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ORIGINAL ARTICLE

Complications of collagen biostimulators in Brazil: Description of products, treatments, and evolution of 55 cases

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Abstract

Background: Complications of temporary and permanent fillers have been extensively studied. However, there is a lack of comparative data regarding poly-L-lactic acid (PLLA), calcium hydroxyapatite (CaHA), and polycaprolactone (PCL) known as collagen biostimulators.

Aims: This study addressed the complications of collagen biostimulators concerning their diagnosis, type of product, treatment, and monitoring.

Patients/Methods: An electronic questionnaire was sent to Brazilian dermatologic ultrasound experts to identify complications related to biostimulators. The type of biostimulator, location of application, number of vials injected, application plan, time between injection treatment and complication, injector profile, treatment, and prognosis were assessed.

Results: Fifty-five cases were identified, of which 49.1% were caused by PLLA-Elleva®, 23.6% by CaHA (alone or combined with hyaluronic acid), 20.0% by PLLA-Sculptra®, and 7.3% by PCL. The most affected area was the face (72.7%), with nodules being the most common clinical form (89.1%), generally occurring late (60.0%) (>1 month). Only one case was injected at an incorrect depth (musculoaponeurotic system—SMAS). Despite several treatments, including saline (45.5%), hyaluronidase (25.5%), diluted corticosteroids (23.6%), and energy-based devices (10.9%), only five cases showed complete resolution. Hyaluronidase was beneficial in complications related to fillers when there was an association of calcium hydroxyapatite with hyaluronic acid ($p < 0.01$).

Conclusions: Complications from collagen biostimulators were more common on the face, typically manifesting about 1 month after treatment. These issues seemed to be related more to the properties of the products rather than inadequate technique. Furthermore, hyaluronidase demonstrated efficacy only in cases where there was an association with HA.

KEYWORDS
calcium hydroxyapatite, complications, dermal fillers, nodules, poly-L-lactic acid

1 | INTRODUCTION

Poly-L-lactic acid (PLLA), calcium hydroxyapatite (CaHA), and polycaprolactone (PCL) are classified as synthetic semipermanent fillers with collagen-stimulation capabilities.[1,2] In Brazil, they are called collagen biostimulators and are positioned on the market also as adjuvants to treatment with hyaluronic acid (HA), the most frequently used dermal filler.[1,2]

PLLA is metabolized into carbon dioxide and water over a period of weeks to months, generating an inflammatory reaction capable of stimulating the formation and deposition of collagen by activating fibroblasts. Therefore, PLLA's effects are not observed immediately after injection, so the immediate changes result from the volume of water to be reabsorbed in subsequent days. Currently, there are three PLLAs on the Brazilian market: PLLA-Sculptra®, PLLA-Elleva®, and poly-D-L-lactic acid-Aesthefill®.[1,3]

CaHA is a constituent of human teeth and bones. Similar to PLLA, its effects remain for approximately 1–2 years because its microspheres are phagocyted and enzymatically metabolized slowly before being completely degraded and eliminated via the kidneys as ionic calcium and phosphate.[1] In Brazil, CaHA is known by the trade names Radiesse® and Rennova Diamond®. Recently, the association of CaHA with hyaluronic acid (HArmonyCA®) has provided both the volumizing effect of the latter and the CaHA's collagen stimulation.[4]

Additionally, PCL promotes an immediate correction through the carrier gel carboxymethylcellulose (CMC), which is reabsorbed and gives way to the action of PCL microspheres, which stimulate the production of new collagen. In Brazil, PCL's commercial name is Ellansé®.[1]

The complications of temporary and permanent fillers (e.g., hyaluronic acid, poly-methyl methacrylate, silicone, and polyacrylamide gels) have been extensively studied, but there is a lack of data regarding the complications of collagen biostimulators, their main presentations, and their characteristics, including their sonographic patterns.

Currently, complications from temporary and permanent fillers and collagen biostimulators are diagnosed using high-frequency dermatologic ultrasound. This noninvasive, affordable, efficient imaging method identifies the type of product analyzed, its application plan, vascular occlusions, presence of inflammation or infection, and migration.[5–7]

This study generated data on the complications of collagen biostimulators, including descriptions of the products, their ultrasonographic aspects, types of treatments implemented, and prognosis.

2 | METHODS

The research consisted of two stages. First, experts in dermatologic ultrasound and references in complications from injectables were contacted in two Brazilian states (Goiás and São Paulo). Subsequently, these experts were asked to recruit patients from their clinical database, after 2021, whose clinical histories and ultrasound diagnoses were compatible with complications from collagen biostimulators. Both doctors and patients included in the research signed an informed consent form and responded to specific electronic questionnaires sent via WhatsApp or by phone.

The study protocol was approved by the local ethics committee (CAAE:68540623.7.0000.5078), and the study was conducted from March to September of 2023. Study participants included patients over 18 years of age, both male and female. Patients receiving other dermal filler or energy-based treatments with collagen biostimulators, increasing the chance of complications, were excluded, as were those who refused to answer any part of the questionnaire or did not complete it.

In cases of uncertainty regarding the commercial name of the collagen biostimulator informed by the patient, this information was assessed by the ultrasonographic characteristics. In cases of persistent doubt or incompatibility between the ultrasound appearance and the report provided by the patient, the information was verified by contacting the injecting professional.

Information from the electronic questionnaires included the following: type of collagen biostimulator; trade name (if mentioned); type of injector (medical or nonmedical); type of complication (nodule, edema, vascular occlusion, or infection); body location; amount of product; ultrasound appearance; migration; time between injection and complication; treatment instituted; and prognosis (total, partial, or no resolution).

Subsequently, high-frequency ultrasound was performed with linear transducers above 15 MHz. The ultrasound diagnoses of the various collagen biostimulators were based on certain sonographic aspects already described: for CaHA, hyperechogenic deposits (calcium), with varying degrees of posterior acoustic shadow, depending on their dilution[6]; for PLLA, subtle hyperechoic focal areas[8]; and for PCL, a hypoechoic matrix with hyperechoic foci and comet tail artifact.[9]

The statistical analysis considered the proportions between the variable comparisons using the chi-squared test in the IBM SPSS 29v. software, and significance was defined as $p < 0.05$.

3 | RESULTS

Fifty-five patients with complications from collagen biostimulators were identified. Of these complications, 49.1% were caused by PLLA Elleva®, 23.6% by CaHa (HArmonyCA®, CaHA Radiesse®, and CaHA Diamond®), 20.0% by PLLA Sculptra®, and 7.3% by PCL (Ellansé®; Table 1).

Nearly half of the complications occurred after injections performed by physicians. The most common clinical presentation was nodules (89.1%; Figures 1, 2, 3, and 4), followed by edema and

TABLE 1 Main clinical data of the 55 patients with complications from collagen biostimulators.

Variables	Values
Type of collagen biostimulator; *n* (%)	
PLLA–*Elleva*®	27 (49.1%)
PLLA–*Sculptra*®	11 (20.0%)
CaHA–*Calcium hydroxyapatite*	10 (18.2%)
Polycaprolactone–*Ellanse*®	4 (7.3%)
CaHa + AH–*Calcium hydroxyapatite and hyaluronic acid*	3 (5.4%)
Medical injector, *n* (%)	31 (56.4%)
Type of complication, *n* (%)	
Nodule	49 (89.1%)
Edema	9 (16.4%)
Bacterial infection	6 (10.9%)
Other	6 (10.9%)
Location, *n* (%)	
Face	40 (72.7%)
Neck	12 (21.8%)
Abdomen	4 (7.3%)
Other	3 (5.5%)
Product migration, *n* (%)	4 (7.3%)
Late event (>1 month), *n* (%)	33 (60.0%)
Treatments, *n* (%)	
Saline solution injection	25 (45.5%)
Hyaluronidase injection	14 (25.5%)
Corticosteroid injection	13 (23.6%)
Microfocused ultrasound	6 (10.9%)
Surgical excision	5 (9.1%)
Distilled water/lidocaine injection	5 (9.1%)
5FU injection	3 (5.5%)

Abbreviations: 5FU, 5-fluorouracil; CaHA, calcium hydroxyapatite; HA, hyaluronic acid; SS, saline solution; PLLA, poly-L-lactic acid.

infection. The face was the most affected region (72.7%), and more than one vial of collagen biostimulator was used in 50% of cases. Most complications (60%) were late (>1 month; Table 1).

The various substances and brands of collagen biostimulators were not associated with the professional injector ($p = 0.235$), product migration ($p = 0.663$), or later complications ($p = 0.359$).

The association between CaHA and HA was related to the development of edema ($p < 0.01$). Ultrasonographic evaluation showed application in the superficial subcutaneous plane depth in all cases, except for one case of PLLA-Sculptra® injected into the SMAS (Figure 3).

The patients underwent different treatments that included injecting saline solution (SS) (45.5%), hyaluronidase (25.5%), diluted intralesional corticosteroids (23.6%), and microfocused ultrasound (10.9%), combined or not. Overall, 66% of patients were subjected to more than one session.

Only five patients (9.0%) achieved complete resolution. One patient treated with CaHA evolved with spontaneous regression; two patients treated with CaHA associated with HA (HArmonyCa®) were treated with intralesional corticosteroids, antibiotics, and hyaluronidase; and two patients treated with PLLA-Sculptra® were treated with distilled water and systemic corticosteroids. The other patients experienced little or no improvement, especially those with complications arising from PLLA-Elleva® ($p < 0.05$).

4 | CONCLUSIONS

Complications from collagen biostimulators are less frequent than those with HA,[10] and no study has specifically addressed the complications of this category of injectables. The collagen biostimulator with the highest frequency of complications in this study was PLLA Elleva®, a new poly-L-lactic acid concerning which few studies have been published.[8]

The comparative analysis of complications among medical professionals and nonmedical practitioners elucidates the prevailing dynamics within the Brazilian injectables market. However, this analysis does not provide conclusive insights into whether a differential prevalence of complications exists between these two categories of injectors. Nevertheless, all interventions in this study were executed within the correct subcutaneous plane, except one involving application to the superficial musculoaponeurotic system (SMAS). Although it is known that incorrect injection plans can cause complications,[11] the adverse effects of collagen biostimulators were unrelated to the application technique in this study.

In a series of 1748 cases of filler complications, nodules were more frequently related to complications caused by PLLA-Sculptra® (36.1%), while CaHA (Radiesse®) was more frequently associated with edema (40.0%; even without the presence of HA).[12] In another series of 2813 cases of complications from fillers and collagen biostimulators, 288 from CaHA (Radiesse®) and 85 from PLLA (Sculptra®), the first presented more edema (56.3%) than nodules (13.9%), while 60% of Sculptra® complications were from nodules.[13]

The most common clinical presentation in this series was nodules, whose presentation differed from that of HA-based products, whose main complication was edema. Furthermore, coincidentally, edema was more frequent in the hybrid filler, which associated CaHA with HA, suggesting that this clinical presentation could be associated with the presence of HA and the nodules with collagen biostimulators.

Clinically, most collagen biostimulator nodules (PLLA, CaHA, and PCL) do not present inflammatory signs. The precise mechanism of its development has not yet been fully defined, but certain theories have been discussed, including excess product, lack of massage with consequent "trapping" of the product in a certain region, incorrect injection depth, particle size,[14] injection into the muscle,[15] untrained injector, and product injected in a highly mobile location.[16] Additionally, incorrect dilution of these products can cause nodule formation, as previously reported concerning PLLA-Sculptra®.[17]

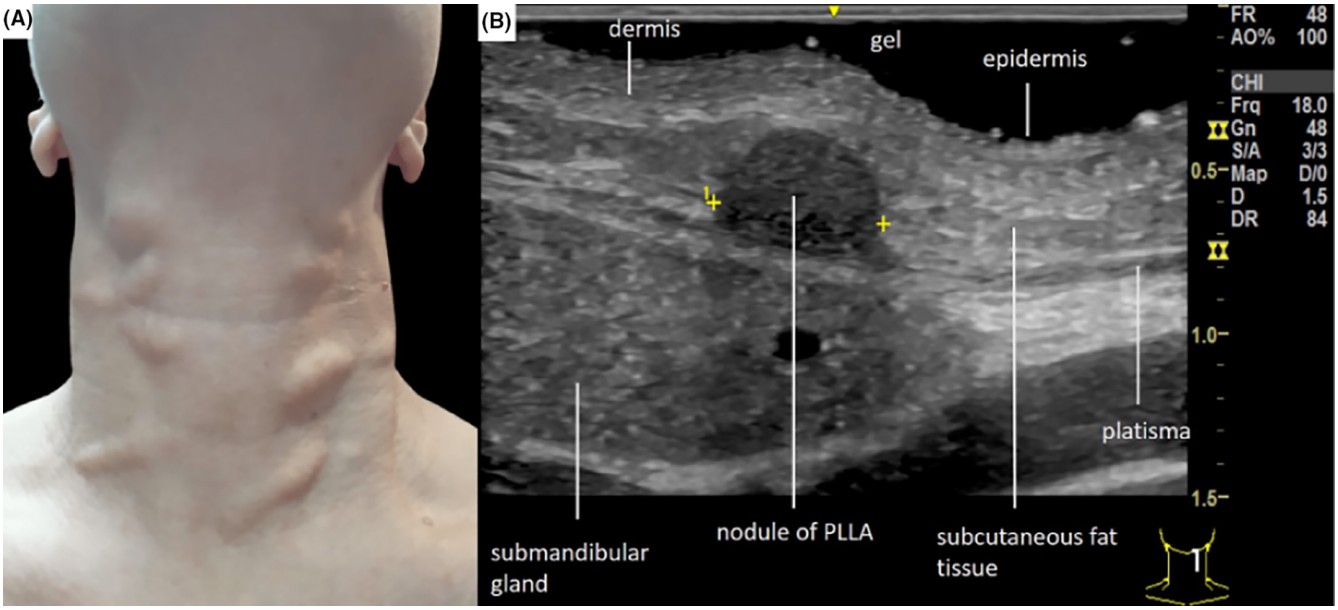

FIGURE 1 (A) Nodules of poly-L-lactic acid (PLLA–Elleva®) on the neck. (B) High-frequency grayscale ultrasound (18 MHz), longitudinal incidence, hypoechoic PLLA nodule (Elleva®) from the same patient, which was injected in the correct plane—in the pre-platysmal fat.

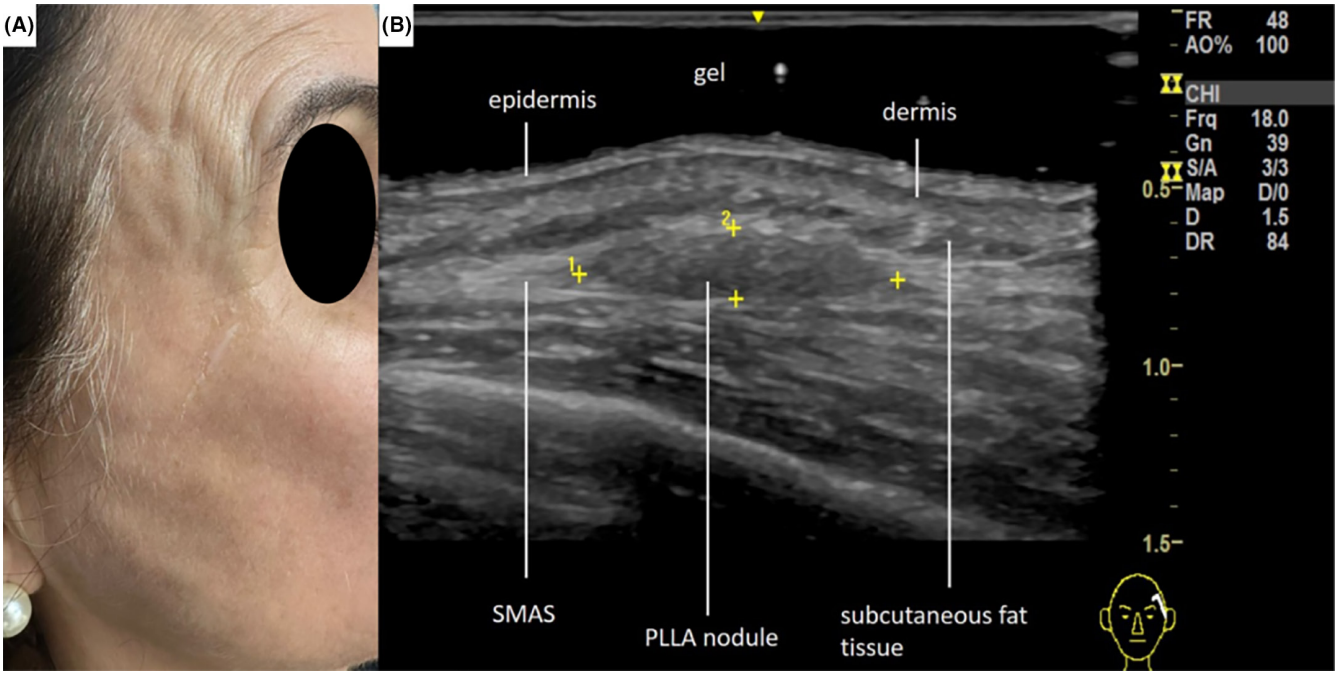

FIGURE 2 (A) Nodules of poly-L-lactic acid (PLLA–Sculptra®) in the temporal and parotideomasseteric region. (B) High-frequency grayscale ultrasound (18 MHz), longitudinal incidence, of another patient shows a hypoechoic nodule of PLLA (Sculptra®) in the SMAS, which was injected in the wrong plane.

Another factor that could influence complications, especially those related to PLLA, is the dilution (hydration) time. Although PLLA dilution was propagated to be performed between 24 and 72 h to prevent nodule formation, two recent studies have validated immediate reconstitution for PLLA-Sculptra®.[18,19] The first in vitro study comparing different dilution times (0, 2, 24, and 72 h) of PLLA-Sculptra® showed that its physicochemical properties retained a nearly constant pH, particle distribution, and stability with lidocaine.[18]

The second study evaluated 26 women undergoing PLLA-Sculptra® with immediate reconstitution, revealing nodules in 3.4% of the participants, indicating that this procedure would be safe.[19] However, the new PLLA on the Brazilian market still lacks efficacy and safety data for both in vitro and in vivo studies. There is only

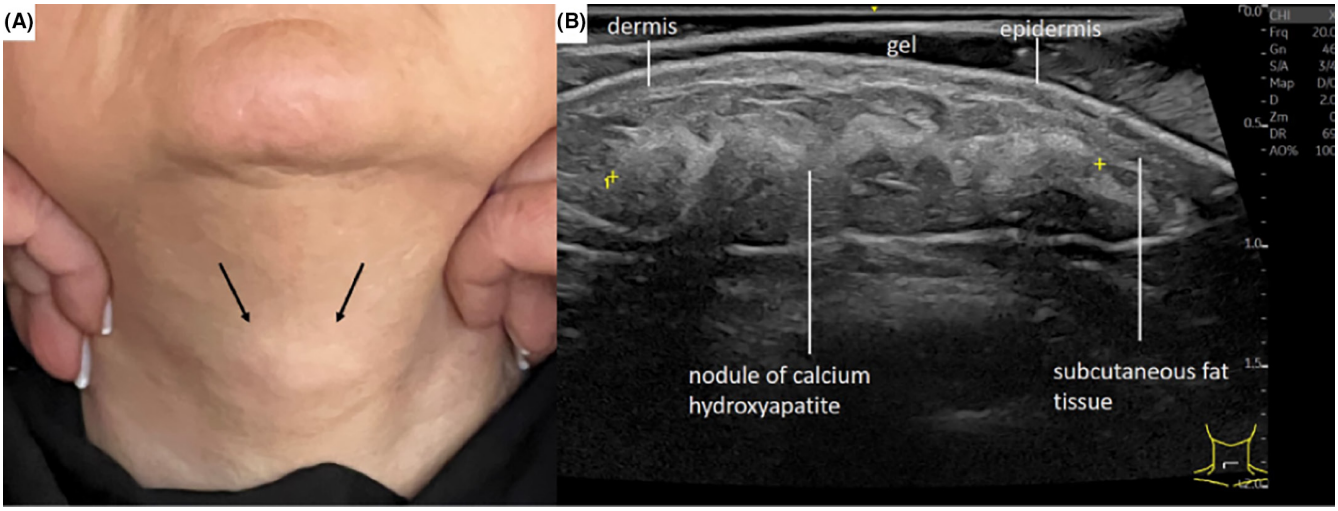

FIGURE 3 (A) Nodules of calcium hydroxyapatite (CaHA–Radiesse®) on the neck. (B) Grayscale high-frequency ultrasound (20 MHz), cross-sectional view, shows an elongated hyperechoic structure, with acoustic shadowing, corresponding to CaHA (Radiesse®).

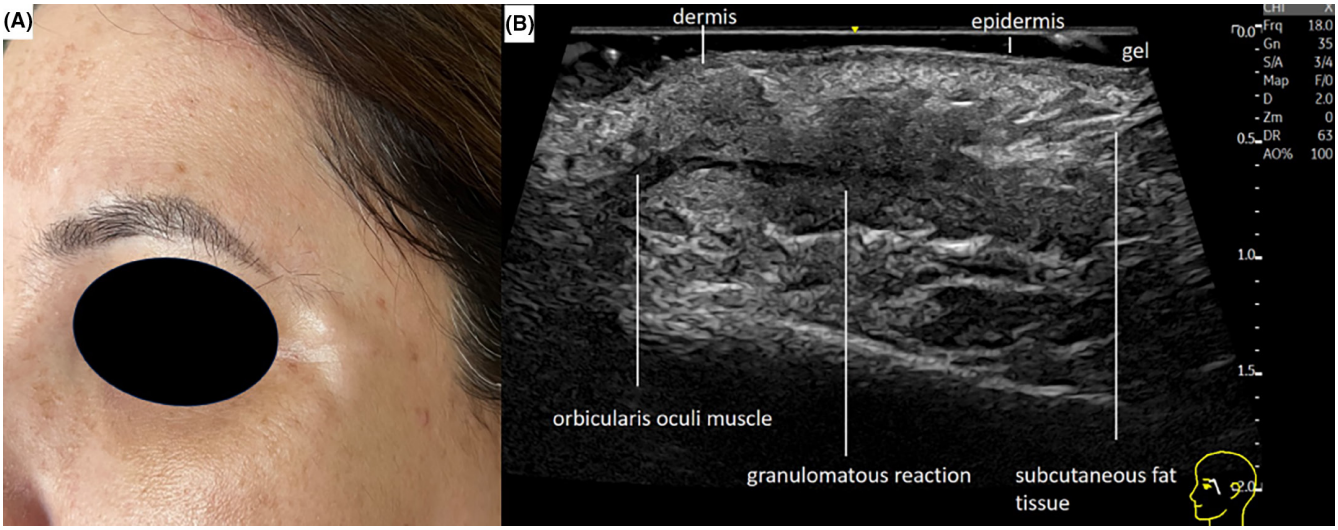

FIGURE 4 (A) Nodules of polycaprolactone (PCL–Ellansé®) at the medial limit of the temporal region. (B) High-frequency grayscale ultrasound (18 MHz), longitudinal incidence, demonstrates poorly defined hypoechoic granulomatous tissue where polycaprolactone was injected.

one study comparing PLLA-Elleva® and PLLA-Sculptra®, with immediate dilution, injected in each arm of four patients, showing that PLLA-Elleva® presented greater homogeneity on ultrasound.[18]

From a histopathological perspective, the debate persists regarding whether nodular formations arising from collagen biostimulators represent an accumulation of product or the manifestation of a foreign body-type granuloma. Some authors have postulated that the preponderance of biostimulator-induced nodules indicates product accumulation. This accumulation would be distinguishable from a granuloma, which signifies an exaggerated host tissue reaction to a small quantity of product. This effect implies an immunological origin contingent upon the host's immune status or incidents provoking alterations in immune dynamics. Regarding prognosis, most nodules disappear spontaneously within 3 months to 3 years.[20]

While the diagnosis of granulomas relies on histopathology, there are sonographic features associated with granulomatous reactions that have been previously documented (references added at the end). Ill-defined hypoechogenic tissue, nodules, or pseudonodules have been identified as indicative of granulomatous reactions. In contrast, the accumulation of filler maintains the initial sonographic pattern of the filler when injected, before the occurrence of any foreign-body reaction.[21]

In this study, the most affected area was the face, the site most commonly subjected to injectable aesthetic procedures.[12,13] Half of the patients underwent more than one treatment with collagen biostimulators (in a single session or serial sessions), but the researchers were unable to infer whether the number of vials influenced complications, so prospective studies should further explore this association.

Generally, complications from collagen biostimulators tend to be late (60.0% after 1 month).[10] After treatment, only five cases (9.0%) in this series achieved complete resolution. Hyaluronidase may have helped in two cases of CaHA associated with HA, which did not occur in the cases of isolated collagen biostimulator and nodular presentation. Despite multiple treatments for these complications, therapeutic resolution remains challenging.[22]

Typically, complications involving hyaluronic acid are addressed through hyaluronidase intervention. Conversely, there is no definitive treatment for complications arising from collagen biostimulator injections. Diverse therapeutic modalities have been documented, including saline infusion, 5-fluorouracil, diluted injectable corticosteroids, hyaluronidase, and sodium thiosulfate (for calcium hydroxyapatite).[23] Energy-based devices, such as intense pulsed light and microfocused ultrasound, have also been reported. However, there is still no singularly efficacious treatment for these complications. Consequently, these interventions are frequently conducted more than once, yielding outcomes that are not universally satisfactory. In select instances, expectant management could be considered, whereas more severe cases may necessitate surgical excision.[7,16,17,24,25]

The present study had certain limitations. First, only two states in Brazil were included. Next, there was a lack of knowledge about product dilutions and the division of the Brazilian market concerning the brands mentioned. Beyond this, other limitations include: data on the long-term follow-up (cross-sectional study), recall bias (with the possibility of additional or multiple treatments not reported by the patients) and no inclusion of poly acid D-L-lactic (Aesthefill®) because of its recent release in the country. However, these data constitute the first basis for information on this subject.

In conclusion, complications of collagen biostimulators seem to be related more closely to the product than to the inadequate application technique. The most common site was the face, with a clinical presentation of nodules and, in most cases, unsatisfactory treatment. Hyaluronidase was effective only in cases where there was an association with HA.

AUTHOR CONTRIBUTIONS

Dr Mayra Ianhez, Dr Isabella Faria, and Dr Hélio Miot elaborated the protocol, collected, and tabulated the data. Dr Rosa Maria S. Sigrist, Dr Paula T Colpas, Dr Giselle de Góes, Dr Meire Parada, and Dr Isabella Faria collected and tabulated the data. Dr Rosa Maria S. Sigrist, Dr Paula T Colpas, and Dr Giselle de Góes performed the ultrasound exams. Dr Mayra Ianhez and Hélio Amante Miot carried out the statistical analyses. All the aforementioned authors have made substantial contributions to the conception, acquisition of data, analysis, and interpretation. All authors reviewed and have given final approval of this versions.

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CONFLICT OF INTEREST STATEMENT

Dr Mayra Ianhez is a speaker of Galderma, Abbvie, Janssen, Novartis, Pfizer, Sanofi-Genzyme, Theraskin, and FQM; Dr Rosa Maria S. Sigrist is a speaker of Galderma, Clarius, and General Electric (GE); Dr Paula T Colpas is a speaker of Abbvie and a consultant in Theraskin; Dr Meire Parada is a speaker of Galderma. Dr Hélio A Miot is a consultant of Abbvie, Merz, La Roche Posay, Pfizer, Eucerin, and Pierre-Fabre. Dr Giselle de Góes and Dr Isabella Faria have no conflicts of interest. All authors have no conflicts of interest related to this research.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

All participants provided their informed consent before participating in the study. The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the research ethics committee of the Hospital das Clínicas of the Universidade Federal de Goiás – UFG on 05/02/2023. CAAE 68540623.7.0000.5078. The methodology of the article was based on the application of a questionnaire containing descriptive data on the application of collagen biostimulators provided by the physicians' experts in dermatologic ultrasound and their patients. The identity of the patients was kept confidential, and they were identified by a number during the research.

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