SEVEN
publicações acadêmicas

Adverse events associated with the vaccine and SARS-CoV 2 virus in patients with facial aesthetic procedures

https://doi.org/10.56238/sevened2023.004-020

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ABSTRACT
Objective: To identify adverse events associated with the vaccine and the Sars-Cov 2 virus in patients with facial aesthetic procedures (botulinum toxin type A and hyaluronic acid fillers) through a systematic literature review. Methodology: The Methodi Ordinatio methodology was used to select the portfolio of the most relevant articles in the area. The search was conducted in the PubMed database considering the period from 2019 to 2023. The final portfolio consisted of 33 articles. Results: The results show events that include filler site reactions, such as pain, edema, erythema, pruritus, bruising, infection, hypersensitivity, nodules, asymmetry, facial contour defects, skin discoloration, side effects, and tissue necrosis. Conclusion: The main contribution of this study was to share information on adverse events, considering the risks and implications arising from the vaccine and the Sars-Cov 2 virus along with facial aesthetic procedures, in order to guide injecting professionals on how to act in the market considering the pandemic.

Keywords: Covid-19, Filler, Vaccines, Botulinum toxin, Hyaluronic acid.

1 INTRODUCTION

It is observed that the use of tissue fillers is among the most popular non-surgical aesthetic procedures worldwide and is currently being used for both facial and non-facial areas. Aesthetic medicine has become more pronounced in recent years for many reasons, such as the constant search for youthfulness, the influence of artists, or even premature aging caused by stress, anxiety, and depression (Cassaniti et al., 2020).

There are different types of biostimulators and tissue fillers, such as hyaluronic acid (HA), calcium hydroxyapatite (CaHA), polymethylmethacrylate (PMMA), poly-L-lactic acid (PLLA), and collagen-based products. It is believed that an ideal dermal filler should be safe, non-allergenic, non-immunogenic, non-carcinogenic, non-migratory, cost-effective, and stable for the desired time in the target tissue. However, several adverse reactions associated with dermal fillers have been reported in scientific research (Guo et al., 2021).

Complementing facial aesthetic procedures, botulinum toxin type A is also among one of the alternatives for rejuvenation within aesthetic clinics. It acts through the action of relaxation of the muscles. The addition of botulinum toxin type A (BTX)-induced facial muscle paralysis to target the muscles of the upper (visible) half of the face, especially the corrugator and procerus muscles, may act

as a therapeutic solution by its suppression of glabellar lines. The treatment of the glabella complex allows to inhibit the negative emotions of the treated individual (Nestor et al., 2020).

Since the emergence of the coronavirus pandemic in 2019, caused by the Sars-Cov 2 virus, several vaccines have been marketed to people around the world. And, several adverse events associated with the different COVID-19 vaccines have been reported and, notably, cases of adverse events in patients with tissue filler after vaccination (Beamish et al., 2022).

COVID-19 emerged in the midst of the high number of aesthetic procedures, significantly affecting the immune system, disfavoring the performance of aesthetic procedures and impacting on several factors, including the decrease in the durability of botulinum toxin and causing inflammatory processes in patients with facial fillers, caused by the side effects of vaccines and also during infection with the SARS-CoV-2 virus (Beamish et al., 2022).

COVID-19 can present several signs and symptoms, adverse events, which are still being studied. However, many cutaneous, respiratory, and muscular manifestations, among others, have already been analyzed and reported, for example, patients with facial fillers may present an ETIP-type reaction (delayed intermittent edema), triggered by SARS-CoV-2 infection or vaccines (Zhang, 2020).

These reactions are mediated by T lymphocytes and can be triggered by influenza-like illnesses, including SARS-CoV-2 infection. The authors Cavallieri et al. (2017) contribute by stating that vaccination can also induce a response leading to hypersensitivity of fillers in the body, also causing PITT.

The COVID-19 pandemic then led to research on the relationship between facial aesthetic procedures (botulinum toxin type A and hyaluronic acid fillers) as well as the development of inflammatory reactions in patients infected with SARS-CoV-2 or after vaccination (Naouri et al., 2023). There are already studies that report that SARS-CoV-2 binds to and blocks angiotensin-converting enzyme 2 (ACE2) via the S (spike) protein to access the cell, which may be a potential mechanism for the development of adverse events in those vaccinated or infected with COVID-19 in patients who have received HA filler injections or botulinum toxin type A, for the purpose of facial aesthetic procedures (Li et al., 2023).

In human cells, ACE2 is expressed in keratinocytes, fibroblasts, dermal vascular endothelium, and adipocytes of the subcutaneous tissue, where HA is deposited. The accumulation of angiotensin II triggers a pro-inflammatory reaction and increases the activity of CD44 glycoprotein, which has an affinity for pro-inflammatory properties and are present in the infiltration that develops around the deposits injected into the skin in the subcutaneous tissue (Azzouz et al., 2023).

It is important to emphasize that there is a need to discuss clinical considerations for aesthetic procedures, even if all safety protocols against COVID-19 are respected based on the competent health agencies and scientific evidence, they still bring uncertainties about the sensitivity of the tests and the

incubation time of the virus, as well as the systemic and immunological mechanism of action of the infection in asymptomatic patients (Cassaniti et al., 2020; Zhang et al., 2020).

Therefore, this study is justified by the lack in the research area, considering the limited number of studies that investigate adverse events related to the influence of the vaccine on minimally invasible aesthetic procedures performed in offices, such as the application of botulinum toxin type A and facial fillers with absorbable hyaluronic acid. To this end, a systematic bibliographic search was used in the PubMed database, considering the works published in the period between 2019-2023, to find out which are the most relevant publications on the subject.

Thus, the objective of this study is to evaluate the adverse events of the vaccine and the Sars-Cov-2 virus in patients with facial aesthetic procedures (botulinum toxin type A and hyaluronic acid fillers)through a systematic review of the literature.

The study may provide a comprehensive overview of reported cases of reactions to fillers and application of botulinum toxin type A after COVID-19 vaccination, as well as in patients who have had the disease, in order to address various considerations that should be taken into practice and also bring better guidance to injecting professionals and the general population.

2 METHODOLOGY

In order to identify adverse events related to the vaccine and the Sars-Cov-2 virus in patients with facial aesthetic procedures (botulinum toxin type A and hyaluronic acid fillers)through a systematic literature review, a survey of materials published in the PubMed database from 2019 to 2023 was carried out.

To achieve the proposed objective, we opted for the methodology for systematic literature review proposed by Pagani, Resende and Kovaleski (2017), the Methodi *Ordinatio.* Relevant articles published with significant impact factors used the methodology to conduct systematic reviews, validating the method developed by the authors, such as Cunha et al. (2019), Gao et al. (2019), Muller et al. (2019), Pinto et al. (2019), Souza et al. (2019), Corsi et al. (2019) and Salvador et al. (2019).

The methodology provides a sequence of nine steps, which were used to follow the methodological path:

Table 1: New passos to Methodi Ordinatio

STEPS	DEVELOPMENT
Step 1: Establish search intent;	We sought to delimit the existing research gap considering the Theme – adverse events associated with the vaccine and the Sars-Cov-2 virus in patients with facial aesthetic procedures.
Step 2: Preliminary exploratory search with the keywords in the databases;	The preliminary research consisted of inserting the following keyword combinations: Covid-19 **AND** the toxin* Covid-19 **AND** "hyaluronic acid *" vaccines **AND** "botulinum toxin *"

	vaccines" **AND** "hyaluronic acid *"
Step 3: Definition and combinations of keywords and databases;	After the preliminary exploratory research, the following combinations were defined: Covid-19 **AND** the toxin* Covid-19 **AND** "hyaluronic acid *" vaccines **AND** "botulinum toxin *" vaccines" **AND** "hyaluronic acid *" To define the databases, we chose the most widely used database in the health area: PubMed.
Step 4: Definitive search in the databases;	As shown in Table 2.
Step 5: Filtration procedures;	As foreseen in the methodology, the filters were as follows: Duplicates; Conference papers, books, and book chapters; InOrdinatio Negatives and By Title.
Step 6: Identification of the impact factor, year and number of citations;	For this step, the Journal Citation Reports (JCR) metric was *considered as the first option for impact factor,* and in case the journal did not present JCR, the Cite Score metric was chosen. To obtain the citation number of each article, a Google Scholar search was performed.
Step 7: Ordering of the articles by means of *InOrdinatio*;	To order the articles, the equation InOrdinatio = (Fi / 1000) + α* [10 - (APe – APu)] + (∑ Ci) was applied, in which the established α value was 10, prioritizing the most recent articles. At this stage, it was possible to locate 1 article with negative InOrdinatio, which was excluded from the research as foreseen in the methodology used.
Step 8: Localization of the articles in full format;	The articles were located using the selected databases, the Capes portal and Google Scholar.
Step 9: Systematic reading and analysis of the articles.	The readings and analyses were performed with a focus on the established theme, following the exclusion criteria in Table 3. Excel was used to organize the information and systematically analyze the articles.

Fonte: Pagani; Resende; Kovaleski (2017).

After defining the databases for the research, the searches for documents were carried out using the descriptors established in step 3. As a result, the number of documents from each database was obtained, as shown in Table 2.

Table 2: Number of documents from the database used in the search

Key words and combinations **Period** (2019 to 2023)					
Databases	((Covid-19 OR (Sars-Cov 2)) AND (botulinum toxin*)	((Covid-19 OR (Sars-Cov 2)) AND (botulinum toxin*) AND **("**hyaluronic acid *"**)**	((Covid-19 OR (Sars-Cov 2)) AND (Vaccines) AND **("**hyaluronic acid *"**)** "botulinum toxin *"	((Covid-19 OR (Sars-Cov 2)) And (Vaccines) AND **("**botulinum toxin *"**)**	**Total**
PubMed	Search results: **67** results Search fields: Article title, abstract, keywords.	Search results: **78** results Search fields: Article title, abstract, keywords.	Search results: **29** results Search fields: Article title, abstract, keywords.	Search results: **6** results Search fields: Article title,	**180**

	Document type: Newspapers	Document type: Newspapers	Document type: Newspapers	abstract, keywords. Document type: Newspapers	
Total	**67**	**78**	**29**	**6**	**180**

Source: Prepared by the author (2023).

After searching the databases, the filtering procedures were performed, as described in step 5. Exclusion by title and abstract followed the criteria described in Table 3.

Table 3: Filtering (exclusion) procedures performed in the survey.

Exclusion Criteria	Total
Duplicate	18
Books, Book Chapters & Conferences	79
Title and abstract (papers that are not directly related to the research theme)	74
Total	**33**

Source: Prepared by the author (2023).

Inclusion and exclusion criteria comprised all original studies that presented cases that manifested adverse reactions of fillers or botulinum toxin type A, after receiving COVID-19 vaccines or studies of patients who had the disease and had associated adverse events. Only studies that were directly related to the objectives of this research were included. The exclusion criteria considered duplicate articles, books, book chapters and conferences, and materials that did not present a case related to the research theme. Exclusion criteria were also considered to be studies that reported only reactions and adverse events in isolation, with an approach to other types of vaccines or only with the use of fillers or botulinum toxin type A, not associated with the object of study of this research.

Based on these exclusion criteria, a total of 33 articles were obtained, which gave rise to the final portfolio for the construction of the systematic literature review. This selection of articles allowed us to carry out comparative analyses between them, in order to achieve the objective proposed in this study.

2.1 REVIEW AND DATA COLLECTION PROTOCOL

Research questions: What are the adverse events associated with the vaccine and the Sars-Cov-2 virus in patients with facial aesthetic procedures (botulinum toxin type A and hyaluronic acid fillers)? In this way, the systematic bibliographic analysis provides an overview of the research that can contribute to the proposed theme. To this end, the following questions were also asked:

i. How many works are published per year? This question aims to demonstrate when this type of research was of interest in the academic community.

ii. What are the main media in which these studies were published, as well as which works were most referenced by the body of literature evaluated? These questions can determine which *journals* and authors show greater interest in the topic addressed, enabling the creation and solidification of a theoretical basis for the study, in order to list the most significant authors in the field.

iii. Which articles have a central theme similar to the one addressed in this systematic review? The identification of studies that are similar to the study discussed here can foster ideas about the means of conducting the research, as well as allow interaction between related researchers.

Thus, the theme addressed in this article may offer some answers to the challenge of understanding whether there are adverse events/influence of the vaccine and the Sars-Cov-2 virus in patients with facial aesthetic procedures (botulinum toxin type A and hyaluronic acid fillers).

3 RESULTS AND DISCUSSION

The results and discussions section is divided into *literature exploration* and adverse events of the vaccine and the Sars-Cov 2 virus in patients with facial aesthetic procedures (botulinum toxin type A and hyaluronic acid fillers).

3.1 LITERATURE EXPLORATION

According to the inclusion and exclusion criteria of the materials from the systematic literature review and taking into account the objective of the research, 33 scientific articles that presented similarity with the theme and central objective of this research were analyzed. All of them deal with the subject and base their analyses on the perspective of presenting adverse events, reactions to the vaccine and the Sars-Cov-2 virus in patients with facial aesthetic procedures (botulinum toxin type A and hyaluronic acid fillers), to carry out an evaluation, a clinical study, an analysis of results or a literature review. Table 4 summarizes the results of the systematic review, grouping the studies that were directly related to the objectives addressed in this research. The table made it possible to answer the research question that guided the study: what are the adverse events associated with the vaccine and the Sars-Cov-2 virus in patients with facial aesthetic procedures (botulinum toxin type A and hyaluronic acid fillers)?

Table 4: Summary of published articles on adverse events in patients with facial aesthetic procedures (botulinum toxin type A and hyaluronic acid fillers)

Study	Historical	Symptoms	Research contributions
Aryanian et al . (2022)	Reports of some skin reactions in patients undergoing various cosmetic procedures, including butolinum toxin filling or injection	Oedema, erythema and tenderness in the injected areas and lip angioedema	Most vaccine-induced reactions in previously cosmetically manipulated areas are delayed reactions, usually occurring within 10 days of vaccination.
Azzouz et al. (2023)	Case of a 43-year-old woman with a type 4 delayed hypersensitivity reaction to hyaluronic acid cosmetic filler triggered by COVID-19 mRNA vaccination	Late-onset nodule formation after filler injection, inflammatory reaction, and delayed hypersensitivity reaction	Delayed hypersensitivity type IV/delayed inflammatory reactions usually manifest as induration, edema, nodules, and granuloma at the injection site. The mechanism of the delayed/type IV inflammatory reaction has yet to be elucidated, but one theory is that the LMW-HA and HA oligosaccharides may haptenize the autoprotein and make them immunogenic
Batifol et al. (2022)	Comparative studies, over three months, of the impact of SARS-CoV2 in patients injected with botulinum toxin for functional purposes	Protective effect	Botulinum neurotoxin type A (BoNT/A) is known to block acetylcholine (ACh) as well as many other neuroreceptors and neuromodulators. The recent mention of a potential protective effect of nicotine on COVID 19, through the blocking of ACh.
Beamish et al. (2022)	Association of Delayed Inflammatory Reactions to Dermal Fillers in Response to mRNA COVID-19 Vaccination	Induration, edema, painful nodules, and discoloration at dermal filler injection sites	The symptoms appeared suddenly 6 weeks after receiving the second dose of the Pfizer vaccine. This may represent a potential delayed inflammatory reaction to vaccination, but alternative immunogenic triggers cannot be ruled out
Bono et al. (2021)	Best practice recommendations on how to organize the work of a clinic	Protective effect	Effective injection method that can prevent SARS-CoV-2 virus infection. In order to

	performing botulinum toxin treatments.		minimize the risk of transmission of SARS-CoV-2 during botulinum toxin treatment in the COVID-19 era
Calvisi (2022)	Three cases of dermal filler reactions after mRNA vaccination against SARS-CoV-2; All patients received the filler months or even years before the vaccine	Delayed inflammatory reaction after vaccination	Adverse Events in Patients With Dermal Fillers After Receiving SARS-CoV-2 mRNA Vaccine. Cases of an inflammatory reaction triggered by the COVID-19 Spike protein to HA dermal filler. Prevention of delayed reactions or type IV hypersensitivity should include a thorough patient history and education and a waiting window between vaccine and dermal filler
Cavallieri et al.	Reports of 33 cases of local edema associated with the presence of hyaluronic acid. Episodes of edema have been reported as recurrent, either in the previously affected area or at another injection site	Late complication after facial filling with hyaluronic acid Edema local	Use of the term intermittent and persistent late edema to group late adverse reactions to hyaluronic acid, which translate into late local edema, of an intermittent nature, triggered by specific triggers and which persists as long as there is the presence of hyaluronic acid in the tissue.
Dresler and Saberi (2020)	Research through a standardized questionnaire on the therapeutic forms of butolinum toxin	Protective effect	Therapeutic forms of botulinum toxin type A applications can be considered as a potent treatment against Covid-19
Goodman et al. (2020)	Study of the application of botulinum toxin type A during the pandemic in patients who need follow-up in neurological conditions	Protective effect	Therapeutic forms of botulinum toxin type A applications in patients with neurological conditions

Guo et al. (2021)	2 subacute cases of allergic reactions to BTA in facial cosmesis after Covid-19 vaccination	Hypersensitivity reaction	Infection and vaccination by Corona virus disease 2019 (Covid-19), can induce specific and non-specific activation of the immune system, induce delayed inflammatory reactions to previously injected hyaluronic acid fillers.
Hamed et al. (2022)	Study of immediate or early-onset side effects (occurring up to several days after treatment)	Injection site reactions such as pain, oedema, erythema, pruritus, bruising, infection, hypersensitivity, nodules, asymmetry, facial contour defects, skin discolouration, adverse reactions and tissue necrosis	Reduced Efficacy and Safety of Botulinum Toxin Type A (BTA) Injections After COVID-19 Vaccination
Kalantari et al. (2022)	Systematic search conducted in the Scopus, Web of Science, and PubMed/MEDLINE databases for articles published from the beginning of the pandemic until October 21, 2021, in order to determine the characteristics of patients with filler reaction after vaccination against COVID-19 and to address various considerations that should be made in practice	Injection site reactions such as oedema, pain, erythema, pruritus and ecchymosis, hypersensitivity reactions, herpes simplex virus infections, abscess or cellulitis, surface irregularities and nodules, vascular occlusions such as local tissue necrosis and blood vessel embolisation	All patients who developed delayed-type reaction (TRD) after COVID-19 vaccination were middle-aged women with no known history of food or drug allergy. All patients had a history of hyaluronic acid (HA) filler injection in the head and neck and demonstrated particularly swollen symptoms, from <1 day up to 10 days after the first or second dose of vaccines. Lisinopril, hyaluronidase, and corticosteroids appear to have good treatment results
Kandasamy (2020)	Overview of SARS-CoV-2-Mediated Pathological Impact on the Lungs, Heart, and Brain, Therapeutic Uses of Butolinum Toxin Against Lung Failure, Cardiac Arrest, and Neurological Deficits	Therapeutic effect	Botulinum toxins are potent neurotoxins that can induce muscle paralysis and acute respiratory arrest in humans. A mild dose of the purified form of butolinum toxin may attenuate the chronic cough, dyspnea, pneumonia, acute respiratory failure, abnormal circulation,

			heart defects, and various neurological deficits that have been recognized as the prominent clinical symptoms of COVID-19
Kato et al. (2022)	Study of Patients With Symptoms of Acute Inflammatory Reactions After HA or Human Collagen Filler Injection in a Clinic	Acute inflammatory reactions	The sharp increase in acute inflammatory reactions coincided with the COVID-19 pandemic. Possible explanations include immune system changes caused by extensive changes in household and personal hygiene, prolonged and elevated stress levels, and subclinical COVID-19 infection
Li et al. (2023)	Case study reporting delayed inflammatory reactions in a patient whose neck erythema appeared three weeks after injection of hyaluronic acid into the necklines and a delayed inflammatory reaction was diagnosed	Delayed inflammatory reactions	Delayed inflammatory reactions are a relatively rare complication and are often confused with common or non-HA-related infections due to their insidious onset and diverse manifestations. The study highlights the need for attention from health professionals
Lopes (2022)	An observational, retrospective, comparative, multicenter, non-interventional study in a real-life setting was conducted with patients treated with facial injections of hyaluronic acid from May to September 2021, with testing to rule out SARS-COV 2 or who had been vaccinated	Reactions in Unvaccinated and Vaccinated Patients	Adverse events following facial hyaluronic acid injections were higher among patients with a history of, but not among those diagnosed with COVID-19. The new scenario related to COVID-19 infections or vaccines would require readaptation criteria for the application of hyaluronic acid injections
Lopes et al. (2023)	This article reviews the pathophysiological mechanisms and symptomatology of dermal filler RITs associated with COVID-19 infection. At the same time, an analysis is	Reactions to fillers in times of COVID-19	RITs secondary to HA dermal fillers are classified according to the time of onset: early, from 14 days to one year after filling, or late, when they appear more

	made of the most frequent alterations of dermal fillers described secondary to vaccination campaigns, as well as their diagnosis and treatment		than one year after the procedure
Michel (2023)	The purpose of the study was to determine whether delayed-fill granulomas are more common after the onset of the COVID-19 pandemic	Presence of granulomas in patients with filler	Granuloma formation is a rare complication of hyaluronic acid injection that appears to be occurring more frequently in the wake of the COVID-19 pandemic. Practitioners administering dermal fillers should be aware of this complication and its apparent increased incidence
Michon (2021)	A 39-year-old woman who previously had her tear area treated with soft tissue filler with hyaluronic acid developed swelling days after receiving the Pfizer-BioNTech mRNA COVID-19 vaccine	Edema after vaccination	The late-type inflammatory reactions observed in this case report are likely to be immunologically related to the interaction of incoming COVID-19 mRNA vaccine and HA soft tissue fillers
Munavalli et al. (2022)	4 cases with clinical histories of inflammatory reactions at the filling site	Inflammatory reactions at the filling site	The interaction of the Spike protein with dermal ACE2 receptors favors a pro-inflammatory locoregional TH1 cascade, promoting a CD8+T cell-mediated reaction to incipient granulomas, which have previously formed around residual HA particles.
Naouri (2023)	Research on the relationship between facial aesthetic procedures (botulinum toxin type A and hyaluronic acid fillers) as well as the development of	Inflammatory reactions	The frequencies of complications linked to facial aesthetic procedures may be high due to the increased rate of vaccination and also of infection in the population

	inflammatory reactions in patients infected with SARS-CoV-2 or after vaccination		
Nestor et al. (2020)	Study of the protective effect of botulinum toxin type, where the authors highlighted the benefit of maintaining care with one's appearance in times of pandemic. Procedure in which it provides benefits to the patient even with the use of the mask, since the medication is used in the upper use of the face	Protective effect	The authors concluded in their research that the application of botulinum toxin is indeed a positive solution to reduce negative emotions and promote the well-being of the individual
Ortigosa et al. (2022)	5 cases describing delayed reactions in patients undergoing facial rejuvenation treatments and vaccinated against COVID-19	Late Adverse Events	All case reports showed a hypersensitivity reaction to HA dermal filler more than 24 hours after vaccination for COVID-19, characterized by a delayed hypersensitivity or type IV reaction, a cell-mediated hypersensitivity triggered by T lymphocytes
Owczarczyk-Saczonek et al. (2021)	Risk of late-onset immune-mediated adverse reactions related to dermal fillers in patients carrying HLA-B*08 and DR1*03 haplotypes. This combination of HLA subtypes has been linked to a nearly four-fold increase in the likelihood of developing adverse reactions	Immune-mediated adverse reactions	After regression of inflammation and elimination of the remnants of tissues injured by macrophages, the LMW-HA molecules are removed via CD44-dependent endocytosis.
Pajo et al. (2021)	The effects of COVID-19 violate not only the realm of public health, but also psychosocial interaction and	Psychosocial interaction	Botulinum toxin can offer a positive solution to decrease negative emotions and promote well-being for both the

	communication, particularly with the advent of mask-wearing		mask wearer and everyone who comes into contact with that individual.
Roncati et.al. (2020)	Severe Acute Respiratory Syndrome (SARS-CoV-2), the etiological agent of the disease, triggers a T-helper immune response	Immune response	Illustration of the immune mechanism to train the immune system for a more effective and less symptomatic T-helper 1 immune response, to be explored against SARS-CoV-2.
Rowland-Warmann et al. (2021)	Case report on delayed-type hypersensitivity after hyaluronic acid dermal filler treatment of the nose and subsequent SARS-CoV-2 infection	Hypersensitivity reaction in hyaluronic acid filler in the nose region	The incidence of hypersensitivity reactions to hyaluronic acid dermal fillers is between 0.3 and 4.25%, mediated by T lymphocytes.
Sapphir et al. (2022)	Delayed inflammatory reactions (DIRs) to hyaluronic acid-based dermal fillers following COVID-19 vaccination have been reported in a few anecdotal reports and in small case series	Delayed inflammatory reactions	The delayed inflammatory reaction associated with BNT162b2 vaccination is rare and tends to resolve spontaneously or with short-term medical intervention
Savva et al. (2021)	Case study of a 38-year-old female patient with a confirmed hypersensitivity reaction after administration of BNT162b2 vaccine (Pfizer, USA)	Hypersensitivity reaction	Dermal fillers have a very low risk profile, with side effects that include local and transient bruising and edema. They are non-allergenic, non-carcinogenic, and generally represent a stable and cost-effective choice for the patient

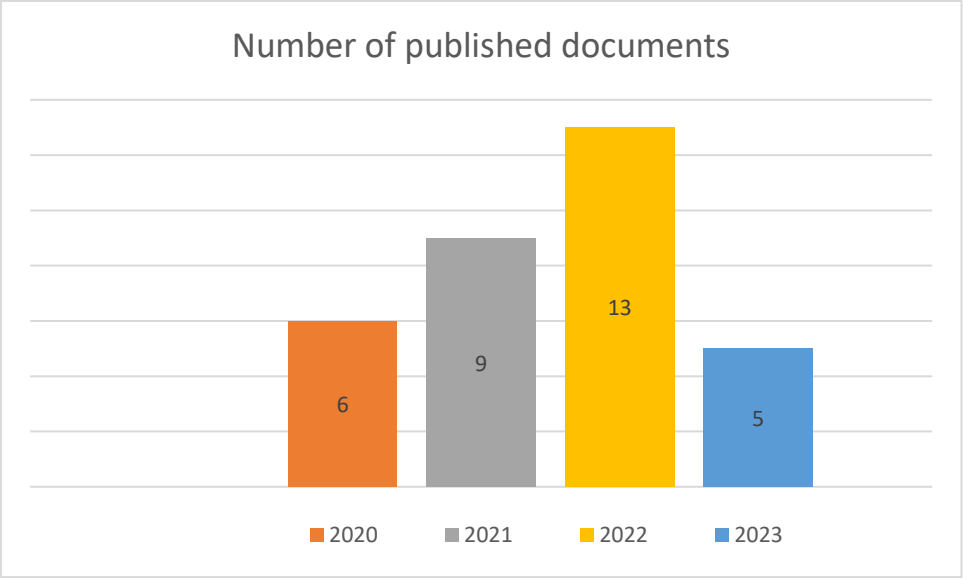
Shome et al. (2021)	Clinical case of a 32-year-old woman treated at The Esthetic Clinics, Mumbai, in February 2020 for facial rejuvenation. She was rejuvenated by using dermal fillers in various locations on her face	PITT (Delayed Intermittent Edema)	The exact etiology of the delayed reaction in relation to HA fillers and influenza virus/COVID-19 antibody infection remains incompletely understood and needs further research and discussion. This will certainly help in the future management of reported cases
Tarantino et al. (2021)	The COVID-19 pandemic has had a negative effect on the care of patients with neurological conditions, as it is well known that all chronic neurological conditions require regular and accurate follow-up	Neurological conditions	The importance of BT therapy to treat these patients and the need to administer it regularly and without major interruptions are essential in order not to lose its clinical benefits, so any type of suspension or delay in treatment should be absolutely avoided
Zhang (2020)	Aim to investigate clinical and coagulation features in patients with Coronavirus 2019 (COVID-19) critical illness and acro-ischemia.	Coagulation	Coagulation parameters should be closely monitored in critically ill COVID-2019 patients. The timing and protocol of anticoagulant therapy are still under investigation based on more clinical data

Source: Prepared by the author (2023).

In the studies presented, the inflammatory reactions at the filling site are highlighted; pain, edema, pruritus, bruising, and hypersensitivity were the adverse reactions most reported by the authors.

The number of papers published per year is shown in graph 1 below.

Figure 1: Number of publications per year

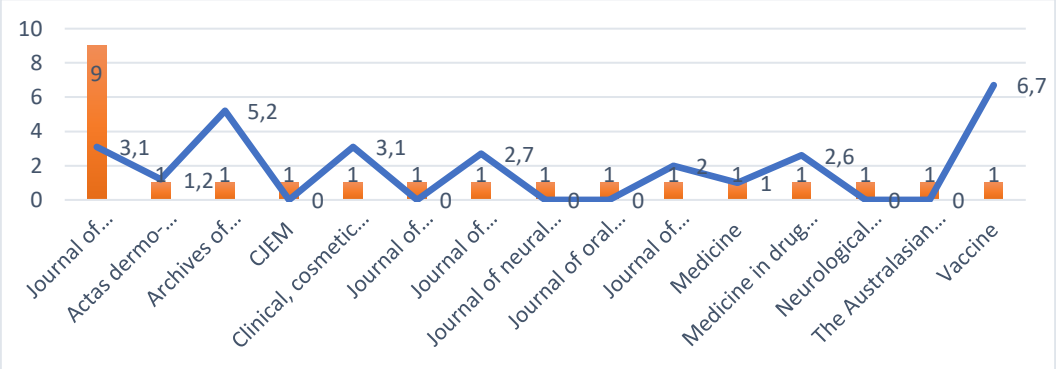


Source: Prepared by the author (2023).

According to the inclusion/exclusion criteria of the works in the sample of this research, the works referring to the period from 2019 to 2023 were selected. In 2019, no publication was found referring to the theme studied in this research, given that it may be related to the beginning of the emergence of cases of the disease related to the Sars-Cov-2 virus. It can be observed that the largest number of publications takes place in the years 2021 and 2022, portraying the important development in the research area, even considering the novelty of the theme. The year 2023 presents the continuity of interest in the theme addressed.

Regarding the main media in which these studies were published, Graph 2 presents the synthesized information, including the value of the *Journal Citation Report* (JCR) of the journals.

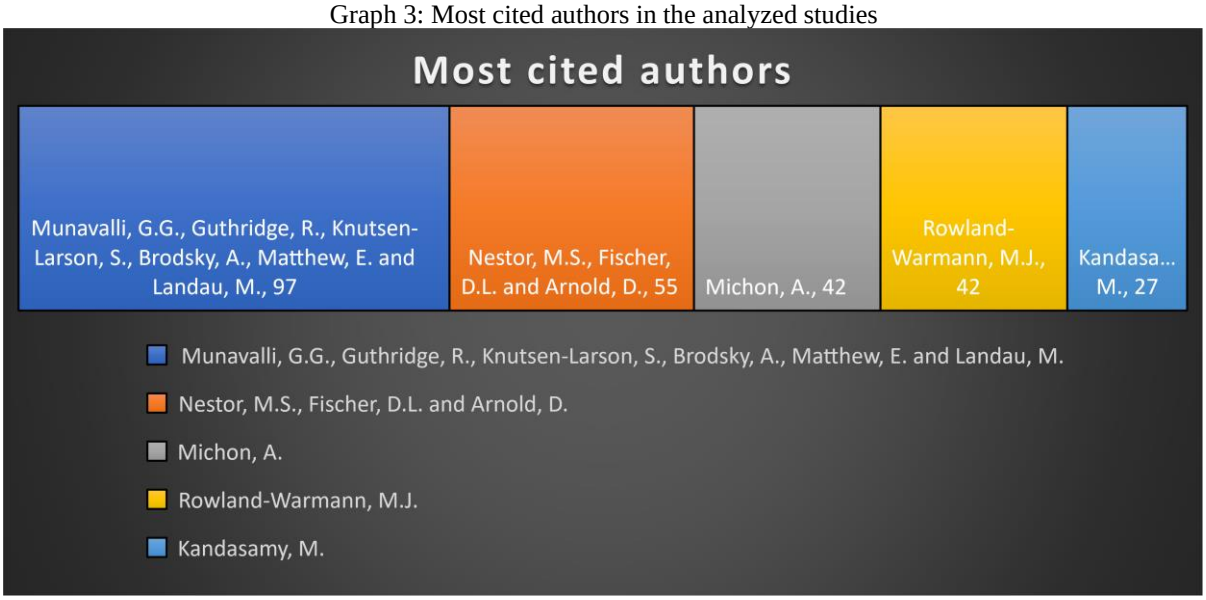
Figure 2: Main media in which the studies were published



Source: Prepared by the author (2023).

The other research question that guided the development of the study was "which works were most cited by the body of literature evaluated"? Graph 3 shows the grouping of the five most cited authors in the studies analyzed.

Graph 3: Most cited authors in the analyzed studies



Source: Prepared by the author (2023).

3.2 ADVERSE EVENTS OF THE VACCINE AND THE SARS-COV 2 VIRUS IN PATIENTS WITH FACIAL AESTHETIC PROCEDURES (BOTULINUM TOXIN TYPE A AND HYALURONIC ACID FILLERS)

According to the criteria established for this systematic review, 33 articles were included in the research that address the possible reactions caused in patients with hyaluronic acid fillers and patients who use botulinum toxin, whether for aesthetic purposes or not, in the face of the Covid-19 vaccine or even Covid-19 infection.

The following text presents the synthesis of the research of the articles addressed in the systematic literature review.

Facial rejuvenation or shaping with hyaluronic acid (HA) and botulinum toxin have been on the rise recently due to their results and safety. However, several factors have been identified that can also increase the incidence of side effects, such as skin infections or inflammation, systemic diseases, viral diseases, and metabolic or coagulation disorders, among other conditions. Different causes may be responsible for delayed inflammatory reactions after hyaluronic acid and botulinum toxin injections, including several mechanisms of SARS-CoV-2 (Lopes, et al., 2023). For the authors Lopes, et al. (2023), several studies have shown a relationship between the patient's inflammatory and immunological status and the development of dermatological changes.

Munavalli et al. (2022), reported cases of immediate side effects to HA fillers. In the study, the authors presented cases of reaction after the administration of the first dose of the mRNA-1273 vaccine (Moderna, Cambridge, MA); another case, after administration of the BNT162b2 vaccine (Pfizer, New York, NY). According to the authors, Munavalli et al. (2022), inflammatory reactions in patients with hyaluronic acid filler may also have been triggered due to the COVID-19 spike protein. This protein

generates a pro-inflammatory response in the localization of dermal fillers by blocking one of the pathways, in the case of cutaneous inhibitory ACE2.

Savva et al. (2021) also published the case of a 38-year-old patient, with no history of allergy, who had been injected with HA on the lips and had a moderate adverse reaction after vaccination with the Pfizer vaccine. Michon (2021), published two cases of women aged 39 and 61 years who developed a late AS after vaccination with the Pfizer-BioNTech mRNA vaccine. Michon (2021), in his article, also points out that delayed inflammatory reactions in patients who have dermal fillers are self-limiting, with frequent spontaneous resolution. However, considering the worldwide demand for vaccines against Covid-19, professionals working in the field of aesthetics should be aware of the risks presented by the interaction of such vaccines in patients who have already undergone aesthetic procedures or who will undergo them.

Ortigosa et al. (2022) published five cases describing delayed reactions in patients undergoing facial rejuvenation treatments and vaccinated against COVID-19; three of them with the Pfizer-BioNTech mRNA vaccine and two with the AstraZeneca vaccine. The authors reported late adverse events after SARS-CoV infection, such as those seen after COVID-19 vaccination.

Rowland-Warmann et al. (2021) reported the case of a 22-year-old female patient, with no history of allergies, who underwent non-surgical rhinoplasty with hypertension and subsequently developed moderate symptoms compatible with SARS-CoV-2 infection. Three weeks later, the patient developed an adverse reaction with edema, hardening, erythema, moderate tenderness, and tightness in the radix area. The authors add in their case report that they realized that these reactions triggered by hypersensitivity to hyaluronic acid dermal fillers are between 0.3 and 4.25% mediated by T lymphocytes, that flu-like illnesses can trigger immunogenic reactions at the site of filler placement (Rowland-Warmann et al., 2021)tag.

Shome et al. (2021) published the case of a patient with no history of AEs undergoing treatment with HA who contracted COVID-19 9 months after facial rejuvenation treatment with HA and who developed AS 1 month after infection (at 10 months of treatment) in the treated area. Calvisi (2022), contributes by stating that these reactions are self-limiting and that even the reinforcement of vaccination can cause these symptoms.

Owczarczyk-Saczonek et al. (2021), point out that the occurrence of unpredictable reactions to hyaluronic acid indicates that they cannot be treated as neutral or non-allergenic. According to the authors Safir et al. (2022), the volume of filler used may be associated with greater severity of reactions, however, reactions are rare and tend to resolve spontaneously or with short-term intervention.

Beamish et al. (2022), highlighted the importance of the growing number of cases suggesting that delayed inflammatory reactions to fillers may occur after vaccination, more specifically to mRNA

Covid-19 vaccines. However, the overall risk of these delayed inflammatory reactions in response to the vaccine is probably very low. However, they can result in adverse events and complications for patients.

Kalantari et al. (2022), analyzed through a systematic literature review 13 cases of patients who developed a reaction after vaccination against Covid-19, with no known history of allergy to food or medications. All selected patients had hyaluronic acid fillers and demonstrated symptoms of swelling from 1 day to 10 days after the first or second dose of the vaccine. And, although it is rare to happen, injecting professionals should be aware of this phenomenon. The application of hyaluronidase and administration of corticosteroids had good results in the treatment of adverse events.

Two cases of subacute hypersensitivity reactions to botulinum toxin after Covid-19 vaccination were reported in the article by Guo et al. (2021). The two main concerns of the reported cases were the previous vaccination to Covid-19 and the subacute progressive manifestation of allergic reaction that was different from the anaphylaxis that the authors previously reported in the patients in the study. Naouri et al. (2022) mention that the frequencies of these complications may be high due to the increase in the vaccination rate and also the rate of infection in the population.

The authors Nestor et al. (2020), in their research, addressed the protective effect of botulinum toxin type A and highlighted the benefit of maintaining care with one's appearance in times of pandemic. Procedure in which it provides benefits to the patient even with the use of the mask, since the medication is used in the upper use of the face. The authors concluded in their research that the application of botulinum toxin is indeed a positive solution to reduce negative emotions and promote the well-being of the individual. Batifol et al. (2022), in their published work reported that botulinum neurotoxin type A is known to block acetylcholine as well as other neuroreceptors and neuromodulators. The study was due to a potential protective effect of botulinum toxin against Covid-19, this is due to the fact that acetylcholine is blocked.

Bono et al. (2021) state that it is necessary to follow the instructions of good practices and safety regarding aesthetic procedures. These, when followed, make the procedures safe for the patient and the professional. In addition, new knowledge about SARS-COV-2 infection may lead to changes in the rules of good practice. The authors stress the importance of recommended intervals after vaccination or illness, a period in which the immune system undergoes repairs.

In the studies by Aryanian et al. (2022), the therapeutic forms of botulinum toxin type A applications can be considered as a potent treatment against Covid-19, however, high precautionary measures should be taken. Another article by Dresler and Saberi (2020) is also based on this same theme and states that botulinum toxin type A applications are important in times of Covid-19, as a protective effect, as they rescue the self-esteem of the individual who receives the application.

The authors Tarantino et al. (2021), and Goodman et al. (2020), reported the importance of continuing the application of botulinum toxin type A during the pandemic in patients who need follow-up in neurological conditions, as it is known that all neurological conditions require regular and accurate follow-up. Therefore, any type of suspension or delay in botulinum toxin treatment should be avoided.

From the systematic review, it was possible to observe that cases of adverse events and also of the influence of the vaccine with facial aesthetic procedures (botulinum toxin type A and hyaluronic acid fillers) are reported, where the authors present the main implications arising from these processes: hypersensitivity reactions, reduced efficacy, inflammatory processes, triggered by vaccination or Covid-19 disease.

Immediate or early-onset adverse reactions (occurring up to several days after treatment) include injection site reactions such as pain, oedema, erythema, pruritus, bruising, infection, hypersensitivity, nodules, asymmetry, facial contour defects, skin discolouration, side effects, and tissue necrosis (Hamed et al., 2022). Case reports of late adverse reactions (occurring weeks or even years after treatment) in addition to edema, nodules, pain, and infection have also been observed, including foreign body granuloma, migration, infection, immune reactions, persistent scarring, accumulated discoloration, and skin affectation (Kato et al., 2022).

Finally, there were some research findings where the authors reported the importance of the use and continuity of botulinum toxin type A in times of pandemic, considering the action of the aesthetic procedure beneficial for self-esteem; there are also studies where they consider botulinum toxin type A as a potent treatment against Covid-19, in neurological cases and, other researches, where they presented the case of the action of botulinum neurotoxin type A acting on the blockade of acetylcholine, as well as other neuroreceptors and neuromodulators

4 FINAL THOUGHTS

SARS-CoV-2 infection and associated vaccines have given rise to several dermatological reactions in individuals previously undergoing aesthetic procedures or aesthetic interventions. It is observed from the cases presented in this review that adverse reactions in relation to soft tissue filling occur after SARS-CoV-2 infection or vaccination. The relationship between these factors seems to be possible, as they occur within a few hours up to several weeks after an infection or vaccination. The underlying mechanism includes the immune response to the viral spike protein and the resulting skin reactions.

However, to avoid these complications, some recommendations can be made: first, advise pre-vaccination in patients who want to perform aesthetic procedures. Subsequently, before the procedure, patients should be asked about allergies, medications to obtain a patient history and avoid possible

adverse events related to botulinum toxin filling or application. A 2- to 4-week window between filler and botulinum toxin injections with vaccination in general and two months longer for immunocompromised patients (i.e., patients on immunosuppressive medications, chemotherapy, or immune disorders) should also be considered. In cases of residual complaints, studies have shown that hyaluronidase can be effective. Although not all studies report on the type of filler used, those that do report mention AH as the largest filler injected in these patients. If patients seek filler treatments in the months prior to vaccination, other filler options (e.g., calcium hydroxyapatite, poly-L-lactic acid, or laser resurfacing) may be prioritized. These recommendations are for HA fillers, since these fillers are the most used worldwide in most aesthetic clinics.

Lastly, the risk of becoming infected with SARS-CoV-2 outweighs the risk of developing adverse events related to botulinum toxin type A filler and reduced efficacy. Currently, the only option to reduce the number of infections and deaths is through global SARS-CoV-2 vaccination programs. Therefore, patients with fillers are advised to participate in current vaccination programs, as complications related to fillers seem to be extremely rare and SARS-CoV-2 infections are of great risk, and may lead to future sequelae.

It is suggested for future research to deepen knowledge regarding vaccination and the disease in the face of the immune system's response in injectable aesthetic procedures, since the number of aesthetic procedures performed in the world is increasing.

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