereas in the other 10 patients (45.5%), the filler was not clearly attributable to one filler substance causing the adverse reactions.

**Conclusions** With the continuous changes in the filler market, the combination of different fillers in one area becomes more likely. Based on our data, there is not a lot of evidence that the combination of different injectable fillers, specifically biodegradable fillers, in the same region increases the risk of adverse reactions.

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## Keywords

combination, combined, complications, fillers, injectable, reactions

## Conflict of interest

None declared.

## Introduction/background

Injectable filler substances together with botulinum toxin injections dominate aaesthetic dermatology.[1] Collagen-based fillers have been and hyaluronic acid (HA)-based fillers are the most commonly used products for soft tissue augmentation.[2] However, besides these, a multitude of other fillers exists, e.g. hydroxylapatite and alginates and more are to come.

Although injectable fillers are considered to be very safe, significant adverse reactions may occur.[3–6] With the advent of new injectable fillers and the discontinuation of others, the combination of multiple fillers in a single facial area is more likely to happen or even purposely attempted.[7] However, some authors suggest that combining different fillers in one area might increase the risk of adverse reactions and, therefore, recommend not to inject a filler in an area previously injected with another filler – specifically if that filler is a permanent product.[8,9]

So far, no large study has been published focusing on this question. We report an analysis based on 161 registered patients with the aim to describe the risk of adverse reactions in this cohort for patients consecutively treated with different fillers in the same facial area.

## Methods

The Injectable Filler Safety Study, is a partially population-based patient registry with the aim to collect adverse reactions to injectable filler substances. The registry is run by the Division of Evidence-Based Medicine and was reviewed and approved by the Ethics Committee of the Charité-Universitätsmedizin, Berlin.[6,10–13]

Patients derive mostly from the Berlin area. However, some patients were reported outside Berlin, specifically from two private practices specialized in the treatment of these adverse reactions (L. Wiest, Munich, P. Becker-Wegerich, Zürich). And, with increasing publicity of the registry, patients started to report directly to the registry as well.

To be included in the registry, a patient (i) must have been treated with an injectable filler substance and (ii) developed a reaction in at least one of the treated areas, (iii) that lasted for at least 2 weeks and (iv) was not because of overcorrection. Adverse reactions were defined clinically and assessed by using a standardized atlas of clinical symptoms. The intensity of reactions was assessed by a three-point scale with 1 = mild to 3 = severe. To be defined as a combination patient, at least two different classes of filler substances had to be injected in the same facial region. To describe causality, the time between injection and onset of adverse reactions was another criterion. To account for prolonged efficacy after repeated treatment with HA-based fillers[14] and because of lack of contradicting knowledge, we assumed a possible impact of collagen or HA-based fillers no longer than 2 years after the last injection, i.e. HA- or collagen-based fillers injected 2 years before onset of adverse reactions were considered as causal irrelevant. Patients were further differentiated in patients: (i) in whom a specific filler was attributable to the adverse reactions and (2) in whom no specific filler was attributable to the adverse reactions (Fig. 1). To calculate the time between injection and onset of adverse reactions and to account for the different biodegradability of the fillers in patients who received the same filler more than once, we considered the first injection date for permanent and the last injection date for temporary fillers as causal relevant.

The decision, if a reaction was attributable to a specific filler, was based on the clinical symptoms (e.g. characteristic nodules), the area of the reactions (e.g. if reactions to permanent products occurred in all treated areas), as well as the time sequence between injection and appearance of the reaction (see above).

For this analysis, each case was discussed individually. The analysis is descriptive, and some results are given with localization and dispersion measurements, such as mean, standard deviation, frequency, percentage and median.

## Results

Until 9 July 2009, 161 patients were registered in the Berlin registry. Of the 161 patients, 153 were female and eight male. The average age of the patients was 49.6 years (SD 10.7) ranging from 23 to 82 years of age.

As many as 72 (44.7%) of the patients were treated with a permanent injectable filler, whereas 67 (41.6%) of them were injected with bio-degradable fillers. Of the latter, 45 patients (28% of all patients and 67.2% of the patients injected with bio-degradable fillers, respectively) were treated with temporary filler substances whereas 22 (13.7% and 32.8%, respectively) received the semi-permanent product poly-L-lactic acid (PLA). In 22 of the 161 patients (13.7%), two or more different fillers were injected consecutively into the same facial region.

These 22 patients were all female with an average age of 50.6 (SD 13.6) years ranging from 23 to 82 years of age. In 18 of these 22 patients (77.3%), two different fillers were used in the same facial region. Four patients (18.2%) were injected with three different fillers.

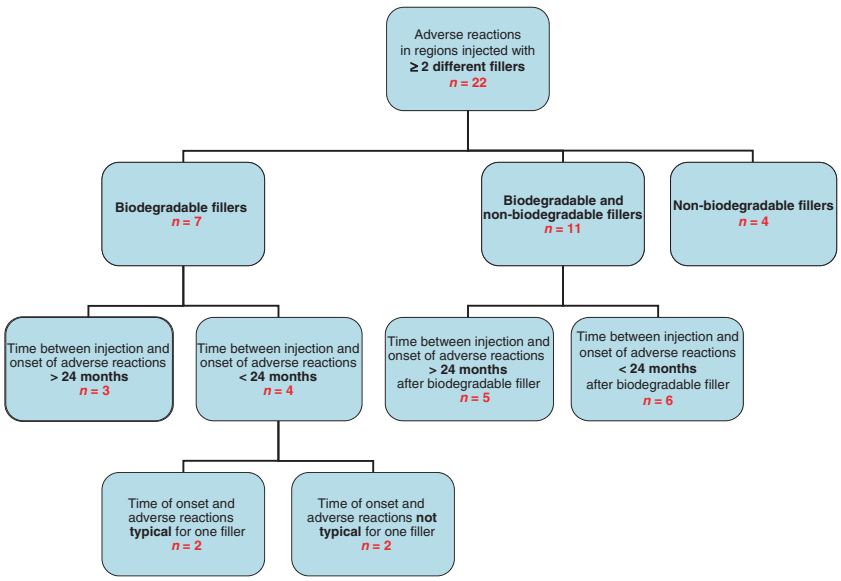


**Figure 1** Distribution of patients included in this analysis according to the class of filler injected and the time between injection and onset of adverse reactions.

Nine of the 22 patients (40.9%) had two, six of 22 (27.3%) patients had three, and seven of 22 (31.8%) patients had four treatment sessions in total with any of the fillers.

In 11 of the 22 patients (50.0%), permanent and bio-degradable injectable fillers were combined in the same region. In four of the 11 patients (36.4%), the bio-degradable product was injected after the permanent product whereas six patients (54.5%) received the bio-degradable product first. In one case (9.1%), the bio-degradable product was given in between two permanent products.

### Patients in which the causative filler can be identified

In 12 of the 22 patients (54.5%), the specific filler was attributable to the adverse reactions.

### Combination with poly-L-lactic acid

For five of the 12 patients (41.6%, 1 to 5), PLA (NewFill®/Sculptra®, Sanofi Aventis, Frankfurt, Germany) was attributable to the adverse reactions because of the time between injection and onset of adverse reaction and the adverse reaction seen in these patients (Table 1). In addition, in two patients (3 and 5) adverse reactions occurred in adjacent regions treated with PLA only. Nodules were reported in all (100%) of the five patients. Pruritus, erythema, pain, and abscess formation occurred in only 20% of the patients. In two patients (40%, 1 and 5), nodules were assessed exclusively. In average, the adverse reactions occurred with a latency of 6.4 ± 2.9 months ranging from 2 to 9 months. In three (2, 4, and 5) patients, the adverse reactions occurred more than 24 months after the last injection of either HA- (2) or collagen- (4 and 5) based fillers.

### Combination with hydroxyethylmethacrylate and ethylmethacrylate particles in hyaluronic acid

In six of 12 patients (50%, 6–11), adverse reactions were attributable to hydroxyethylmethacrylate and ethylmethacrylate particles in HA (Dermalive®, Dermatech S.A., Paris, France; HEMA/EMA) because of the clinical symptoms and the latency of adverse reactions (Table 2). The most commonly seen adverse reactions were nodules and pruritus reported in all (100%) of the patients followed by erythema in five of six (83.3%), discoloration in four of six (66.7%), swelling in three of six (50%), and pain and abscess formation in two of six (33.3%) of the patients. The reactions developed with a latency of 29 ± 16.3 months after the injection. Only in two of these patients (10 and 11), adverse reactions occurred after the consecutive injection of a biodegradable filler (Table 3). In three patients (6, 7, and 9), adverse reactions occurred more than 24 months after the last injection of either HA- (9) or collagen- (6 and 7) based fillers.

### Combination with polymethylmethacrylate

In one patient (12), polymethylmethacrylate (Artecoll®, Artes Medical Inc., San Diego, CA, USA) was injected after collagen

**Table 1** Combination with poly-L-lactic acid (NewFill®/Sculptra®). Patients with adverse reactions (AR) following the injection of poly-L-lactic acid (PLA) and either hyaluronic acid (HA)- or collagen-based fillers in the same facial region. In all of these patients, AR are most likely ccaused by PLA. Latency = time between injection of filler and onset of adverse reaction

| Combination with poly-L-lactic acid (NewFill®/Sculptra®) | | | | | | |
|---|---|---|---|---|---|---|
| **Patients** | **Location and AR** | **Latency (months)** | **First product (location)** | **Latency (months)** | **Second product (location)** | **Most likely product and reasons for that** |
| 1 | Upper lip<br>Nodules | 16 | HA (upper lip) | 6 | PLA (upper lip) | PLA: latency and reaction |
| 2 | Upper lip<br>Abscess formation, nodules | 61, 50 | HA (2×) (upper lip) | 9 | PLA (upper lip) | PLA: latency (and reaction)<br>HA: latency > 24 months |
| 3 | Upper lip<br>Pruritus, nodules | 16, 15 | Collagen (2×) (upper lip) | 10, 9 | PLA (2×) (upper lip) | PLA: latency, reaction, and other region |
| | Corner of the mouth<br>Pruritus, nodules | 16, 15 | Collagen (2×) (corner of the mouth) | 10, 9 | PLA (2×) (corner of the mouth) | PLA: latency, reaction, and other region |
| | Chin<br>Pruritus, nodules | 9 | PLA (chin) | | | PLA: latency, reaction, and other region |
| | NLF<br>Nodules | 15 | Collagen (chin) | 10, 9 | PPLA (2×) (chin) | PLA: latency, reaction, and other region |
| 4 | Upper lip<br>Nodules, erythema, pain | ~48 | Collagen (upper lip) | ~2–3, 1–2 | PLA (2×) (upper lip) | PLA: latency (although short for PLA) and reaction<br>Collagen: latency > 24 months |
| 5 | Upper lip<br>Nodules | ~24 | Collagen (upper lip) | 6 | PLA (upper lip) | PLA: latency and reaction, and other region<br>Collagen: latency ~ 24 months |
| | Corner of the mouth<br>Nodules | 6 | PLA (corner of the mouth) | | | See above |

**Table 2** Combination with hydroxyethylmethacrylate and ethylmethacrylate particles in hyaluronic acid (Dermalive®). Patients with adverse reactions (AR) following the injection of hydroxyethylmethacrylate and ethylmethacrylate particles (HEMA/EMA) and either hyaluronic acid (HA)- or collagen-based fillers in the same facial region. In all of these patients, AR are most likely caused by HEMA/EMA. Latency = time between injection of filler and onset of adverse reaction

| Combination with hydroxyethylmethacrylate and ethylmethacrylate particles in hyaluronic acid (Dermalive®) | | | | | | |
|---|---|---|---|---|---|---|
| **Patients** | **Location and adverse reactions** | **Latency (months)** | **First product (location)** | **Latency (months)** | **Second product (location)** | **Most likely product and reasons for that** |
| 6 | Corner of the mouth<br>Abscess formation, pruritus, nodules, erythema, pain, swelling, discoloration | ~108 | Collagen (corner of the mouth) | 13 | HEMA/EMA (corner of the mouth) | HEMA/EMA: latency and reactions<br>Collagen: latency > 24 months |
| | NFL<br>Nodules, erythema, discoloration | ~108 | Collagen (NLF) | 13 | HEMA/EMA (NLF) | HEMA/EMA: latency and reactions<br>Collagen: latency > 24 months |
| 7 | Upper lip<br>Pruritus, nodules, pain | ~50 | Collagen (upper lip) | 20, 18, 17 | HEMA/EMA (3×) (upper lip) | HEMA/EMA: latency and reactions<br>Collagen: latency > 24 months |
| | NLF<br>Pruritus, nodules, erythema, discoloration | ~50 | Collagen (NLF) | 20, 18, 17 | HEMA/EMA (3×) (NLF) | HEMA/EMA: latency and reactions<br>Collagen: latency > 24 months |
| 8 | Crow's feet<br>Abscess formation, nodules | 25 | HEMA/EMA (crow's feet) | 19 | HA (crow's feet) | HEMA/EMA: latency and reactions |
| | Glabella<br>Nodules | 25 | HEMA/EMA (glabella) | 19 | HA (glabella) | HEMA/EMA: latency and reactions |
| | Periorbital region<br>Nodules, swelling | | | | | |
| | NLF<br>Nodules | 25 | HEMA/EMA (NLF) | 19 | HA (NLF) | HEMA/EMA: latency and reactions |
| | Upper lip<br>Pruritus, nodules | 25 | HEMA/EMA (upper lip) | 19 | HA (upper lip) | HEMA/EMA: latency and reactions |
| | Lower lip<br>Nodules | 25 | HEMA/EMA (lower lip) | 19 | HA (lower lip) | HEMA/EMA: latency and reactions |
| 9 | Upper lip<br>Pruritus, nodules, erythema | ~44 | HEMA/EMA (upper lip) | | | HEMA/EMA: see below |
| | Lower lip<br>Nodules, erythema | ~44 | HEMA/EMA (upper lip) | | | HEMA/EMA: see below |
| | NLF<br>Nodules, erythema, discoloration | ~55 | HA (NLF) | ~44 | HEMA/EMA (NLF) | HEMA/EMA: latency and reactions, and other region<br>HA: latency > 24 months |


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**Table 3** Adverse reaction to hydroxyethylmethacrylate and ethylmethacrylate particles (HEMA/EMA). Patients with adverse reactions (AR) following the injection of hydroxyethylmethacrylate and ethylmethacrylate particles (HEMA/EMA) and hyaluronic acid (HA)-based filler in the same facial region. In these patients, AR are possibly triggered by the additional injection of HA. Latency = time between injection of filler and onset of adverse reaction

| | Adverse reactions to hydroxyethylmethacrylate and ethylmethacrylate particles potentially triggered by consecutive injection of hyaluronic acid | | | | | |
|---|---|---|---|---|---|---|
| **Patients** | **Location and AR** | **Latency (months)** | **First product (location)** | **Latency (months)** | **Second product (location)** | **Most likely product and reasons for that** |
| 10 | Upper lip<br>Nodules, erythema, swelling | 18, 6 | HEMA/EMA (2×) (upper lip) | 1.5 | HA (upper lip) | Typical latency and reactions for HEMA/EMA. Onset possibly triggered by HA injection |
| | Corner of the mouth<br>Nodules, erythema, swelling, discoloration | 18, 6 | HEMA/EMA (2×) (corner of the mouth) | 1.5 | HA (corner of the mouth) | See above |
| | NLF<br>Nodules, erythema, swelling, discoloration | 18, 6 | HEMA/EMA (2×) (NLF) | 1.5 | HA (NLF) | See above |
| 11 | NLF<br>Nodules, erythema, swelling, discoloration | ~54, 47, 45 | HEMA/EMA (3×) (NLF) | 1 | HA (NLF) | Typical latency and reactions for HEMA/EMA. Onset possibly triggered by HA injection |

(Table 4). Because of the latency of more than 90 months for collagen and 72 months for polymethylmethacrylate, respectively, and because of the adverse reactions resembling nodules, erythema, swelling and discoloration, polymethylmethacrylate was likely to be the causative filler substance. Because of the latency, collagen was unlikely contributing to the adverse reactions in this patient (see 'Methods').

### Patients in which the causative filler cannot be identified

In further 10 patients (45.45%), the filler substance was not clearly attributable to the adverse reactions.

### Combination of biodegradable filler products

In one patient (13), adverse reactions were seen early (within days) after HA injection and about 5 months after collagen was injected in the same region of the face (Table 5). The adverse reactions pruritus, erythema, and swelling as well as the latency were likely for both filler substances.

In another patient (14), adverse reactions were reported 3 months after PLA (NewFill®/Sculptra®) and 5 months after the last injection of HA. The latency was a bit short for PLA and a bit too long for HA. Although nodules are more commonly seen after PLA, the injectable filler was not clearly attributable.

### Combination of biodegradable and non-biodegradable filler products

In seven patients, different permanent products were consecutively injected into one region for which one causative substance could not been singled out (Table 6).

One patient (15) received collagen, poly(acrylamide-co-DADMA) (Evolution®; Laboratoires ProCytech, Bordeaux, France), and PLA. Adverse reactions and latency were not specific for any of the three filler substances. The collagen-based filler was very unlikely a contributing factor (see 'Methods').

In another three patients (16–18), adverse reactions were either caused by HEMA/EMA (Dermalive®) or by polyacrylamide (Aquamid®, Contura International S.A., Soeborg, Danmark). In one patient (16), adverse reactions occurred 20 months after HA injection in a region (nasolabialfolds) consecutively treated with different products and within 1 day in regions solemnly treated with HA (upper and lower lips). Although HA could be excluded most likely because of latency, adverse reactions and latency did not allow to distinct between HEMA/EMA and polyacrylamide in causing these adverse reactions. In the following patient (17), the adverse reaction occurred 1 month after injection of polyacrylamide respectively 3 months after HA injection respectively 72 months after injection of HEMA/EMA. Because of the short latency, polyacrylamide might have triggered the reactions. In another patient (18), HA and polyacrylamide were injected in the same facial regions (upper and lower lips). The adverse reactions were likely for both injectable fillers, but the early onset caused by the

**Table 4** Combination with polymethylmethacrylate (Artecoll®). Patient with adverse reactions (AR) following the injection of polymethylmethacrylate (PMMA) and collagen-based fillers in the same facial region. AR are most likely caused by PMMA. Latency = time between injection of filler and onset of adverse reaction

| Combination with polymethylmethacrylate (Artecoll®) | | | | | | |
|---|---|---|---|---|---|---|
| **Patients** | **Location and AR** | **Latency (months)** | **First product (location)** | **Latency (months)** | **Second product (location)** | **Most likely product and reasons for that** |
| 12 | Upper lip<br>Nodules, erythema, swelling, discoloration | ~110, 100, 90 | Collagen (3×) (upper lip) (corner of the mouth) | ~72 | PMMA (upper lip) | PMMA®: latency and reaction<br>Collagen: latency > 24 months |

**Table 5** Combination of different biodegradable filler products. Patients with adverse reactions (AR) following the injection of poly-L-lactic acid (PLA)-, hyaluronic acid (HA)-, or collagen-based fillers in the same facial region. AR cannot be attributed to any of the fillers. Latency = time between injection of filler and onset of adverse reaction

| Combination of different biodegradable filler products | | | | | | |
|---|---|---|---|---|---|---|
| **Patients** | **Location and AR** | **Latency (months)** | **First product (location)** | **Latency (months)** | **Second product (location)** | **Most likely product and the reason for that** |
| 13 | Others<br>Pruritus, erythema, swelling | 5 | Collagen | None | HA | Latency and adverse reactions likely for both products |
| 14 | NLF<br>Nodules, swelling | 35, 11, 5 | HA (NLF) | 3 | PLA (NLF) | Latency too long for HA and too short for PLA; reactions more likely for PLA |

additional injection of polyacrylamide was more likely than a belated onset following HA injection.

### Combination of non-biodegradable filler products

In one patient (19), the two permanent fillers HEMA/EMA and polyacrylamide were combined in one facial region (corner of the mouth) (Table 7). For both, latency and adverse reactions were likely.

In three patients (20–22), polymethylmethacrylate and other permanent products were injected in at least one common region. Patient 20 presented adverse reactions in two facial regions (cheek and nasolabialfolds) injected with polymethylmethacrylate and HEMA/EMA. The adverse reactions were commonly seen after injection of either one of the two filler substances and the latency was not specific for one of them. In the next patient (21), similar adverse reactions (nodules) occurred in both of the polyacrylamide-treated areas (upper and lower lip) wherefore polyacrylamide was more likely to be the causative substance. However, adverse reactions caused by polymethylmethacrylate could not be excluded in the upper lip. In the last patient (22), silicone and polymethylmethacrylate were injected in the corner of the mouth. Latency and adverse reactions were typical for polymethylmethacrylate; however, silicone might have been a contributing factor.

## Discussion

Although in a retrospective study there might be some doubt on the accuracy to identify the causative filler used, we are quite confident that the right filler was identified in most of the patients because of good clinical data from the treating physician (who was accessible and willing to cooperate in most of the cases) or a clear filler specific adverse reaction (e.g. granulomatous nodules after HEMA/EMA).

In contrast to the hypothesis that injecting different fillers in the same facial area increases the risk of adverse reaction,[15] only a small subgroup of patients reported to our registry had received more than one filler in the same facial area. In fact, only 13.7% (22 of 161) of the included patients were injected with two or more different injectable fillers in the same facial regions. Therefore, most patients (86.3%) were treated with one filler substance only. These results are similar to the results of Alijotas-Reig *et al.*[16] who describe 25 patients with adverse filler reactions of which four (16%) were consecutively injected with different fillers in the same region.

Therefore, at the moment, our data and the data of Alijotas-Reig *et al.*[16] do not support the theory that the combination of different fillers in the same facial region increases the risk of adverse reactions. A proportion of approximately 15% might be the subset of patients that receive more than one filler in a region.

Although unlikely, we cannot rule out that the combination of different fillers may, in some cases, increase the risk of adverse reactions. But what is the theoretical background for an increased risk of adverse reactions if different fillers are combined in one area?

Every injection causes a wound that consecutively triggers the healing process.[8] A trauma such as another injection or surgery to

**Table 6** Combination of biodegradable and non-biodegradable filler products. Patients with adverse reactions (AR) following the injection of different biodegradable fillers such as poly-L-lactic acid (PLA)-, hyaluronic acid (HA)- or collagen-based fillers and non-biodegradable fillers such as hydroxyethylmethacrylate and ethylmethacrylate particles (Dermalive®, HEMA/EMA), poly(acrylamide-co-DADMA) (PAA-co-DADMA, Evolution®), and polyacrylamide (PAA, Aquamid®)in the same facial region. For all of these patients, the causative filler cannot be distinguished clearly. Latency = time between injection of filler and onset of adverse reaction

| Combination of biodegradable and non-biodegradable filler products | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Patients** | **Location and AR** | **Latency (months)** | **First product (location)** | **Latency (months)** | **Second product (location)** | **Latency (months)** | **Third product (location)** | **Most likely product and reasons for that** |
| 15 | NLF<br>Abscess formation, erythema, swelling, discoloration | 140 | Collagen (NLF) | 1–10 | PAA-co-DADMA (NLF) | Same month | PLA (NLF) | Latency to short for PLA and for PAA-co-DADMA (exact latency unclear); latency > 24 months for collagen |
| 16 | Upper lip<br>Nodules | ~1 day | HA (upper lip) | | | | | See below |
| | Lower lip<br>Nodules | ~1 day | HA (lower lip) | | | | | See below |
| | NLF<br>Nodules, discoloration | 31 | HEMA/EMA (NLF) | 22 | PAA (NLF) | 20 | HA (NLF) | Similar reactions but with different latency in other but adjacent facial regions caused by HA as well; however, reactions in non-treated regions have been reported before. Latency and reactions are more likely attributable to HEMA/EMA or PAA |
| 17 | Lower lip<br>Nodules, pain, swelling | 5 | PAA (lower lip) | | | | | See below |
| | NLF<br>Nodules, erythema, pain, swelling, discoloration | 72 | HEMA/EMA (NLF) | 3 | HA (NLF) | 1 | PAA (NLF) | For PAA, similar reactions occurred in another treated region (lower lip) as well, however, for the cheek the latency is quite short for PAA but quite long for HEMA/EMA, either. The latency for HA is in the right range but reactions to permanent fillers is more likely |
| 18 | Upper lip and lower lip<br>Erythema, swelling, nodules, discoloration, abscess formation, pain | 10 | HA (upper lip) (lower lip) | same month | PAA (upper lip) (lower lip) | | | Adverse reactions are likely for both fillers. The latency is too long for HA and too short for PAA |


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**Table 7** Combination of non-biodegradable filler products. Patients with adverse reactions (AR) following the injection of different non-biodegradable fillers such as hydroxyethylmethacrylate and ethylmethacrylate particles (Dermalive®, HEMA/EMA), polymethylmethacrylate (Artecoll®, PMMA), polyacrylamide (Aquamid®, PAA), and silicone in the same facial region. For all of these patients, the causative filler cannot be distinguished clearly. Latency = time between injection of filler and onset of adverse reaction

| Combination of non-biodegradable filler products | | | | | | |
|---|---|---|---|---|---|---|
| **Patients** | **Location and AR** | **Latency (months)** | **First product (location)** | **Latency (months)** | **Second product (location)** | **Most likely product and reasons for that** |
| 19 | Corner of the mouth Pruritus, nodules, discoloration | 58 | HEMA/EMA (upper lip) (lower lip) | ~12 | PAA (corner of the mouth) | For both, latency and adverse reactions are typical |
| 20 | NLF Inflammation, swelling Cheek Inflammation, nodules, swelling, discoloration | ~150 | PMMA (2×) (NLF)‘ | 72, 62 | HEMA/EMA (2×) (NLF) | Although the latency for PMMA is very long and atypical, the causality cannot be excluded. For HEMA/EMA as well the latency is long but not unusual. However, it is not possible to definitely state which the attributable filler is |
| 21 | Upper lip Nodules | 40 | PAA (upper lip) | 21 | PMMA (upper lip) | As similar reactions occurred in both of the treated regions, reactions to PAA are more likely. However, in the upper lip, reactions to PMMA cannot be excluded |
| | Lower lip Nodules | 40 | PAA (lower lip) | | | See above |
| 22 | Corner of the mouth Pruritus, nodules, erythema | ~192 | Silicone (corner of the mouth) | 19 | PMMA (corner of the mouth) | Latency and spectrum of reactions are typical for PMMA; however, silicone might be still a contributing factor |

**Table 8** Absolute and relative frequencies of adverse reactions caused by biodegradability of fillers. The biodegradable filler substances comprise collagen- and hyaluronic acid-based fillers. The slow biodegradable filler substances consist of poly-L-lactic acid fillers only. The non-biodegradable filler substances include all of the permanent fillers

| **Adverse reaction** | **Biodegradable filler substances (*n* = 41)** | | **Slow biodegradable filler substances (*n* = 28)** | | **Non-biodegradable filler substances (*n* = 84)** | |
|---|---|---|---|---|---|---|
| | **Absolute (*n*)** | **Relative (%)** | **Absolute (*n*)** | **Relative (%)** | **Absolute (*n*)** | **Relative (%)** |
| Nodules/hardening | 30 | 73 | 28 | 100 | 81 | 96 |
| Discoloration | 17 | 41 | 9 | 32 | 48 | 57 |
| Erythema/inflammation | 36 | 88 | 7 | 25 | 44 | 52 |
| Swelling | 32 | 78 | 5 | 18 | 41 | 49 |
| Pain | 17 | 41 | 4 | 14 | 22 | 26 |
| Pruritus | 6 | 15 | 4 | 14 | 19 | 23 |
| Abscess formation | 14 | 34 | 3 | 11 | 14 | 17 |
| Ulceration | 1 | 2 | 1 | 4 | 0 | 0 |
| Dysaesthesia | 2 | 5 | 0 | 0 | 2 | 2 |
| Others | 6 | 15 | 0 | 0 | 2 | 2 |

the area where another filler has been injected previously may result in the activation of the immune system.[17] This basically may lead to an increased durability as Narins *et al.*[14] was able to show for a HA preparation. However, at the same time a foreign body formation could be stimulated through the activation of macrophages in some patients as well.

The second hypothesis is the so called ‘biofilm theory’. Christensen *et al.*[18–20] suggest, based on her experience with adverse reactions to polyacrylamide, that inflammatory nodules are likely to be caused by a low-grade infection maintained within a biofilm (a film comprising bacteria, their nutrients, and their waste products) harbouring especially hydrophilic fillers. According to Christensen *et al.*,[20] complications are caused by infection with bacteria which have been inserted into the gel during injection. The injection of another filler in the same region as well as surgical procedure or trauma could cause that infection possibly inducing the

**Table 9** Time between injection and onset of adverse reactions

| Product | Latency* | Latency† |
|---|---|---|
| Collagen | Few weeks‡ | Limited data |
| Hyaluronic acid | 2.51 ± 6.50 | Limited data |
| Poly-L-lactic acid | 7.38 ± 6.16§ | 6.4 ± 2.9 |
| Polyacrylamide | 5.43 ± 7.64 | Limited data |
| Polymethylmethacrylate | Limited data | Limited data |
| Polyhydroxyethylmethacrylate/ethylmethacrylate | 29.20 ± 26.23¶ | 29 ± 16.3 |

*Partially unpublished results from the IFS-study (total number of patients in the registry).
†Results from the subpopulation of this analysis.
‡Data from [35].
§Published in [11].
¶Published in [13].

onset of adverse reactions. Wiest *et al.*,[21] however, did not find bacteria in any of their investigated specimen when performing electromicroscopy on biopsies of patients with adverse reactions to hydroxyethylmethacrylate and ethylmethacrylate particles in HA. This shows clearly that the biofilm theory might not apply to all kind of fillers.

What else might be important? Nicolau[8] and Laeschke[22] describe different factors that might modify foreign body reactions and may also play a role for different fillers injected in one area: (i) implant size and volume; (ii) implant morphology; (iii) surface area; (iv) chemical composition; (v) electrical charge; and (vi) implantation site. Smaller particles, for example, may be phagocytised faster[23] and may initiate local necrosis.[24,25] Therefore, the detachment of single small-sized particles from the main mass of an implant may lead to reactivation causing an acute adverse reaction.[26] Furthermore, the chemical characteristics of the implants might have an impact as well.[25,27,28] Whether a particle is hydrophobic or hydrophilic seems to play a role in phagocytosis.[17] Although hydrophobic compounds may facilitate cellular adhesion and inflammatory reaction,[8] hydrophilic particles may be less readily phagocytosed.[17,29] Therefore, the injection of a second or third filler substance might result in unfavorable chemical interactions and adverse reactions. Finally, the surface charge of the filler may have an impact. Positively charged implants may increase phagocytosis[17] and attract and activate macrophages[30,31] fostering formation of foreign body giant cells, negative surface charge may decrease phagocytosis[17] and repel some negatively charged bacteria.[32] Consequently, the injection of an additional filler substance might negatively influence the dielectric environment leading to a change in local intermolecular interactions[24,33,34] and to onset or recurrence of adverse filler reactions. Freitas,[29] however, reports no significant effect of neither positive nor negative surface charge.

In literature, some reports discuss a causal relationship between injections of new fillers in an area previously treated with permanent products. Nicolau[8] and Pons-Guiraud[9] report the appearance of inflammatory granuloma after the injection of HA-based fillers in regions previously treated with permanent fillers especially Dermalive®. Likewise, Alijotas-Reig *et al.*[16] report four of 25 patients consecutively treated with different fillers in the same region. Three of the four were treated with HA-based fillers (Restylane®; Q-med AB, Uppsala, Sweden) in a region previously treated with either of the two permanent filler products, silicone or polymethylmethacrylate. Adverse reactions occurred within 3 months in all of them. According to these authors, the injection of HA might have triggered adverse reaction in regions previously treated with permanent fillers. Nevertheless, it could also be just a coincidental association.[9]

In six of the 22 patients (27%) who received more than one filler (10, 11, 14, 15, 17, 19), the adverse reaction occurred shortly (within few months) after the injection of a subsequent filler. In two patients (10 and 11), adverse reactions occurred 1.5 months respectively 1 month after the injection of HA whereas, in another two patients (8 and 16), a consecutively administered HA-based filler did not shorten/trigger the onset of adverse reactions although the circumstances were similar: HA had been injected in the same facial region in which the permanent filler HEMA/EMA (Dermalive®) had been injected previously. In another two patients (17, 19), adverse reactions occurred within 1 month after the injection of polyacrylamide (Aquamid®) in a region previously treated with HA. One (17) of the two had been treated with HEMA/EMA 6 years before the onset of adverse reactions. In patient 15, adverse reactions occurred within 1 month after injection of PLA. This patient had been treated with poly(acrylamide-co-DADMA) (Evolution®) 1–10 months before PLA injection.

We cannot rule out that only in this small fraction (27% or six of 22 patients of our study subpopulation or in about 3.7% of the total study population of the Berlin registry) the additional injection of another filler in the same area may have influenced the onset of the adverse reactions observed.

## Conclusion

With the continuous development of the filler market, the consecutive injection of different fillers in one area becomes more likely. Based on our data, there is not a lot of evidence that the consecutive injection of different fillers in the same region increases the risk of adverse reactions. Only a small number of patients (22 of 161) were reported to our registry with adverse reactions to different consecutively injected fillers in the same facial region. However, in seven of these patients (2, 4–7, 9, and 12), the biodegradable filler had been injected more than 2 years before the onset of adverse reactions presenting an unlikely candidate for a contributing factor. Therefore, only 15 patients (9.3%) remained, in which the filler associated with the adverse reactions could not be established or where it might have been a combination of different fillers that had elicited the adverse reactions. Because of the small number of patients from the subpopulation (six of 22) in

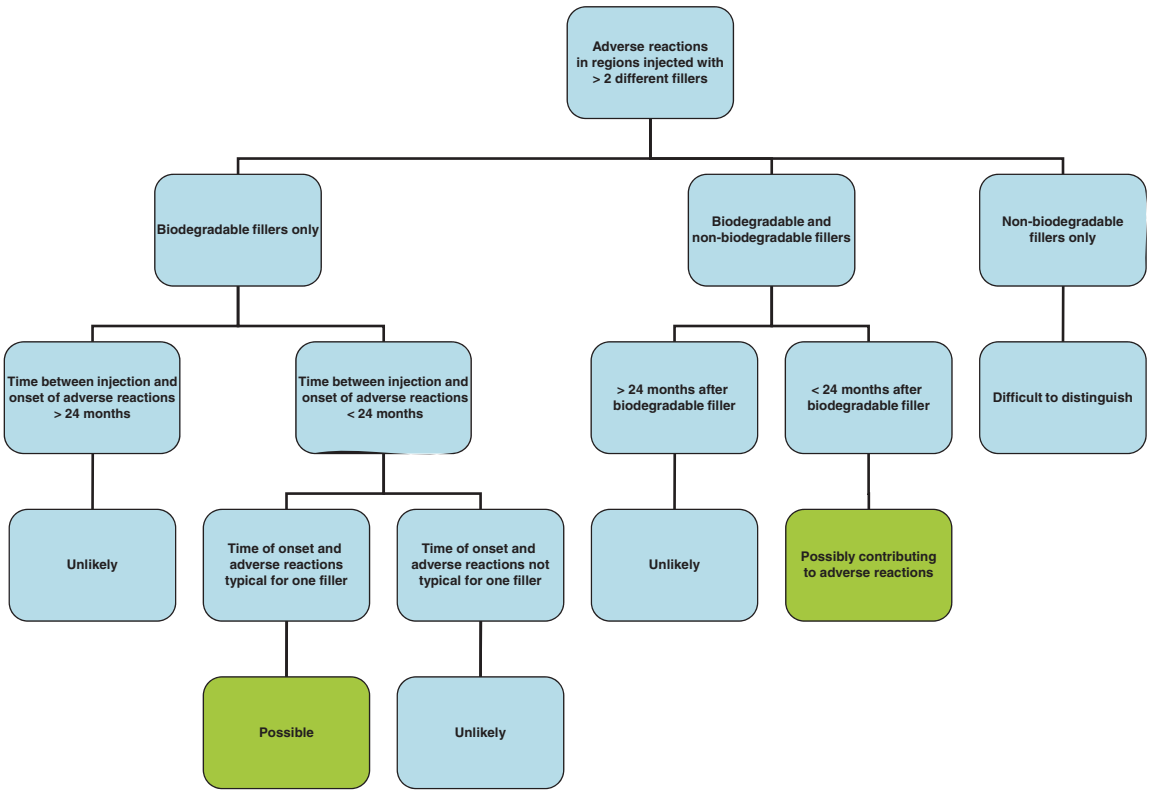


**Figure 2** An algorithm to help to identify the causative filler. As the number of different fillers is growing, the number of patients that will be injected with more than one filler into the same area will increase making the identification of the causative filler an important issue. The algorithm suggested follows several steps. In the first step, the adverse reactions should be investigated if they are very typical and distinct for one of the injected fillers (Table 8). IF NOT, the different fillers should be classified into: (i) biodegradable fillers such as HA, collagen or PLA only; (ii) the combination of biodegradable and non-biodegradable fillers; and (iii) non-biodegradable fillers only. If dealing with biodegradable fillers, one has to check the time between injection and onset of symptoms. For most biodegradable fillers, after a single injection a time line after 24 months can be drawn after the last injection. Beyond that line, a contributing effect of that filler is quite unlikely. If more than one filler is still left, again, the time of onset (Table 9) and the type of the adverse reactions (Table 8) might be helpful in identifying the responsible filler. IF dealing with a combination of biodegradable and non-degradable fillers in one region, the non-degradable filler is most likely to be the responsible agent. However, the temporary filler might be a contributing factor. Again, the time line of 24 months applies for the biodegradable fillers (see 'Methods'). If onset of symptoms is beyond 24 months, the biodegradable filler is unlikely to be a contributing factor. If less than 24 months, a contribution to whatever extent cannot be ruled out completely. In case, the non-biodegradable filler is injected after the biodegradable filler, the rule of time line applies. If the biodegradable filler is injected after the non-degradable filler, check: (i) if time of onset and adverse reactions are typical for the biodegradable filler; (ii) if the biodegradable filler triggered the reaction; and (iii) if the biodegradable filler is a contributing factor at all (apply rule of time line). If dealing with non-degradable fillers only, the distinction is difficult or even impossible. Based on the experience with our patients, the algorithm should help to identify in approximately 50% the causative agent. This is important (i) for regulatory purposes and (ii) for the sake of the patient who might wish a reinjection of one of the filler materials in another area.

which the adverse reactions occurred rather shortly after the injection of an additional filler, the real number might be even smaller (about 3.7% or six of 161 patients of the total study population).

Although we do not have evidence that combining different fillers in one area increases the risk of adverse reactions, it is clear that it is always more difficult to correlate adverse reactions to the causative filler if different fillers are combined (Fig. 2).

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