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Vascular and Non-Vascular Adverse Reactions to Face Filler: Systematic Review of Case Reports

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Abstract Facial dermal fillers are among the most commonly performed minimally invasive cosmetic procedures, increasingly popular for their ability to promote skin rejuvenation. However, as the number of procedures rises, so does the potential for adverse reactions to these biomaterials. This study aims to systematically identify and analyze case reports and series of both vascular and non-vascular adverse reactions caused by facial fillers and biostimulators, as well as their treatments. By examining these cases, the research seeks to uncover potential factors that may trigger or amplify certain reactions and to evaluate which treatments are more or less successful in resolving these complications. Using the Cochrane methodology and following PRISMA 2020 guidelines, this systematic review included 378 cases of adverse reactions. Data selection and extraction were performed using the CARE tool. The findings showed a predominance of vascular reactions, particularly those associated with hyaluronic acid, while autologous fat presented the greatest risk for severe outcomes such as visual loss. Non-vascular reactions, especially late-onset cases, were more frequent with non-biodegradable substances. These results highlight the importance of healthcare professionals being well-informed about the potential for moderate to serious adverse reactions, enabling early recognition and management. A thorough understanding of these risks is essential for enhancing prevention strategies and improving treatment outcomes.

Keywords Facial injections, Fillers, Biostimulators, Adverse reaction

1. Introduction

Facial dermal fillers are a cosmetic procedure that is becoming increasingly popular because it promotes skin rejuvenation and an improved appearance with lower costs and shorter recovery times when compared to plastic surgery. [1] Depending on their origin, they are classified as autologous [2], homologous [3], heterologous [4] and synthetic. [5]

Synthetic fillers (or biomaterials) are registered with regulatory bodies not as drugs, but as medical devices. According to the World Health Organization (WHO), adverse events of medical devices are unexpected problems that can occur during or after their use and may or may not result in permanent disability, injury or death of the patient or user. [6]

Despite advances in the chemical and biological characteristics of synthetic fillers, transient and/or persistent adverse reactions can occur, even when procedures are carried out by experienced doctors, and can have a substantial impact on patients' lives. [7]

Thus, synthetic fillers can contribute to adverse events due to their complex nature and unique functions or due to errors in use and/or failure to follow care guidelines (intentional or unintentional improper implantation) or inherent patient responses to the biomaterial and biomaterial to the patient (hypersensitivity reactions). [7,8]

Most adverse reactions are mild, transient, reversible and not specific to a particular filler. However, serious adverse reactions can occur, leaving patients with long-term or permanent functional and aesthetic deficits. It is notable that there has been an increase in the number and spectrum of adverse events due to the increase in the number of new indications and new treatments. [6] However, the incidence of adverse events has not yet been properly mapped in the literature, which would be an important step towards developing strategies to prevent such adverse reactions.

2. Methods

This was a systematic review of case reports and series carried out in accordance with the relevant chapters of the Cochrane Handbook for Systematic Reviews of Interventions [9] and developed in the Translational Medicine Postgraduate Program of the Department of Medicine of the Federal University of São Paulo.

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The protocol for this systematic review was registered in the PROSPERO review database (CRD42020147555) and the review is being reported in accordance with the PRISMA 2020 guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Harms). [10]

2.1. Study Inclusion Criteria

The population of interest includes adult individuals of any sex or gender identity, focusing on vascular and non-vascular adverse reactions associated with aesthetic interventions like dermal fillers in the face, performed by any health professional and observed at any time after the procedure. This encompasses reports related to any substance injected into the face, including but not limited to hyaluronic acid (HA), poly-L-lactic acid (PLLA), polyprolactone, calcium hydroxyapatite (CaHa), polymethylmethacrylate (PMMA), polyacrylamide (PCL), and silicone. The study design consists of case reports or series.

2.2. Outcomes

Outcomes include the general frequency of adverse events observed, as well as the frequency of these events categorized by substance and injection site. Additionally, the review describes the types of adverse events and classifies reported cases based on their evolution, considering cases resolved when the patient's symptoms were satisfactorily treated. The time interval between the procedure and the onset of symptoms is critical for guiding diagnosis and therapy.

However, there is no consensus on the classification by time of onset of adverse reactions to fillers and/or biostimulants. Based on the literature, for the purposes of this review the classification by time of onset was established in three intervals: immediate, early non-immediate and late. This choice was made due to the didactic function of this review, allowing practical reasoning and early conduct by the doctor, and avoiding permanent damage. Thus, each interval was considered as: (i) immediate: up to 24 hours; (ii) early non-immediate: from 24 hours to two weeks; and (iii) late: more than two weeks.

2.3. Search and Selection of Studies

The following electronic databases were searched: name in full (MEDLINE), Embase and the Cochrane Library on May 28, 2021. An additional search was carried out in the Opengrey gray literature database and annals of congresses in the field. The data selection and extraction process was carried out independently in duplicate to identify potentially relevant studies for inclusion, using the Rayyan platform.

2.4. Data Extraction and Analysis

The data extracted and identified as homogeneous was aggregated and evaluated using statistical analysis. A descriptive analysis of the results was also carried out. The results of each study are presented individually and in narrative form. Adverse events were counted and related to each of the respective fillers. A standardized data extraction form was used and the quality of the publication of the reports and case series included was assessed using the CARE (Case Report Guidelines) checklist. [11]

Electronic and manual searches retrieved 7,577 references. After the study selection process, 256 were included, presenting a total of 378 cases of adverse events associated with facial injection of fillers or biostimulants. Figure 1 shows the study selection flowchart.

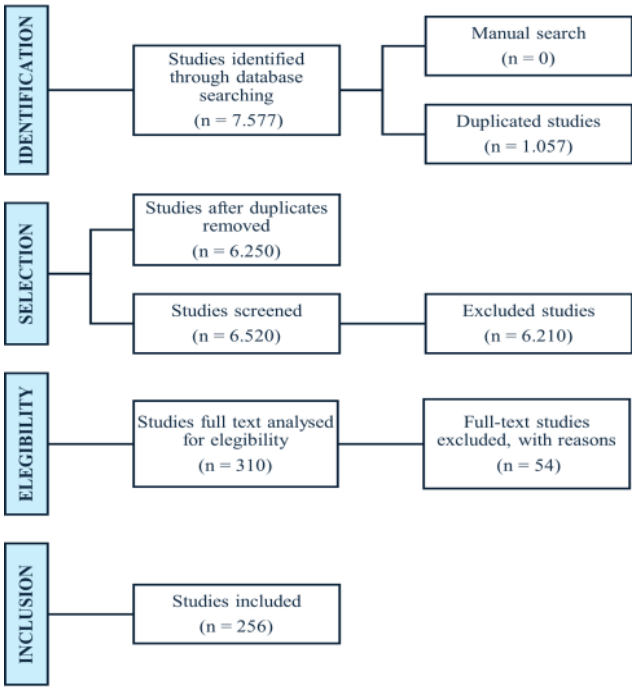

Figure 1. Study selection and inclusion flowchart

3. Results

From the total sample of 378 cases analyzed, the following results were found: (i) 96 cases of vascular adverse reactions (25%); (ii) 270 cases of non-vascular reactions (71%); and (iii) 12 cases in which it was not possible to identify the type of reaction (3%), which were excluded for the purposes of this analysis.

Nine reports of abscess formation after filling were found, six of which being late and three early non-immediate cases. All early non-immediate events were associated with the use of HA. Different triggering factors were also identified.

3.1. Vascular Reactions

Ninety-six cases of vascular adverse reactions, including arterial and venous, were identified without distinction, as the differentiation is not mentioned in the majority of the case reports.

The main substances causing vascular reactions were HA (67% of cases), CaHA (13%), autologous fat (8%), and PMMA (6.25%). Other substances, such as PLLA, silicone, and PMMA with bovine collagen, were reported in only one patient each.

The main symptoms observed in cases of vascular adverse

reactions were pain and changes in skin color. All identified symptoms are presented in Table 1 individually, according to the citations in the articles. Sets of signs and symptoms, such as Nicolau Syndrome, were not included as isolated symptoms.

Table 1. Number of cases according to symptoms presented

Symptoms	Number of cases
Pain	20
Not informed	18
Discoloration and pain	11
Pain and necrosis	8
Pain and others	8
Symptoms	**Number of cases**
Discoloration	7
Pain and swelling	4
Others	4
Discoloration and others	4
Necrosis	3
Pain and erythema	2
Hematoma	1
Hematoma and inflammation	1
Necrosis and discoloration	1
Edema and erythema	1
Ulceration	1
Erythema	1
Erythema and others	1
Total	**96**

The most common site of vascular reactions was the nasal dorsum (26% of cases), followed by the nasolabial fold (19%), glabella (17%), forehead (9.17%), cheek (7.29%), and lips and chin, which were affected in 3.12% of patients each. The temporal area was affected in 2% of patients, while the mentolabial and zygomatic areas were affected in 1% of patients each. Approximately 8% of patients were affected in others, however this information was not clear in the publications.

Regarding the timing of symptom onset, most (75%) of the vascular reactions occurred immediately, with 14% appearing early but not immediately, and in 10% of the cases, this information was not reported. There were no reports of vascular reactions with delayed symptom onset.

Out of the 83 cases in which the development of the vascular reaction was reported, 55% included a description of case resolution, 11% described partial improvement, and 34% did not provide a description of case resolution. Of the 66 cases with immediate onset, 25 (38%) did not report a description of resolution. All cases of early non-immediate reactions reported and described their resolution (10 cases).

Regarding the frequency at which vascular reactions leave sequelae, it was observed that 35% (34) of the cases evolved without sequelae, 47% (45) left permanent sequelae, and in 18% (17) the authors did not report this outcome.

Considering the 45 cases in which permanent sequelae were reported, in 29 of them, the patient became blind (in one or both eyes). In seven cases, partial vision loss was reported, and in other seven cases, scarring was the only identified sequela. The analysis of facial sites in relation to the likelihood of permanent sequelae related to vision loss or scarring is shown in Table 2.

Vascular reactions on the nasal dorsum (25) accounted for 26% of the total cases with vascular sequelae, representing 36% of the cases of blindness and partial vision loss. The cases involving fillers in the glabella totalled 16 cases, but they were responsible for 33% of the cases of blindness or partial vision loss. In the glabella, 75% (12 out of 16) of the cases resulted in blindness (either total or partial), while in the nasal dorsum region, this proportion was 52% (13 out of 25).

Table 2. Relation between the site of application of the filler and the sequelae developed

Local	Blindness (1 or 2 eyes)	Scar	Other	Partial vision loss	Not informed	Total
Nasal dorsum	10	2	1	3	9	25
Nasolabial	3	1	-	-	17	21
Glabella	10	2	-	2	2	16
Front	4	1	-	1	3	9
Cheek	-	-	-	-	7	7
Others	1	-	-	1	2	4
Not informed	1	-	-	-	3	4
Lips	-	-	-	-	3	3
Mento	-	-	-	-	3	3
Temporal	-	-	-	-	2	2
Mentolabial	-	1	-	-	-	1
Zygomatic	-	-	1	-	-	1
Total	**29**	**7**	**2**	**7**	**51**	**96**

Regarding the diagnostic method for vascular reactions, of the 24 cases wherein this information is described, in 21 cases, the method used was imaging diagnosis (including all imaging examination methods mentioned in these reports). In only 2 cases a bacterial culture was requested, and in 1 case, a histopathological examination was performed.

The treatments used to resolve the adverse events were not reported in 24 cases (25%) out of a total of 96 cases of vascular reactions. In 72 cases (75%) where the treatment applied was described, hyaluronidase was used in 39 cases (40%). Most cases were treated with a combination of medications and/or procedures. Other commonly used treatments included antibiotics (22 cases) and corticosteroids (20 cases), regardless of the administration route.

Considering only the 39 cases treated with hyaluronidase, 10 cases (25%) reported sequelae, with seven experiencing partial or total vision loss. In the 33 cases where hyaluronidase was not included in the treatment, 19 cases (58%) had sequelae reported, with 15 cases experiencing partial or total vision loss.

3.2. Non-Vascular Reactions

Table 3. Non-vascular adverse reactions

Symptoms	Number of cases
Edema	95
Nodule	92
Erythema	43
Granuloma	27
Pain	24
Hardening	20
Abscess	10
Migration	7
Others	40
Not Informed	31

This review identified 270 cases of non-vascular adverse reactions related to facial fillers.

The most commonly used substance described in cases of non-vascular adverse reactions was HA (107 patients), followed by silicone (67 patients), PMMA (34 patients), CaHA (20 patients), PLLA (14 patients), acrylic hydrogel in HA (9 patients), polyacramide (8 patients), polyprolactone (1 patient), and PLLA combined with HA (1 patient). In nine cases, it was unclear which substance was used.

Regarding the symptoms, as shown in Table 3, edema (95 cases) and nodules (92 cases) were the most commonly reported, followed by erythema (43 cases) and granuloma (27 cases). It was noted that the total number of cases in Table 3 exceeds the actual number of cases, as this adverse reaction can cause more than one symptom or clinical sign.

Of the 95 cases that had edema as one of the symptoms, HA was used in 54 patients and silicone in 23. Table 4 presents the time of onset edema and the filler used. Table 5 shows the sites where the adverse event "edema" occurred most frequently.

Notably, the substance with the highest number of nodule occurrences was silicone (27), followed by HA (20), as shown in Table 6. It is also observed that there were no cases of immediate onset nodules.

The facial areas with the highest number of non-vascular adverse reactions cases were the lips (53), cheeks (43), nasolabial fold (40), eyelid (20), glabella (15), nasal dorsum (14), and forehead (7). The right midface, chin, and zygomatic area were affected in five patients each, the temporal area in four, perioral in three, malar and labial commissure in two each and the mentolabial area in just one patient. The area where the non-vascular adverse event occurred was not reported in 51 cases.

Regarding the onset time of symptoms for non-vascular adverse reactions, it was noted that immediate reactions are very rare, with only 2 cases reported. In about 10% of cases (27 patients), the reaction manifested as early non-immediate, while in the vast majority of cases (212, or 78%), the manifestation was delayed.

Regarding the resolution of non-vascular reaction cases (270), in 129 cases (48%), the authors reported whether or not the reaction was resolved. Among these, only 2 cases did not respond to treatment, 3 cases experienced recurrence, 10 cases showed partial improvement, and 114 were reported as resolved.

Table 4. Relation between filler and edema onset time

Substance	Imme- diate	Early non-immediate	Late	Not informed	Total
Hyaluronic Acid	2	11	38	3	54
Silicone	-	-	21	2	23
PMMA	-	-	7	-	7
Polyacrylamide	-	-	4	-	4
CaHa	-	2	-	-	2
PLLA	-	-	2	-	2
Acrylic Hydrogel in HA	-	-	1	-	1
Olher	-	-	2	-	2
Total	**2**	**13**	**75**	**5**	**95**

Table 5. Places where edema appeared most frequently

Face location	Number of cases
Lips	23
Cheek	17
Others	9
Eyelid	9
Nasolabial	8
Not informed	7
Nasal dorsum	5
Middle third/Face D	3
Glabella	3
Mento	3
Front	2
Malar	2
Mentolabial	1
Zygomatic	1
Lip commissure	1
Temporal	1
Total	**95**

Table 6. Relation between filler used and time to appearance of nodule

Substance	Not informed	Early non-immediate	Late	Total
Silicone	4	-	23	27
Hyaluronic acid	4	3	13	20
PLLA	-	2	8	10
PMMA in bovine collagen	-	-	17	17
CaHa	4	1	3	8
Other	-	-	5	5
Acrylic hydrogel in AH	1	-	3	4
Polyacrylamide	-	-	1	1
Total	**13**	**6**	**73**	**92**

No sequelae were reported in 171 cases, so for these patients, it is impossible to determine whether there were truly no sequelae or if they went unreported. Among the remaining 99 cases where sequelae were documented, only 10 cases (10%) resulted in permanent sequelae, while the vast majority (89 cases, or 90%) did not lead to any permanent effects.

The permanent sequelae observed in the ten cases were scars. In one case, the scar was associated with weakness of the frontal muscles, and in two other cases, with nerve injury. The first case was due to permanent dermal filler, specifically polyacrylamide. After the patient underwent more than forty surgeries to attempt to remove the material, in addition to the scars, there was also a reduction in the contraction strength of the left frontal muscle due to damage to the temporal branch of the left facial nerve and altered sensation in the left cheek due to damage to the maxillary branch (left infraorbital nerve) of the trigeminal nerve. [12]

Regarding the locations of the procedures with the most reported sequelae, no specific region showed a significant prevalence. The mid-third of the face and the nasolabial fold had the highest number of cases, with 3 and 2 cases, respectively. All other locations had only one occurrence each.

Of the 101 cases in which a diagnostic method was mentioned, histopathological examination was the most common diagnostic approach, used in about 70 cases (approximately 70%). Imaging studies (regardless of the technology used) were employed in 19 cases, while bacterial cultures were utilized in 12 cases. In 169 cases (approximately 63% of the total non-vascular reaction cases), the diagnostic method was not reported.

Apparently, the majority of non-vascular reactions manifest later (212 cases). Regarding the type of filler substance, there was a notable predominance of non-biodegradable substances (107 cases) compared to biodegradable ones (97 cases). Among non-biodegradable fillers, silicone was by far the most common substance (60 cases). For biodegradable fillers, HA was the most frequently used (76 cases). Table 7 presents the collected data on late reactions according to the type of filler used.

Table 7. Late onset according to filler used

Substance	Number of cases
Biodegradable	**97**
Hyaluronic Acid	76
PLLA	10
AcHa	9
Polyprolactone	1
PLLA and HA	1
Non-Biodegradable	**107**
Silicone	60
PMMA in Bovine Collagen	19
PMMA	12
Acrylic Hydrogel in HA	8
Polyacrylamide	8
Not Informed	**8**
Total	**95**

According to the timing of the reaction's onset, only HA, CaHA, and PLLA had a significant number of cases reporting early non-immediate reactions, accounting for approximately 17%, 15%, and 21% of cases, respectively, as shown in Table 8.

Specifically regarding non-vascular reactions caused by HA (107 cases), the most commonly reported location was the nasolabial fold, with 24 cases, followed by the cheeks with 16 cases, and the lips with 15 cases. For silicone (67 cases), the most frequent locations of reactions were the cheeks (14 cases), lips (13 cases), and nasal dorsum (9 cases).

Almost all reactions with non-biodegradable fillers (99%) were late-onset reactions, while 79% of reactions caused by biodegradable fillers were also late-onset.

Of the 270 cases of non-vascular reactions, 70 did not specify the treatment used. Similar to vascular reactions, the treatments described for non-vascular reactions were mostly a combination of medications and/or procedures. Among the 200 cases where treatment was reported, corticosteroids were the most commonly used (89 cases), followed by surgical excision (55), antibiotics (46), and hyaluronidase (31).

Most publications do not mention the presence of triggering or exacerbating factors for non-vascular adverse reactions. The triggering factors described in the reports included flu-like syndrome as the most common, with 17 cases, followed by COVID-19 (4 cases). Other factors mentioned were: Hepatitis C vaccine, dental issues such as cavities and abscesses, gastrointestinal disorders, microneedling, and infection by Streptococcus anginosus.

4. Discussion

The objective of this review was to identify relationships between factors that could cause or exacerbate specific adverse reactions and to identify practices or treatments that had a higher success rate in resolving cases.

Only 52 publications (20.7%) included an introduction with a case summary and scientific basis. Of these, 40 were classified as "partially complete" by the CARE tool, as they provided only a brief case summary without the necessary support. Information regarding interventions performed, adopted protocols, and potential changes was found in only 39 studies, while 80 did not mention any treatment. Concerning patient follow-up and the summary of disease progression, 86 publications provided partial information, and 71 did not present any information.

There was also difficulty in identifying complete descriptions of the facial region with adverse reactions, especially in the mid-third. Some authors described the area as the mid-third, while others referred to it as the cheek, malar region, or zygomatic area, complicating analysis and presenting challenges in data description. Regarding the treatment of adverse reactions, most reports involved three or more medications and/or procedures, limiting the ability to identify which was most commonly used.

Table 8. Relation between filler used and time to appearance of nodule

Substance	Not informed	Imme-diate	Early non-immediate	Late	Total
Hyaluronic acid	11	2	18	76	107
Silicone	6	-	1	60	67
PMMA in Bovine Collagen	2	-	1	31	34
CaHa	8	-	3	9	20
PLLA	1	-	3	10	14
Acrylic hydrogel in AH	1	-	-	8	9
Polyacrylamide	-	-	-	8	8
Other	-	-	1	7	8
Polyprolactone	-	-	-	1	1
Not informed	-	-	-	1	1
PLLA and AH	-	-	-	1	1
Total	**29**	**2**	**27**	**212**	**270**

This systematic review identified adverse events described and reported as moderate to severe, according to the WHO classification. [13] Moderate to severe adverse events are considered rare [14], but important due to their impact on both patients and physicians. [15,16] However, according to Haneke (2015), most adverse events are considered mild and easily managed, such as pain, erythema, transient edema, or bruising, which generally resolve within three to five days and are often not reported. [17]

A frequent difficulty observed in such cases is that when patients experience an adverse reaction, they often seek another doctor, different from the one who performed the initial procedure, making it challenging to identify the biomaterial and obtain a full case history.

The relevance of moderate to severe adverse events is highlighted by the number of publications and the need for a better understanding of this process [18], considering that facial dermal fillers (or biostimulation) are an aesthetic procedure performed on healthy patients seeking to improve their appearance.

It is important for physicians to discuss the potential benefits and risks of using fillers with patients before the procedure. An informed and consensual decision brings clarity and enables improvements in terms of technological development and clinical practice.

4.1. Vascular Adverse Reactions

The regions where vascular adverse reactions with partial or total vision loss occurred, as evidenced in this study, were not different from those reported by other authors [19,20], demonstrating that the nasal dorsum, glabella, forehead, and nasolabial fold are higher-risk areas of the face due to the vascularization involving anastomosis of branches of the external and internal carotid arteries.

Occlusion of the external and internal carotid branches by synthetic fillers or autologous fat can result in a series of symptoms, such as skin necrosis, blepharoptosis, strabismus, blurred vision, partial visual loss and blindness. Irreversible total visual loss in these regions of the face arises as a result of this anastomosis, allowing the central retinal artery to be compromised. [19,20]

Among the 21 reports of vascular adverse reactions that resulted in visual impairment diagnosed by imaging, fundoscopy or fluorescein angiography were the diagnostic methods used to detect visual loss. Additional tests, such as MR angiography or computed tomography, were used to investigate ischemia or intracranial changes. In only 1 of the 21 cases, color Doppler ultrasound was immediately performed at the procedure site.

Although various authors have highlighted the lower risk of visual complications associated with HA [21], the data from this review indicate that HA was responsible for the majority of case reports with visual complications. This review included case reports published over a period of more than 50 years, but due to the lack of information in the reports, it was not possible to compare the incidence of these complications with the total number of procedures performed. Despite the apparent risk, this serves as a warning to professionals regarding HA injections in facial regions, as there was a higher frequency of severe adverse reactions in the forehead, glabella, nasal dorsum, and nasolabial fold areas.

Furthermore, the data from this review reveal that not all vascular adverse reactions are immediate. Five cases of adverse reactions were recorded that occurred 72 hours or more after the dermal filler, evolving into skin necrosis: one case from PMMA [22], one from CaHa [23], and three from HA. [14,19,24]

None of these five reports showed typical signs of vascular occlusion immediately after the procedure. These cases show that there are not always typical immediate signs of vascular obstruction. Post-procedural discomfort alone may be a symptom of a vascular event and, therefore, should not be ignored. [21]

Vascular adverse reactions with immediate onset had a worse prognosis compared to early but non-immediate ones. While 28% of immediate vascular reactions remained unresolved, among early non-immediate reactions, the resolution rate was 100%.

Treatment with hyaluronidase resulted in a reduction of impairment in 74% of cases of vascular adverse reactions. Hyaluronidase has the ability to diffuse the product or any material, and it seems likely that the reduction of local edema may contribute to the improvement of blood flow and reflex vasospasm caused by vascular damage. [25]

The reports did not mention the recommended dose of hyaluronidase or the ideal timing for starting treatment.

Other treatments commonly used were antibiotics, corticosteroids, acetylsalicylic acid, hyperbaric oxygen therapy and peripheral vasodilators - nitroglycerin and heparin. Most of the treatments applied included three or more drugs and/or therapies, which makes it very difficult to identify which might actually have an effect. The small number of cases in which heparin was used as a treatment is noteworthy, since low molecular weight heparin is capable of improving the vascular endothelium and preventing the formation of microthrombi due to vascular damage. [26]

The scarcity of in-depth studies on treatments for vascular adverse reactions prevents the development of objective protocols to guide doctors in the search for more effective treatments, with the aim of minimizing complications.

4.2. Non-Vascular Adverse Reactions

The most important clinical presentation described in the adverse reactions in this review was edema. Most reports of edema were of the late-onset or early non-immediate type, as most immediate edemas are mild adverse events associated with the procedure and disappear within a few hours, thus not typically being the subject of study.

The substances that most frequently caused edema were HA and silicone. Only 2 cases of immediate-onset edema were reported, both related to type I hypersensitivity reactions.

Late-onset edema was commonly accompanied by erythema (22 cases) and nodules (20 cases). There were no cases of nodules associated with edema, and no other relevant clinical manifestations were found.

The second most common clinical presentation was nodules. Non-inflammatory nodules are usually seen immediately after the procedure and result from superficial technique or the injection of large volumes of filler. In this review, no reports of immediate-onset nodules were found.

Late-onset nodules, on the other hand, are generally inflammatory, have different etiologies, and are difficult to diagnose, potentially being symptoms and clinical signs of biofilm infection or a foreign body reaction [27]. In this review, the most often observed clinical manifestations associated with late-onset nodules were edema and pain, while in 31 cases, the nodule presented in isolation. Among the early non-immediate onset nodule cases, in the majority (4 out of 6), the nodule was the only symptom, while in one case, it was associated with an abscess and in another, with migration.

The biomaterial most commonly associated with late-onset nodules was silicone, followed by PMMA, accounting for more than half of the total late-onset nodule cases. It was observed that non-biodegradable biomaterials, especially silicone and PMMA, present a higher risk of causing late-onset nodules than biodegradable ones.

HA has a longevity of approximately six to 18 months [17]; however, this review identified the formation of late-onset nodules up to 12 years after its implantation.

The majority of non-vascular reactions, across all clinical manifestations, occurred late. When analyzing each substance in relation to the onset time of reactions, it was noted that only HA, CaHa, and PLLA had a significant number of early non-immediate reactions, with approximately 19%, 25%, and 21% of cases, respectively.

In the vast majority of cases, treatment for non-vascular reactions proved effective: 124 cases had complete resolution, and 14 cases showed partial improvement. Only 5 cases, all late-onset, were unsuccessful in treatment:

- Late-onset nodule and hardening (1 year) in the lips, caused by PMMA and treated with corticosteroids;
- Late-onset edema (16 years) in the lips, caused by silicone and treated with corticosteroids;
- Late-onset edema and abscess (6 years) in the malar region, caused by polyacrylamide and treated with incision, drainage, and lifting;
- Late-onset edema and nodule (1 year) in the lips and nasolabial region, caused by HA and treated with antibiotics; and
- Late-onset edema (3 years) in the cheek, caused by silicone and treated with corticosteroids and antibiotics.

Of these cases, only one was caused by a biodegradable substance (HA), and the rest were caused by PMMA, silicone, and polyacrylamide. The higher incidence of severe complications (unresolved after treatment) with non-biodegradable materials is supported by Haneke (2015) [15], who reports that, although no significant difference in the frequency of adverse reactions caused by biodegradable and non-biodegradable substances was noted, those reactions caused by permanent materials tend to be more severe.

Additionally, Groen and colleagues (2017) [28] stated that, in general, long-lasting (non-biodegradable) fillers tend to cause more severe and late-onset complications. This is confirmed by the data identified in this review, which reveal a much higher prevalence of late-onset reactions among those caused by non-biodegradable substances (99%), while among reactions caused by biodegradable substances, non-late-onset reactions accounted for 21% of the cases.

5. Conclusions

Among the vascular adverse reactions, HA was the most common material, followed by CaHa and autologous fat. Although some studies suggest that HA has a lower risk of causing visual complications, this review showed that HA was responsible for the majority of reported cases with these complications, pointing to the need for further studies for more precise conclusions.

In non-vascular reactions, late edema was the most frequent sign and symptom, caused mainly by HA and silicone. The second most common clinical manifestation was delayed onset nodules (DONS), with silicone and PMMA being the main causes. These two non-biodegradable biomaterials accounted for more than half of the cases of DONS, as well as presenting a higher risk of serious complications compared to biodegradable materials.

As for the treatment of adverse reactions, the lack of data and the absence of standardization prevented clear conclusions. However, hyaluronidase has been shown to be associated with a lower incidence of serious sequelae in vascular reactions. In non-vascular reactions, most cases evolved without sequelae.

Although few studies mention it, some triggering factors have included flu-like syndromes (such as Covid) and dental treatments. Of the 256 articles analyzed, only 30 provided sufficient information and 70 presented partial data. Although the lack of data or its partial presentation substantially affected the scientific quality of the data in this review, the number of cases reported was relevant to the descriptive analysis.

For a better understanding of adverse events to dermal fillers, it is essential that studies include a complete case history, including the occurrence of previous fillers, triggering factors, treatments and outcomes. Recognizing these adverse reactions makes it possible to establish appropriate treatment early on, enabling more effective action to be taken with the available treatments.

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