

Systematic Review

Adverse Events and Satisfaction Outcomes with Calcium Hydroxylapatite and Polycaprolactone Fillers in Facial Aesthetics: A Systematic Review

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Abstract: Objective: The aim of this study was to systematically review the safety and effectiveness of the injectable biostimulators dermal fillers calcium hydroxyapatite (CaHA) and polycaprolactone (PCL) in facial esthetic procedures. Materials and Methods: Comprehensive electronic searches were executed across six academic databases. The primary outcome focused on safety by examining studies that reported the incidence of adverse events (AEs). The secondary outcome gauged the satisfaction of the patients and injectors by validated esthetic scales. To evaluate biases, the Joanna Briggs Institute Checklist tools were employed. Results: We included a total of 79 studies. In the quantitative assessment of the CaHA, out of 5032 injected patients, 21.8% manifested early AEs, 0.85% experienced delayed reactions, and 0.27% had severe complications. Within the PCL group, consisting of 1119 patients, 83.3% exhibited early AEs, 5.6% had delayed reactions, and none had serious complications. Regarding esthetic satisfaction outcome, both products presented favorable results, but a limited number of studies assessed these data. In the studies evaluated qualitatively, a broad array of AEs were cataloged. Conclusions: The occurrence of serious AEs associated with CaHA and PCL fillers is relatively low. Both CaHA and PCL fillers exhibit favorable safety profiles, with most AEs being transient in nature.

Keywords: biocompatible materials; dermal fillers; foreign body reaction; calcium hydroxylapatite; polycaprolactone



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1. Introduction

Over the last decade, there has been a significant increase in the demand for esthetic facial treatments, particularly by the use of biomaterials in non-surgical procedures [1]. These treatments aim to provide balance, facial symmetry, mitigate signs of aging, and improve patients' self-perception of their image [2]. While traditional surgical procedures often have higher morbidity and are typically irreversible and more costly, orofacial esthetic procedures are less invasive and more affordable [3,4]. This spectrum of procedures includes the application of botulinum toxin, hyaluronic acid fillers, suspension threads, the use of deoxycholic acid for submental fat reduction, and, most recently, collagen biostimulators—the latest generation of fillers, such as calcium hydroxyapatite, polycaprolactone, and poly-L-lactic acid [5].

Collagen biostimulators are gaining increasing market shares in regard to the treatment of expression lines, wrinkles, and some facial modifications arising from aging. These treatments offer longer-lasting results due to their prolonged biodegradation time, and their improved collagen stimulation capacity sets them apart from traditional hyaluronic acid injectables. Calcium hydroxyapatite and polycaprolactone are semi-solid fillers providing

immediate volumizing effects. On the other hand, poly-L-lactic acid, a synthetic polymer similar to absorbable suture material, requires several treatment sessions for desired facial volume restoration and lacks augmenting traits. This review will focus only on calcium hydroxyapatite and polycaprolactone due to their similar properties and indications [5,6].

Calcium hydroxyapatite (CaHA) is a facial filler approved for dermal and subdermal application in Europe since 2003, and which was approved by the FDA in 2006, for correcting moderate to severe facial wrinkles and folds and as an adjunct in the treatment of facial lipoatrophy in HIV-infected individuals [7]. The most well-known CaHA injectable is Radiesse[®], a volumizing filler used for correcting wrinkles, restoring volume, and reshaping contours. The volumizing effect lasts up to 18 months [6].

Polycaprolactone (PCL), another collagen-stimulating dermal filler known by the commercial name Ellansé[®], was approved for injectable use in Europe in 2009; in the U.S., polycaprolactone has been cataloged as a medical device since 2001, as has its carrier agent, carboxymethylcellulose, with both being extensively utilized in the medical field [8]. PCL is used for subdermal implantations in corrections of wrinkles and signs of facial aging, and it has been applied to various facial regions as well as for hand rejuvenation [9].

Both CaHA and PCL fillers have similar side effects, including reactions to the injection such as edema, bruising, erythema, and pain [5]. However, there are reports of more severe adverse effects (AEs), such as nodule formation, facial cellulitis, granulomas, vision loss, and tissue necrosis [10]. In light of these, this study aims to evaluate the efficacy, frequency, and nature of AEs resulting from the use of these substances in orofacial esthetic procedures. A systematic review of the literature was conducted to elucidate the following question: “Are calcium hydroxyapatite and polycaprolactone safe and effective dermal fillers in orofacial aesthetic procedures”?

2. Methods

This review was conducted in accordance with the guidelines for reporting systematic reviews of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) [11]. The review protocol was registered under the number CRD42022295216 on the date of 19 January 2022 on the International Prospective Register of Systematic Reviews (PROSPERO) [12] platform (Supplementary S1).

The following information sets up the “PICO”/“PECO” question depending on the type of study: Population—Individuals of both sexes undergoing orofacial esthetic procedures with injection of CaHA or PCL. Intervention/Exposure—Subcutaneous or supraperiosteal injection of CaHA or PCL in the face. Control—In randomized clinical trials, control can be a placebo or any other inert material. In other studies, the “control” does not apply. Primary Outcome—Incidence and nature of AE related to treatment (early, late, or severe). Secondary Outcome—Level of patient and injector satisfaction with the procedures performed, evaluated by validated scales.

2.1. Top of Form

2.1.1. Search Strategy

Searches were conducted in the PubMed, Web of Science, LILACS, EMBASE, Scopus, and Cochrane Library databases. The search strategy containing the terms dermal fillers AND calcium hydroxyapatite OR polycaprolactone was designed on the PubMed platform and adapted for the other bases (Supplementary S2). Manual searches were also conducted among the references of the most recent review articles on the subject and in the gray literature (Google Scholar and OpenGrey). The search was conducted in June 2022 and updated in July 2023.

2.1.2. Study Selection

The Mendeley software (<https://www.mendeley.com> (accessed on 6 January 2023)) was used for the selection of articles independently by two distinct evaluators (RZ, FS). After a detailed reading of the titles and abstracts of the retrieved articles, publications not

related to the topic were excluded. Studies considered to be potentially eligible were read in full and evaluated by both reviewers in relation to inclusion and exclusion criteria. In cases of disagreement between the researchers, a third evaluator (JS) was requested.

2.1.3. Eligibility Criteria

Inclusion Criteria

Case series, case reports, clinical trials, and prospective and/or retrospective observational studies were selected. The studies included in this review followed the following criteria: (a) human studies; (b) use of at least one substance to be studied (CaHA or PCL in a concentration of 30% microspheres and 70% carrier agent); (c) use of the product on the face. Clinical trials where the comparator group was not a placebo or inert material were included as a single arm, that is, the data were extracted only from the group of interest in which CaHA and/or PCL were applied. Clinical trials, observational studies, and case series with fewer than ten participants, as well as case reports, were included for qualitative analysis of complications but were excluded from the frequency evaluation of AE.

Exclusion Criteria

Studies were excluded in which CaHA and PCL were used in the treatment of facial lipoatrophy in HIV-positive patients due to the altered immune responses of these individuals. Review articles, informational materials, and studies investigating the application techniques of the substances were also excluded.

2.2. Outcome Measures

Primary outcomes of this review were considered: frequency of early, late, and serious AEs after the application of collagen biostimulators on the face. The criteria of Carruthers and Humphrey [13] were used for the classification of AEs, with some modifications, as follows: (1) early—events occurring up to 14 days after material application (edema, bruising, hematoma, erythema, ecchymosis, itching, pain, ulceration, infection, filler extrusion, papule, rash and nodule formation); (2) late—events occurring after 14 days of application (persistent edema, late nodules, keloid formation, granulomas and dyschromia); (3) severe—events, such as facial cellulitis, tissue necrosis, vascular compression, partial vision loss (temporary or permanent), anaphylaxis, or any reaction that requires first aid treatment. These effects were classified in this way, regardless of the period in which they occurred. As a secondary outcome, the level of satisfaction of the patient and injector with the esthetic result was evaluated according to the Global Aesthetic Improvement Scale (GAIS) [14] or Wrinkle Severity Rating Scale (WSRS) [15]. The GAIS evaluates esthetic outcomes on a scale, with −1 indicating “Worse”, 0 indicating “No change”, 1 indicating “Improved”, 2 indicating “Much improved”, and 3 indicating “Very much improved”. In contrast, the WSRS rates the severity of wrinkles from Grade 1, which represents “Not visible”, to Grade 5, indicating “Extremely long and deep”, with intermediate grades describing varying degrees of wrinkle depth and visibility. Patients were assessed before and after treatment. A positive score on the GAIS indicates favorable outcomes, while a decrease in grade on the WSRS signifies improvement.

2.3. Data Collection

From the selected articles, the following information was independently extracted by two researchers: the first author's name, country, year of publication, number of patients involved, sex and age of the patients, material used, amount of substance used, region of the face where the material was applied, average follow-up time, and observed AEs (count [n] and frequency [%] of early, late, and severe events). When the Global Aesthetic Improvement Scale or Wrinkle Severity Rating Scale were applied, data were extracted on the average level of patient and professional satisfaction, where possible, with a 3-month interval. When any of these data were not mentioned in the article, an attempt was made to contact the author to obtain the missing information.

2.4. Quality Rating

To evaluate biases, the Joanna Briggs Institute Checklist tools were employed. We evaluated clinical trials, which were considered single-arm, observational studies, and case series using the Joanna Briggs Institute—Case Series Critical Appraisal Tool [16]. Case reports were assessed using the Joanna Briggs Institute—Case Reports Critical Appraisal Tool. Both tools were utilized for assessing a clear description of a patient's demographic characteristics, medical history and current clinical condition, propaedeutic data, treatment, post-intervention condition, AEs, and lessons learned from the case report. The risk of bias was independently assessed by two researchers (RZ and FS) using the appropriate tool for each study design. The analyses were conducted by the two evaluators, and any disagreements were resolved through discussion among the authors.

2.5. Data Analysis

This systematic review provided an in-depth qualitative assessment of the outcomes reported by the included studies, and no meta-analysis has been performed. All randomized clinical trials were incorporated as a single arm, given the absence of a placebo or inert comparator substance. The results are presented descriptively, and the evidence is displayed in tables, with variables being narratively synthesized and summarized using descriptive statistics (frequencies, percentages). In the tables, the aggregate values for variables representing averages were computed based on the sample sizes of the individual studies. As a consequence, publications with larger sample sizes exerted a more significant influence on the overall results. The data from clinical trials, observational studies, case series with less than 10 patients, and case reports were described qualitatively; they were not included in the frequency of adverse reactions, nor in satisfaction scores.

3. Results

3.1. Study Selection

During the initial database search, 2208 records were discovered. Upon removal of duplicates, 1395 of these records remained for consideration in the selection process. During the first phase, the titles and abstracts of all 1395 articles were scrutinized, leading to the eligibility of 143 articles for the subsequent phase. In the second phase, after a detailed analysis of each article's full text, 79 studies were incorporated into the selection comprising this systematic review. A comprehensive depiction of the article identification and inclusion process can be found in Figure 1, along with the justification for the exclusion of each article detailed.

In one study [17], a series of four cases of adverse reaction to CaHA and one case of reaction to PCL were described; therefore, this study was included in the qualitative analysis of both materials.

3.2. Calcium Hydroxyapatite

The data comprises 66 studies [17–81] (Supplementary S3) conducted from 2004 to 2023, with the total participant count across all studies exceeding 5805 subjects. In the studies that provided sufficient demographic and clinical data, the rate of female to male patients was 5.4 to 1 (84.36% females and 15.63% males) and the mean age was 42.06 years. On average, injection volume was 1.42 mL, and the most frequent region of CaHA application was in the nasal region ($n = 14$), nasolabial folds ($n = 11$), followed by the infraorbital ($n = 9$), middle and lower third of face ($n = 6$) and malar region ($n = 7$), with a mean follow-up of 762.55 days. In 31 studies (12 observational studies, 10 clinical trials and nine case series), a quantitative analysis of AEs was performed. The remaining 33 studies, with less than 10 participants, were reviewed in a descriptive manner to highlight specific findings or unusual observations due to their limited sample sizes.

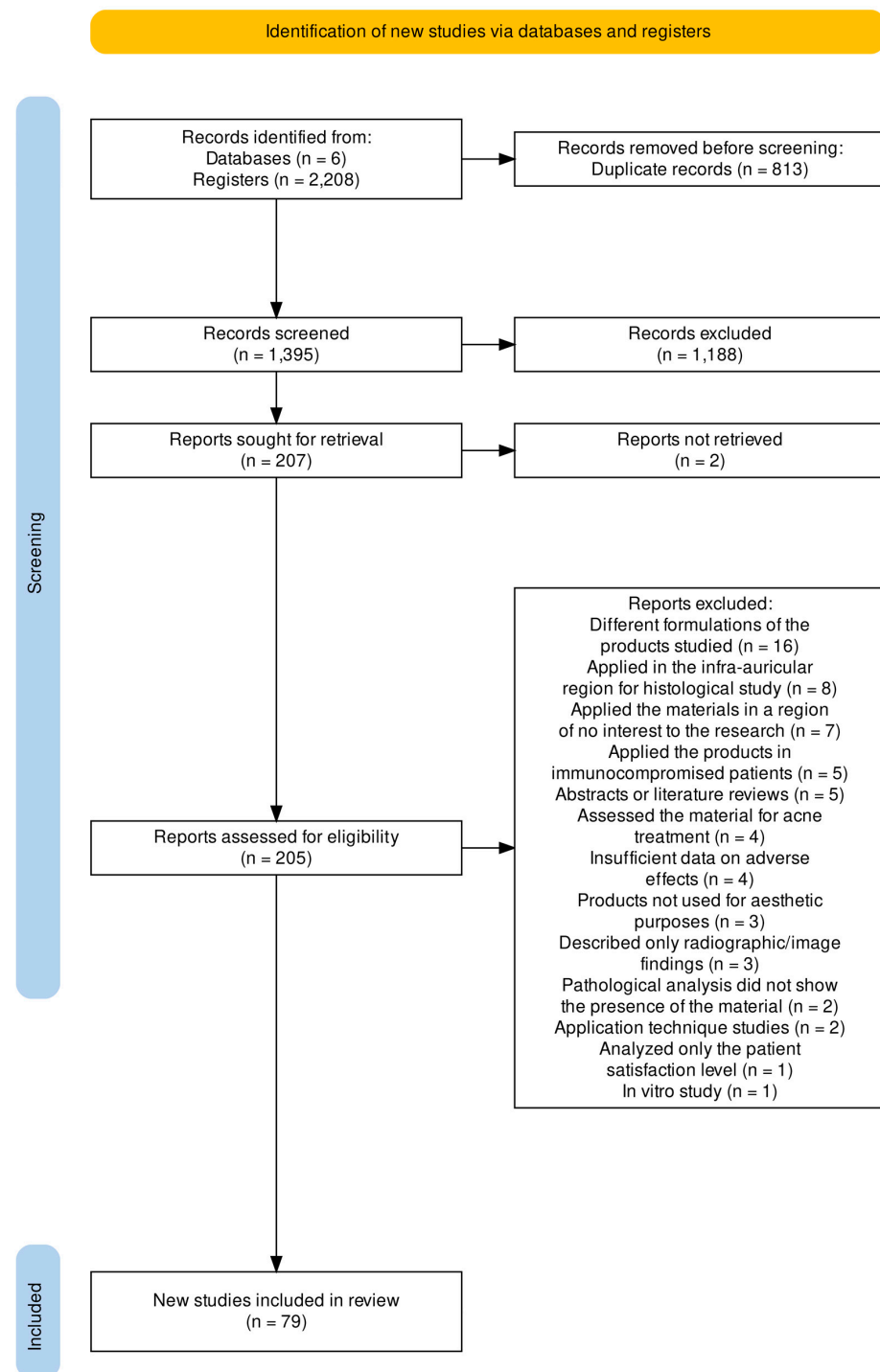


Figure 1. PRISMA 2020 flow diagram for systematic reviews.

Exceptionally, two studies [18,19] were excluded from quantitative analysis due to the lack of adverse event data. One study [18] described 609 subjects that received CaHA fillers in multiple facial sites and reported AEs, including tissue edema, temporary pain and ecchymosis, without quantifying them. An elevated incidence of nodules was observed, occurring in 42 (12.4%) out of 338 subjects who underwent lip augmentation and in six (3.7%) out of 163 patients who received treatment for radial lip line. It is important to note that they did not report whether the appearance of these nodules was early or late. Roy et al. [19], reported on 82 patients who were mostly receiving treatment for nasolabial folds. These patients stated that erythema and minimal edema lasting for several hours were the most

common side effects; additionally, lumps occurred occasionally but were always resolved within two weeks. The frequency of these cited events was not quantified.

3.2.1. Quantitative Analysis

Table 1 presents the results of 31 studies [20,21,23–30,32–42,44–46,48–51,57,58,82] examining CaHA dermal fillers, including a total of 5032 patients. Early adverse events were described in 27 studies, ranging from 0% to 100% of cases, with an average of 21.8%. In the collective analysis, the early AEs most commonly reported were edema, bruising, hematoma, and pain (Table 1). These events typically were characterized by their transient nature. The discrepancy in the results indicates a lack of standardization for the evaluation/measurement of early AEs.

Table 1. Calcium hydroxylapatite studies included in the quantitative analysis of adverse effects (AEs) and satisfaction levels of injectors and patients (n = 31).

Author, Year	N	Injection Sites	Early AE (N/%)	Delayed AE (N/%)	Severe AE (N/%)	GAIS Patient	GAIS Injector	WSRS
Boen et al., 2022 [20]	10	Jawline	0 (0%)	0 (0%)	0 (0%)	2.3	1.6	N/A
Kern et al., 2022 [36]	431	N/A	N/A	N/A	1 (0.08%)	N/A	N/A	N/A
Pavicic et al., 2022 [21]	207	Nasolabial fold, malar, mentolabial sulcus	102 (49.3%)	6 (2.8%)	1 (0.48%)	N/A	N/A	N/A
Alghoul et al., 2021 [44]	20	Infraorbital region	20 (100%)	0 (0%)	0 (0%)	N/A	1.95	N/A
Barbarino 2021 [45]	10	Temporal	5 (50%)	0 (0%)	0 (0%)	N/A	2.8	N/A
Moradi et al., 2021 [23]	180	Mandible	74 (41.1%)	0 (0%)	0 (0%)	2.5	2.7	N/A
Rivkin 2021 [37]	2275	Nasal	116 (5%)	0 (0%)	2 (0.08%)	N/A	N/A	N/A
Corduff 2020 [46]	12	Infraorbital region	10 (83.3%)	0 (0%)	0 (0%)	N/A	N/A	N/A
Rovatti et al., 2020 [38]	40	Middle and lower third of the face	40 (100%)	0 (0%)	0 (0%)	N/A	N/A	N/A
Wollina et al., 2020 [32]	40	Middle and lower third of the face	6 (15%)	0 (0%)	0 (0%)	2.7	2.6	N/A
Muti 2019 [24]	25	Middle and lower third of the face	12 (48%)	0 (0%)	0 (0%)	N/A	N/A	N/A
Ramos et al., 2019 [39]	12	Nasal	12 (100%)	0 (0%)	0 (0%)	N/A	N/A	N/A
Juhász et al., 2018 [48]	20	Temple	7 (35%)	0 (0%)	0 (0%)	N/A	N/A	N/A
Van Loghem 2018 [49]	70	Frontal, temple, superciliary arch	2 (2.8%)	0 (0%)	0 (0%)	N/A	N/A	N/A
Baspeyras et al., 2017 [33]	35	Mandible	27 (77.1%)	2 (5.7%)	0 (0%)	N/A	N/A	N/A
Schuster 2015 [40]	26	Nasal	26 (100%)	1 (3.8%)	2 (7.6%)	N/A	N/A	N/A
Alam et al., 2015 [34]	379	Multiple facial sites	N/A	N/A	3 (0.79%)	N/A	N/A	N/A
Beer 2014 [25]	20	Nasolabial fold	15 (75%)	0 (0%)	0 (0%)	N/A	N/A	N/A
Bernardini et al., 2014 [50]	63	Infraorbital region	22 (34.9%)	2 (3.1%)	0 (0%)	N/A	N/A	N/A
Shahrabi-Farahani et al., 2014 [51]	13	Lips, perioral region, nasolabial fold	N/A	13 (100%)	0 (0%)	N/A	N/A	N/A
Daines et al., 2013 [41]	231	Multiple facial sites	N/A	1 (0.4%)	5 (2.1%)	N/A	N/A	N/A
Moers-Carpi et al., 2012 [26]	116	Malar, zygoma, infraorbital region	80 (68.9%)	0 (0%)	0 (0%)	N/A	N/A	N/A
Marmur et al., 2010 [27]	50	Nasolabial fold	47 (94%)	0 (0%)	0 (0%)	N/A	2.24	N/A
Hevia 2009 [42]	301	Infraorbital region	39 (12.9%)	1 (0.3%)	0 (0%)	N/A	N/A	N/A
Rokhsar et al., 2008 [57]	14	Nasal	9 (64.2%)	0 (0%)	0 (0%)	N/A	N/A	N/A
Moers-Carpi et al., 2007 [28]	50	Nasolabial fold	3 (6%)	0 (0%)	0 (0%)	N/A	2.41	−0.71
Sadick et al., 2007 [29]	113	Nasolabial fold, mentolabial, perioral, infraorbital region	7 (6.1%)	0 (0%)	0 (0%)	N/A	N/A	N/A
Smith et al., 2007 [30]	117	Nasolabial fold	86 (73.5%)	0 (0%)	0 (0%)	N/A	1.75	N/A
Alam et al., 2007 [82]	22	Nasolabial fold	18 (81.8%)	1 (4.55%)	0 (0%)	N/A	N/A	N/A
Jacovella et al., 2006 [58]	40	Glabella, lips, nasolabial folds, nasal and infraorbital region	2 (5%)	0 (0%)	0 (0%)	N/A	N/A	N/A
Tzikas 2004 [35]	90	Multiple facial sites	82 (91.1%)	9 (10%)	0 (0%)	N/A	N/A	N/A
Total	5032		869 (21.8%)	36 (0.85%)	14 (0.27%)	2.52	2.32	−0.71

GAIS: Global Aesthetic Improvement Scale, WSRS: Wrinkle Severity Rating Scale; N/A: not available.

Delayed adverse events were considerably less common and occurred on average in 0.85% of the patients, overall ranging from 0% to 10%, except for one study [51] in particular where all patients experienced delayed events, as the study exclusively enrolled 13 individuals with granuloma lesions. Delayed AEs primarily comprised nodules and granulomas. These were noteworthy and often required clinical intervention due to their persistent or progressive courses [51].

Severe adverse events were reported in only 0.27% of the total patients. The AEs included vascular occlusions leading to skin necrosis, with one patient also presenting an abscess [40]. Those types of AEs underline the inherent risks associated with CaHA fillers [10].

Patient and injector esthetic outcome satisfaction was assessed through GAIS and was positive in the few studies that provided these data, with average scores of 2.52 (ranging from 2.3 to 2.7) and 2.32 (ranging from 1.75 to 2.8), respectively. The overall WSRS score indicated a decrease in wrinkle severity post-procedure (−0.71). However, it is important to highlight that only three studies [20,23,32] assessed patient satisfaction data in a measurable method, with absolute values, and eight studies [20,23,27,28,30,32,44,45] detailed injector satisfaction data. Regarding the wrinkle severity score, only one study [38] described this measure.

3.2.2. Qualitative Analysis

Table 2 comprises data from ten diverse studies, involving a total of 49 patients. Various injection sites and adverse events are documented. Early adverse events like edema, ecchymosis, and bruising were observed in 26 patients across five studies [22,43,47,52,55], while four studies reported delayed events, including foreign body granulomas and nodules, in 12 patients [17,43,53,54]. Serious adverse events, such as vascular occlusion and impending necrosis, were detailed in two studies involving seven patients [31,56].

Table 2. Calcium hydroxylapatite studies not included in the quantitative analysis of adverse effects (AE) and satisfaction levels of injectors and patients (n = 10).

Author, Year	N	Injection Sites	Type of AE	AE/Diagnosis	Management	Outcome
Schelke et al., 2023 [43]	3	Midface and malar	Early/ Delayed *	Nodules, pain	None	Unclear
Durkin et al., 2021 [22]	9	Middle and lower third of the face	Early	Edema, Echymosis	None	Complete resolution
Schelke et al., 2020 [31]	4	Mentum, malar	Severe	Vascular occlusion	Sodium-thiosulphate injections	Complete resolution
Rebellato et al., 2020 [47]	5	Neck region	Early	Pain, bruising	None	Complete resolution
Or et al., 2017 [17]	4	Infraorbital region	Delayed	Xanthelasma-like reaction, swelling, yellow deposits of the lower eyelids	Steroid injection, fractional carbon dioxide laser, 5FU injection, surgical excision	Partial resolution
Wollina 2014 [52]	9	Infraorbital region	Early	Bruising, redness and edema	None	Complete resolution
Moulonguet et al., 2013 [53]	2	Nasal, malar	Delayed	Foreign body granuloma	Surgical excision	N/A
Daley et al., 2012 [54]	8	Lips, perioral region	Delayed	Nodule, yellow mass, foreign body granuloma	Surgical excision	N/A
Vrcek et al., 2012 [55]	2	Infraorbital region	Early	Induration, erythema, irritation	Injection of warmed bacteriostatic saline, non-ablative fractional erbium laser, potassium-titanyl phosphate (KTP) laser	Complete resolution
Dayan et al., 2011 [56]	3	Nasolabial fold	Severe	Erythema, edema, soreness, ulceration, bruising, impending necrosis	An amount of 2% Nitroglycerin paste hyaluronidase, methylprednisolone, aspirin, clindamycin, levofloxacin, valacyclovir, ciprofloxacin, topical treatments, impeding necrosis.	Complete resolution

N/A: not available; * One patient showed early adverse event, two patients delayed adverse event.

Supplementary S4 reviews data from a total of 23 case studies, encompassing 20 females and 3 males, with ages varying between 23 and 64 years. A broad array of adverse events are cataloged, with onset ranging from immediate to 730 days post-procedure. The most commonly observed adverse events were ocular complications (n = 9), foreign body granuloma [59,66,68,81] (n = 4), and skin necrosis due to vascular damage [62,64,75] (n = 3). Other frequently reported symptoms included formation of nodules. The diagnoses were typically confirmed through physical examinations; however, a significant number of cases required the use of advanced imaging techniques, such as computed tomography scans, magnetic resonance imaging, or histopathological analysis. Interventions spanned a wide range of treatments, from pharmacological (topical creams, antibiotics, corticosteroids and antivirals) and injectable (saline and hyaluronidase) treatments to surgical methods such as excision. Some cases required more specialized treatments, including hyperbaric oxygen and fractional carbon dioxide lasers [83,84]. In terms of outcomes, sixteen of the cases reported complete resolution of adverse events following intervention, three cases ended with a partial resolution, and four indicated unclear outcomes.

3.3. Polycaprolactone

Of the 14 studies on the use of polycaprolactone dermal filler (Supplementary S5) in facial esthetic procedures, there were five clinical trials, two retrospective studies, and seven case reports, conducted from 2013 to 2022, including a total of 1126 patients. In studies offering adequate data, the sex ratio was noted to be 12.14 females to 1 male (92.4% females and 7.6% males), with the average age of the participants being 48.91 years. Most injected sites included the nasolabial fold (n = 6) and infraorbital region (n = 4); other sites consisted of the malar, mandibular, and multiple facial regions. The volume of injections fluctuated between 1 mL and 5.04 mL, with an approximate average of 4.4 mL. Patients were monitored for an average period of 716 days (a span from 30 to 850 days). Guided by our methodology, seven studies were subjected to quantitative evaluation and seven were evaluated qualitatively.

3.3.1. Quantitative Analysis

Table 3 summarizes the findings of seven studies evaluating PCL dermal fillers, involving a total of 1119 patients. The majority of patients (83.3%) experienced early adverse events, ranging from 35.9% to 100%, while delayed adverse events were less common (5.6%), ranging from 0% to 7.69%. There were no serious adverse events reported across all studies. The adverse events described were edema, echimosis, hematoma, erythema, lumps, nodules, pruritus, extrusion of the material, pain, and induration (Table 3).

Patient and injector satisfaction, measured using GAIS, showed positive outcomes for patients with average scores of 1.95 [85] and 1.59 [86] (mean 1.82) in two studies and for injectors a mean score of 1.65 (ranging from 1.14 to 2.32) in four studies [86–88]. The WSRS score indicated a decrease in wrinkle severity post-procedure in four studies, with a mean value of −1.07 (ranging from −0.38 to −1.67) [85–87,89].

Table 3. Polycaprolactone studies included in the quantitative analysis of adverse effects (AEs) and satisfaction levels of injectors and patients (n = 7).

Author, Year	N	Injection Sites	Early AE (N/%)	Delayed AE (N/%)	Severe AE (N/%)	GAIS Patient	GAIS Injector	WSRS
Park JW et al., 2022 [85]	59	Nasolabial fold	21 (35.59%)	0 (0%)	0 (0%)	1.95	1.57	−0.85
Zhao H et al., 2022 [89]	80	Nasolabial fold	36 (45%)	0 (0%)	0 (0%)	N/A	N/A	−1.20
Moers-Carpi et al., 2021 [90]	90	Nasolabial fold	47 (52%)	3 (3.3%)	0 (0%)	N/A	N/A	N/A
Jeong et al., 2020 [86]	30	Lateral canthus	15 (50%)	0 (0%)	0 (0%)	1.59	1.14	−0.38
Lin S et al., 2020 [91]	780	Multiple facial sites	780 (100%)	60 (7.69%)	0 (0%)	N/A	N/A	N/A
Galadari et al., 2015 [87]	40	Nasolabial fold	19 (48%)	0 (0%)	0 (0%)	N/A	2.32	−1.67
Moers-Carpi et al., 2013 [88]	40	Nasolabial fold	15 (37.5%)	0 (0%)	0 (0%)	N/A	1.52	N/A
Total	1119		933 (83.3%)	63 (5.6%)	0 (0%)	1.82	1.65	−1.07

GAIS: Global Aesthetic Improvement Scale, WSRS: Wrinkle Severity Rating Scale; N/A: not available.

3.3.2. Qualitative Analysis

Table 4 presents seven case reports about adverse events following facial esthetic procedures using PCL. The cases showed some potential risks associated with PCL administration, such as nodularity, foreign body granulomas and several skin conditions.

The common finding of all the cases was the development of nodules manifesting from 14 to 730 days after procedure. The nodules were linked with skin discoloration in two cases [92,93]. In four cases, these nodules were diagnosed as foreign body granulomas through biopsies [92–95]. Other distinct adverse events were vitiligo [96] and sarcoidosis [97] in two different studies. Additionally, one unusual case of xanthelasma [17] has been reported during treatment. The treatments varied from surgical excision, topical ointment, light therapy and antibiotics to prednisone and methotrexate systemic medication. Outcomes generally showed improvement or resolution of the condition, though one patient was lost to follow-up, and the outcome was not mentioned in another case. These findings emphasize the importance of patient follow-up and vigilance for potential adverse events following facial esthetic procedures with PCL.

Table 4. Case reports describing adverse effects (AE) associated with the use of polycaprolactone in facial esthetic procedures. (n = 7).

Author, Year	Age/Sex of Patient	Site of the AE	Clinical Finding	AE Onset (Days)	Diagnostic Tests	Diagnosis	Management	Outcome
Huang C-H et al., 2022 [96]	23, female	Lower portion of eyelid	Nodularity	14	Wood's lamp examination	Vitiligo	0.1% tacrolimus ointment, 308 nm excimer light	Lesion subsided 5 months later
Chiang CH et al., 2021 [92]	57, female	Inner canthus of lower eyelid	Nodularity (yellowish)	210	Biopsy	Foreign body granuloma	Surgical excision	Lesion had no recurrence
Ortiz-Álvarez et al., 2021 [97]	74, female	Nasolabial folds and zygomatic arches	Nodularity (four subcutaneous and indurated nodules 2 × 2 cm)	90	Biopsy, haemogram, immunoglobulin tests, chest x-ray, head, neck and chest CT scan	Cutaneous and ganglion sarcoidosis	Prednisone, methotrexate	Significant esthetic and symptom improvement
Philibert et al., 2020 [94]	47, female	Malar and mandibular region	Nodularity (multiples subcutaneous indurated nodules from 1 to 3 cm)	270	Biopsy, blood tests	Foreign body granuloma	Regular massages and light therapy sessions, cortivazol, hydroxy-chloroquine, isotretinoin, methotrexate	All nodules disappeared, no recurrence after six months
Skrzypek et al., 2019 [93]	68, female	Nasolabial folds	Nodularity (tiny nodules, bluish discoloration of the adjacent skin)	395	Incisional biopsy, ultrasound scan	Foreign body granuloma	Refused consent to treatment	Lost to follow up
Moon et al., 2017 [95]	36, male	Malar and infraorbital region	Nodularity (multiple asymptomatic firm, immobile subcutaneous nodules)	730	Incisional biopsy ultrasound scan, computed tomography	Foreign body granuloma	Doxycycline	Lesions slightly decreased in size after one month
Or et al., 2017 [17]	48, female	Lower eyelid	Swelling and yellow deposits	180	Physical exam	Xanthelasma	None	N/A

N/A: not available.

3.4. Quality Rating Assessment

The Joanna Briggs Institute Appraisal Tools (JBI) were used to perform a methodological quality assessment and reduce the risk of bias in the included studies (Supplementary S6 and S7). Two researchers answered the questions on the checklist of the JBI assessment instrument with yes, no, or unclear.

In the quality rating critical appraisal of thirty-one case reports, most of them provided a clear description of the patients' demographic characteristics and the current clinical condition of the patients, diagnostic tests, adverse effects, treatment procedures, and post-intervention clinical conditions, as well as takeaway lessons.

Regarding forty-eight case series, observational studies, and clinical trials (included as a single arm), the criteria of inclusion and clinical information of the participants were clearly reported in most studies. However, there was a lack of standardized methods of classification, particularly in cases of early adverse events, in the majority of the studies. Furthermore, few manuscripts indicated complete and consecutive inclusion of the patients. Statistical analyses of outcomes for patient and injection satisfaction were reported in a total of 18 studies.

4. Discussion

This study provides valuable insights into the safety profile of calcium hydroxyapatite (CaHA) and polycaprolactone (PCL) fillers when used in orofacial esthetic procedures; a total of 6931 patients were studied. Only clinical trials, observational studies, or case series with more than 10 participants were included in the quantitative analysis, as case reports and studies with less than 10 patients tend to overestimate the data referring to adverse effects.

Hyaluronic acid and polycaprolactone were approved by the FDA in the early 2000s. However, in Europe, polycaprolactone was only approved by regulatory agencies in 2009. In Brazil, polycaprolactone was only approved in 2017. Several systematic reviews were published investigating the safety of dermal fillers with hyaluronic acid; however, there are still no systematic reviews evaluating such effects of polycaprolactone on the face. Hyaluronic acid is still widely used in facial esthetic procedures; however, in recent years, there has been a growing interest in collagen biostimulators such as polycaprolactone and calcium hydroxyapatite. The significant increase in the number of facial esthetic procedures applying these materials motivated the present systematic review.

In the quantitative analysis of CaHA fillers, the occurrence of serious adverse events was relatively low compared to the total number of patients studied. Out of 5032 patients, 50 individuals (0.99%) showed delayed and severe adverse events. While this number may seem relatively low, it represents a significant figure when considering the large-scale usage of these fillers in orofacial esthetic procedures. Conversely, when analyzing the studies with fewer than 10 participants and case reports, we found that, of the 72 patients, 19 subjects experienced delayed adverse events, most frequently foreign body granulomas, but also late nodule presentation and infection [66,73]. Additionally, 20 patients presented severe AEs, predominantly visual impairments, vascular phenomena leading to occlusion, ischemia, and necrosis of the injected regions [60,64,67]. Factors that may contribute to such outcomes include poor injection technique, the volume of the injected filler, and the anatomical site of application. In a literature review [98], the injection sites identified with higher risk of serious ocular complications were the glabella, nasal region, nasolabial fold, and forehead. An expert consensus statement [99] reported that utilizing lower volumes, serial injections, and blunt cannulas can minimize the risk of adverse events. This present review is incapable of establishing a correlation between the injection site and the incidence of delayed or severe adverse events.

In the quantitative analysis of PCL studies, which included a total of 1119 patients, a higher proportion of delayed adverse events were observed compared to CaHA, with 63 individuals (5.6%) presenting delayed adverse events and no severe adverse events being reported [90,91]. Notably, no cases of vascular complications, necrosis, or ocular damage

were identified in any of the studies included. However, 83.3% of patients displayed early adverse events. This discrepancy might be due to the smaller sample size of the PCL studies, as well as one study, that represents almost 70% of our sample, that classified all patients as having early adverse events [91]. Likewise, this is the result of the lack of standardized criteria for measuring early and mild alterations related to the injection site. While 31 studies were included in the quantitative analysis of CaHA, only seven studies met the criteria to be included in the PCL quantitative analysis, as this material is more recent in the market and has fewer publications; thus, in the imminent future, this systematic review may be updated.

In both groups, the most reported adverse events were transient in nature and typically resolved without long-term consequences. For safer applications, contra-indications of the products must be noted, such as allergies or hypersensitivity to the formulas, active skin infections or inflammation, blood clotting disorders, autoimmune diseases, history of excessive scarring or keloids, and risks for recent facial surgery and pregnancy/breastfeeding patients [10,100]. Moreover, it is noteworthy that certain anatomical regions, which were previously approved by the Food and Drug Administration (FDA), have experienced changes in their approval status. This finding underscores that the current recommendations no longer support the use of CaHA fillers in the lips region due to the observed high incidence of adverse events, mainly nodules, as demonstrated in the study conducted by Jansen and Graivier [18].

Santos et al. (2023) [101] provide valuable insights into the clinical and demographic aspects of foreign body reactions to orofacial esthetic fillers. Their study identifies asymptomatic nodules as the most common presentation, occurring in 50.6% of cases, with the lower lip being the most frequently affected, followed by the upper lip. Similarly, our study reports a high incidence of nodules in 338 patients after CaHA lip augmentation. Surgical removal was the preferred treatment in 35.7% of cases analyzed by Santos et al., underscoring the need for intervention and corroborating the findings of this review. This analysis enhances the understanding of foreign body reactions in esthetic procedures, highlighting the importance of carefully selecting filler materials and anatomical sites during treatment planning.

As highlighted in the Section 3, throughout the 79 studies included in this review, a diverse range of treatment options was assessed for various adverse events. These studies employed different approaches to address specific issues; nonetheless, considering the variability in treatment approaches [17,60,72,94], it is recommended that future studies aim to establish a consensus regarding the most effective treatment options for different clinical scenarios. This consensus would provide valuable guidance for practitioners and help optimize treatment outcomes in diverse situations.

Regarding the patient and injector esthetic outcome satisfaction, both products presented favorable results, but, unfortunately, a limited number of studies assessed these data with a reliable and tangible method [23,28,30,32,36,44,45,85–89]. In the quantitative analysis, the GAIS results of the CaHA group exhibited superior values compared to PCL. Conflicting with the GAIS scale results, the PCL group demonstrated a superior outcome in regard to the WSRS scale. Randomized and controlled clinical trials comparing the safety and efficacy of CaHA and PCL are not available at this time. It is essential to recognize the growing demand for esthetic treatments and higher expectations from patients currently. For all future studies, the use of GAIS, WSRS or other scales is encouraged to measure patient satisfaction to better understand the success and cost–benefit ratio of these procedures. Patient satisfaction was undervalued by most authors, as only five studies [20,23,32,85,86] in this review used this tool for patient assessment.

It is important to note that the lack of consistent criteria to classify early, delayed, and severe adverse events is one of the limitations of this study. For future studies, we suggest implementing the proposed classification by Carruthers and Humphrey [13] to ensure a standardized approach. It is crucial to consider the heterogeneity among the included studies, which encompasses variations in injection techniques, product formulations, patient

populations, and, as mentioned, the different criteria in diagnosing the adverse events encountered. These factors should be considered when interpreting the results. Overall, this study contributes valuable information regarding the safety and efficacy of CaHA and PCL fillers in orofacial esthetic procedures. However, further research with standardized criteria and larger sample sizes is warranted to provide more conclusive evidence and improve our understanding of these material profiles.

Future Directions

The findings from this review emphasize the need for continued research with larger sample sizes and standardized criteria for classifying AEs and assessing esthetic outcomes. Establishing consensus on the best practices for injection techniques, product formulations, and patient selection is crucial for optimizing both the safety and efficacy of CaHA and PCL fillers. Additionally, the development of comprehensive guidelines for esthetic outcome assessment will better inform practitioners and help align patient expectations with realistic results.

Overall, while both CaHA and PCL fillers exhibit favorable safety profiles, with most AEs being transient, the importance of technique, anatomical knowledge, and patient selection cannot be overstated. The growing demand for facial esthetic procedures necessitates ongoing vigilance and research to ensure that these treatments remain both safe and satisfying for patients.

5. Conclusions

In conclusion, this systematic review demonstrates that the occurrence of late and serious adverse events associated with CaHA and PCL fillers is relatively low compared to the number of patients assessed. Both products are effective dermal fillers for orofacial esthetic procedures, as evaluated by GAIS, which demonstrated a high level of satisfaction among patients and injectors. Patient satisfaction should be approached with a comprehensive understanding of patient expectations and the limitations of these procedures. Both CaHA and PCL fillers exhibit favorable safety profiles, with most adverse events being transient in nature. Ongoing monitoring is essential to identify and manage potential early, delayed, and severe adverse events. As studies advance, it is crucial to continue researching and developing materials that improve the techniques and outcomes for professionals and that result in patient safety and satisfaction.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/cosmetics11050165/s1>, S1. International Prospective Register of Systematic Reviews (PROSPERO). S2. Search Strategy of the Study. S3. Clinical trials, prospective and retrospective observational studies, series, and case reports using calcium hydroxylapatite dermal filler in facial esthetic procedures. S4. Case reports with only one patient describing adverse effects (AEs) associated with the use of calcium hydroxylapatite in facial esthetic procedures. S5. Clinical trials, prospective and retrospective observational studies, series and case reports using polycaprolactone in facial esthetic procedures. S6. Joanna Briggs Institute—Case Series Critical Appraisal Tool. S7. Joanna Briggs Institute—Case Reports Critical Appraisal Tool. S8. Checklist—PRISMA 2020 checklist for Systematic Reviews.

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