EFFECTS OF SCULPTRA® (INJECTABLE POLY-L--LACTIC ACID) FOR FACIAL REJUVENATION: A SYSTEMATIC REVIEW

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Abstract: Poly-L-lactic acid (PLLA) is a synthetic, biocompatible and biodegradable polymer of the alpha-hydroxy acid family. This substance has provided satisfactory and safe results in several medical applications in the last three decades. The brand name Sculptra® has been widely investigated in the area of facial cosmetics. The aim of this study was to performed a systematic review of the effects of Sculptra® for facial rejuvenation. This review was registered on the prospero platform under protocol CRD42021277434. A careful search was conducted in the Pubmed, Scopus, BVS, Scielo, Web of Science, LILACS and Cochrane Library databases up to February 2021. Gray literatu-

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re was consulted at Open Grey. In addition, a manual search was performed. Clinical studies were selected, without restriction of publication date or language. Data synthesis and risk of bias assessment of the included studies was performed by two independent authors. Eight clinical studies were selected for data synthesis (three randomized clinical trials, two prospective cohorts and three retrospective cohorts). Data synthesis demonstrated that Sculptra® is considered an effective, safe and long-acting agent for collagen volumization and biostimulation. The assessment of the risk of bias of the RCTs revealed a low risk of bias in all domains, with the exception of the domain of concealment of allocation of participants. Within the limitations of the systematic review, the use of Sculptra® for facial rejuvenation is effective, safe and long-lasting.

Keywords: Facial Fillers; Polymers; Rejuvenation; Aging.

INTRODUCTION

Facial aging involves slow and progressive processes, such as craniofacial bone remodeling, facial fat reduction and biochemical and structural changes in the skin. The search for facial aesthetics is growing in society and considered an important indicator of health and well-being (Bueller, 2018). Due to this, new products and therapeutic strategies for facial rejuvenation were introduced, including fillers and collagen biostimulators, such as polycaprolactone (PCL), calcium hydroxyapatite (CaHA), polymethylmethacrylate (PMMA) and poly-L-lactic acid (PLLA) (Atte-

nello and Mass, 2015; De Melo et al., 2017; Graivier et al., 2018). This widely encouraged research in the area of facial cosmetics (Kim et al., 2019a).

PLLA is a synthetic, biocompatible and biodegradable polymer of the alpha-hydroxy acid family (Simamora and Chern, 2006). This substance has provided satisfactory and safe results in several medical applications in the last three decades (Alam and Tung, 2018). Sculptra® is a sterile glass vial containing a lyophilized powder composed of non-pyrogenic mannitol, sodium carboxymethylcellulose and PLLA crystalline microparticles with irregular size ranging from 40-63 µm in diameter (Alam and Tung, 2018). PLLA microparticles stimulate a local subclinical inflammation in the host, with monocytes, macrophages and fibroblasts recruitment, that promotes a slow material degradation, collagen type I synthesis and increase in skin thickness (Kim et al., 2019b; Kwon et al., 2019). Neocollagenesis starts approximately between 2 and 10 days after product application and remains for a period of 8-24 months, until the product is completely degraded and the subclinical inflammatory response ceases (Lacombe, 2009).

The Sculptra® treatment can include multiple sessions and has been shown to provide effective and long-lasting results in improving contour and facial sagging (Lee, Lorenc, 2016). It is indicated to treat sagging skin and volume of depressed areas, such as furrows, wrinkles, skin depressions, atrophic scars, changes resulting from lipoatrophy or bone remodeling (Alessio et al., 2014). This implies an improvement in the

quality and rigidity of the skin, leading to a general rejuvenation of the face (Bohnert et al., 2019).

Due to the great clinical relevance in facial cosmetics, the aim of this study was to performed a systematic review of the effects of Sculptra® for facial rejuvenation.

METHODS

Protocol and registration

The study description followed the Preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines (https://prismastatement.org/) and the Cochrane Manual for systematic reviews of interventions (Moher et al., 2015). Registration was performed in the International Prospective Register of Systematic Reviews (PROSPERO) database (https://www.crd.york.ac.uk/prospero/) under protocol CRD42021277434.

Search strategy

An unrestricted search was performed by two independent authors (EDGLM and ACFC) in seven electronic databases: Pubmed, Scopus, BVS, Scielo, Web of Science, LILACS and Cochrane Library. Gray literature was consulted at Open Grey. The identification of studies was performed through an initial search in these electronic databases with a strategic algorithm developed by the authors. This algorithm was composed by the combination of the Boolean operators AND and OR with the following descriptors registered or not in the Medical Subject Headings (MESH): “Rejuvenation”; “Face”; “Skin”; “Collagen”; “Poly-L-lactic acid”; “Sculptra” (Supplementary File). All studies

published up to February 2021 were consulted, without language restrictions. Additionally, a manual search was performed in the references of the articles included in the review. Any discrepancies between the authors were resolved by a third author (MJS).

Supplementary File. Search strategy.

Database	**Keywords**
Pubmed	("Rejuvenation"[mh] OR "Skin" [mh] OR "Collagen"[mh]) AND ("Poly-L-lactic acid" OR "Sculptra")
Scopus	("Rejuvenation" OR "Skin" OR "Collagen") AND ("Poly-L-lactic acid" OR "Sculptra")
BVS	("Rejuvenation" OR "Skin" OR "Collagen") AND ("Poly-L-lactic acid" OR "Sculptra")
Scielo	("Rejuvenation" OR "Skin" OR "Collagen") AND ("Poly-L-lactic acid" OR "Sculptra")
Web of Science	("Rejuvenation" OR "Skin" OR "Collagen") AND ("Poly-L-lactic acid" OR "Sculptra")
LILACS	("Rejuvenation" OR "Skin" OR "Collagen") AND ("Poly-L-lactic acid" OR "Sculptra")
Cochrane Library	("Rejuvenation" OR "Skin" OR "Collagen") AND ("Poly-L-lactic acid" OR "Sculptra")
Open Grey	("Rejuvenation" OR "Skin" OR "Collagen") AND ("Poly-L-lactic acid" OR "Sculptra")

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Study selection and eligibility criteria

Relevant studies were initially selected by the authors (EDGLM and ACFC) through reading titles and abstracts. After removal of duplicates, the full texts of the references selected in the previous phase were analyzed according to specific eligibility criteria, including: complete scientific articles on the use of injectable PLLA for the therapeutic purpose of facial rejuvenation; retrospective or prospective clinical studies in patients without immunosuppression.

Aiming at a high level of scientific evidence, it was decided to exclude experimental studies in animals or cell cultures, case reports, experience reports, literature reviews and systematic reviews. Studies in which PLLA were not administered by injection were also excluded.

An adaptation of the PRISMA checklist flowchart was used to synthesize all phases of study selection (Figure 1) (Tricco et al., 2018).

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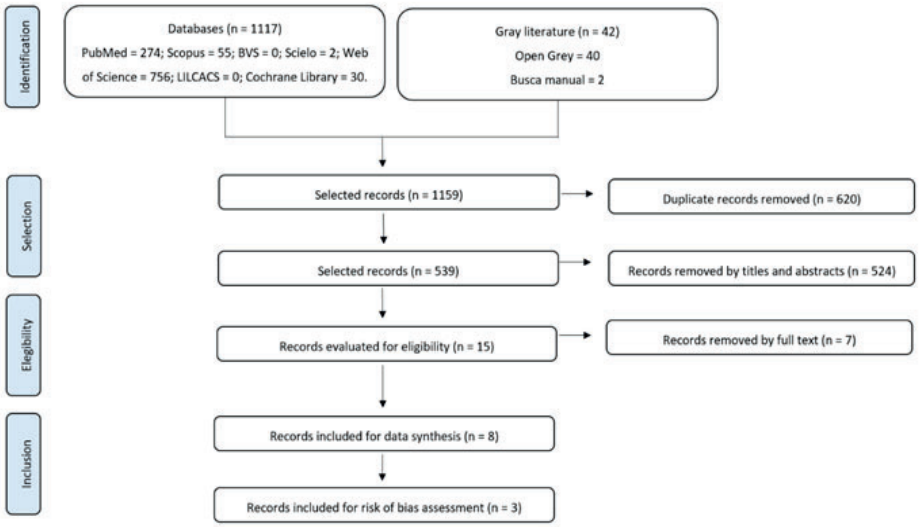
Figure 1. PRISMA flowchart of systemetic review.



Data synthesis process

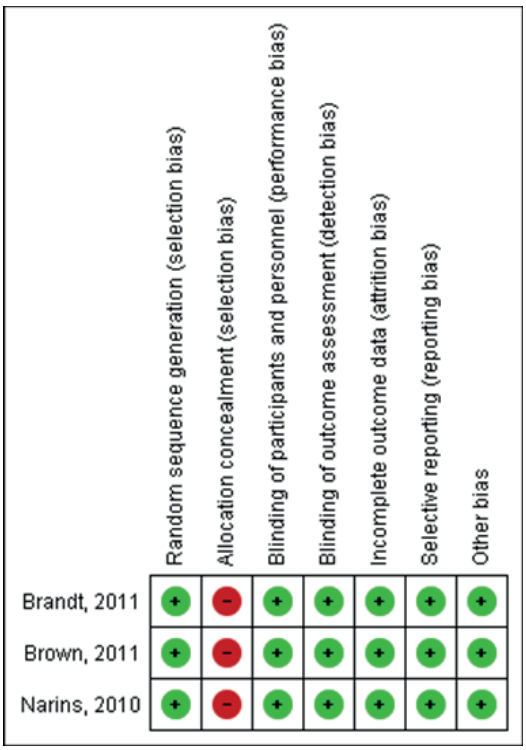
The information from the included studies was synthesized by the two independent authors (EDGLM and ACFC) using tables containing the general characteristics of the included studies (author, year of publication, study type, sample size and age, groups, research objective), specific characteristics of the Sculptra® treatment (purpose of the patient, number of sessions and intervals, injection technique, evaluation method and follow-up time/treatment period) and the main results/conclusions. Doubts and disagreements were solved by a third author (MJS).

Risk of bias assessment

The risk of bias assessment was applied by the two independent authors (EDGLM and ACFC) to randomized clinical trials using the Cochrane

Collaboration tool (Higgins et al., 2011). For this, the following domains were analyzed: (1) random sequence generation - selection bias, (2) allocation concealment - selection bias, (3) blinding of participants and professionals - performance bias, (4) blinding of outcome evaluation - detection bias, (5) incomplete outcome data - attrition bias, (6) selective reporting - reporting bias, and (7) and other biases (Figure 2).

Figure 2. Risk of bias assessment of RCTs.



RESULTS

Study selection

The authors identified a total of 1159 studies in the initial search. After excluding duplicate studies, 539 references remained. Based on the established eligi-

bility criteria, 524 studies were excluded after reading titles and abstracts and 7 studies were excluded after full text reading. Thus, 8 studies were selected for data collection in this systematic review. The risk of bias assessment with the Cochrane Collaboration tool could be applied in only 3 studies (Figure 1).

General characteristics of the included studies

Studies published from 2011 to 2020 were included. All of them were written in English, with the exception of Masveyraud (2011), written in French (Masveyraud, 2011). Regarding the study type, three were randomized clinical trials (Brandt, 2011; Brown, 2011; Narins, 2010), two prospective cohorts (Bravo and Carvalho, 2021; Chen, 2015), and three retrospective cohorts (Masveyraud, 2011; Fabi and Goldman, 2021; Palm, 2010). All studies aimed to evaluate the efficacy and/or safety of Sculptra® injectable PLLA in facial rejuvenation (Brandt, 2011; Bravo and Carvalho, 2021; Brown, 2011; Chen, 2015; Fabi and Goldman, 2021; Masveyraud, 2011; Narins, 2010; Palm, 2010). The sample size of the studies ranged from 15 to 298 patients, with ages ranging from 27 to 87 years (Brandt, 2011; Bravo and Carvalho, 2021; Brown, 2011; Chen, 2015; Fabi and Goldman, 2021; Masveyraud, 2011; Narins, 2010; Palm, 2010). Three studies compared injectable PLLA to human collagen (Bravo and Carvalho, 2021; Brown, 2011; Narins, 2010) and one study combined the use of injectable PLLA with intense pulsed light (Table I) (Fabi and Goldman, 2021).

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Tabela I. General characteristics of the included studies.

Author, year	Study type	Study objetives	Sample	Groups
Brandt, 2011	Randomized clinical trial	Evaluate the efficacy of injectable PLLA to correct nasolabial wrinkles.	233 patients; -.	Injectable PLLA and Human collagen
Bravo, 2020	Prospective cohort	Demonstrate the efficacy and safety of immediate reconstitution of injectable PLLA as a facial biostimulator.	26 patients; 27-80 years.	Injectable PLLA
Brown, 2011	Randomized clinical trial	Evaluate the efficacy of injectable PLLA to correct nasolabial wrinkles.	233 patients; -.	Injectable PLLA and Human collagen
Chen, 2015	Prospective cohort	Demonstrate the efficacy and longevity of injectable PLLA as a volumizer in the middle third of the face.	15 patients; 40-60 years.	Injectable PLLA
Fabi, 2012	Retrospective cohort	Evaluate the efficacy and safety of injectable PLLA combined with intense pulsed light (IPL) in facial rejuvenation.	90 patients; -.	PLLA + immediate IPL and PLLA + IPL 6 days post-treatment

Masveyraud, 2011	Retrospective cohort	Evaluate the efficacy and safety of injectable PLLA for facial rejuvenation.	298 patients; 30-75 years.	Injectable PLLA
Narins, 2010	Randomized clinical trial	Compare the efficacy and safety of injectable PLLA and human collagen in the treatment of nasolabial wrinkles.	233 patients; -.	Injectable PLLA and Human collagen
Palm, 2010	Retrospective cohort	Evaluate the efficacy and incidence of adverse events of injectable PLLA.	130 patients; 38-87 years.	Injectable PLLA

Specific characteristics of injectable PLLA treatment

The purpose of the treatment of the included studies were: correction of nasolabial wrinkles (Bravo and Carvalho, 2021; Brown, 2011; Narins, 2010), correction of facial sagging (Bravo and Carvalho, 2021), general facial rejuvenation (Brandt, 2011; Bravo and Carvalho, 2021; Brown, 2011; Chen, 2015; Fabi and Goldman, 2021; Masveyraud, 2011; Narins, 2010), and volume correction (Masveyraud, 2011; Chen et al., 2015; Palm, 2010). The number of sessions ranged from 1 to 12 sessions, with intervals ranging from 14 to 121 days (Brandt, 2011; Bravo and Carvalho, 2021; Brown, 2011; Chen, 2015; Fabi and Goldman, 2021; Masveyraud, 2011; Narins, 2010; Palm, 2010). The most used injection technique was the fan (Bravo and Carvalho, 2021; Chen, 2015; Fabi and

Goldman, 2021; Palm, 2010). The assessment methods encompassed patient and/or professional perceptions (Brandt, 2011; Bravo and Carvalho, 2021; Brown, 2011; Chen, 2015; Fabi and Goldman, 2021; Masveyraud, 2011; Narins, 2010; Palm, 2010). In the prospective studies/randomized clinical trials, the follow-up time ranged from 3 to 25 months (Brandt, 2011; Chen, 2015). In the retrospective studies, patients treated between 2000 and 2008 were evaluated (Table II) (Masveyraud, 2011; Fabi and Goldman, 2021; Palm, 2010).

Tabela II. Specific information about injectable PLLA treatment.

Author, year	**Purpose**	**Sessions/ intervals**	**Injection technique**	**Evaluation method**	**Follow-up/ Period**
Brandt, 2011	Correction of nasolabial wrinkles	1-4 sessions/ 3 weeks.	Bilateral injections in the nasolabial fold wrinkles.	Investigator Global Evaluations (IGE) scores	25 months
Bravo, 2020	Correction of facial sagging	1-5 sessions/ 28-121 days.	Retrograde injection fan technique at two bilaterally distinct insertion points.	Reports and analysis of three-dimensional pictures	90 days

Brown, 2011	Correction of nasolabial wrinkles	1-4 sessions/ 3 weeks.	Bilateral injections in the nasolabial fold wrinkles.	Subject Global Evaluation (SGE) and Subject Satisfaction scores	25 months
Chen, 2015	Volume correction in the middle third of the face	3 sessions/ 2 weeks (1ª and 2ª session) and 12 weeks (3ª session)	Fan technique in the middle third of the face bilaterally.	Analysis of three-dimensional pictures	48 weeks
Fabi, 2012	Facial rejuvenation (photoaging and sagging skin)	1-5 sessions/ 3-4 weeks.	Supraperiosteal injection using the technique of deposition in the temporal region or subcutaneous injection in the upper region of the face using the fan technique.	Subject interviews	-

Masveyraud, 2011	Rejuvenation and correction of facial volume	1-7 sessions/ -.	Subcutaneous injection in the middle third of the face.	Data from medical records	2000-2007
Narins, 2010	Correction of nasolabial wrinkles	1-4 sessions/ 3 weeks.	Bilateral injections in the nasolabial fold wrinkles.	Wrinkle Assessment Scale scores and subject interviews and case report forms	25 months
Palm, 2010	Volume correction	1-12 sessions/ 4-12 weeks.	Subcutaneous injection with the fan technique.	Patient satisfaction and incidence of adverse reactions	2003-2008

Main results and conclusions of the studies

The main results and conclusions of the included studies are summarized in the table below (Table III). Overall, this systematic review shows that injectable PLLA is considered an effective, safe, and long-acting agent for volumizing and biostimulating collagen (Brandt, 2011; Bravo and Carvalho, 2021; Brown, 2011; Chen, 2015; Fabi and Goldman, 2021; Masveyraud, 2011; Narins, 2010; Palm, 2010).

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Tabela III. Main results and conclusions of the included studies.

Author, year	**Main results**	**Conclusions**
Brandt, 2011	- The IGE scores were significantly higher in patients who received injectable PLLA compared to those who received human collagen. - The general improvement of nasolabial wrinkles with injectable PLLA was 100% three weeks after the final treatment, remaining above 85% until the 25th month. - Both groups had similar security profiles.	- The improvement in the IGE scores was greater with injectable PLLA than with human collagen in all periods evaluated. - The injectable PLLA continued to have a beneficial effect for up to 25 months.
Bravo, 2020	- 29.31% of patients reported pain, 10.34% reported ecchymosis and 3.44% developed a nodule. - No one had significant formation of bruising, edema or papules.	- Immediate reconstitution of PLLA has been shown to be safe, with a very low rate of adverse effects. - The immediate reconstitution of PLLA is a great asset for professionals, as it reduces clinical time and product loss.
Brown, 2011	- From the 3rd to the 13th month after the last session, the patient's global assessment score in the injectable PLLA group was higher compared to the human collagen group. - The SGE scores in the injectable PLLA group were 99% at week 3, 91% at month	- Treatment of nasolabial wrinkles with injectable PLLA resulted in greater global assessment and patient satisfaction than treatment with human collagen at 13 months. - Patients treated with injectable

	13, and 81% at month 25. In the human collagen group, scores decreased by 84%, from 96% at week 3 to 15% at month 13. - The Subject Satisfaction scores were significantly different between treatment	PLLA maintained improvements for up to 25 months after treatment.
Chen, 2015	- There was a significant increase in midface volume at all follow-up periods compared to pre-treatment volume. - There was no significant change in volume between each of the follow-up times.	Injectable PLLA is an effective, long-acting and volumizing agent, providing an increase in mid-facial volume from onset to at least 1 year after treatment.
Fabi, 2012	- 19% of patients reported edema, 17% bruising, 10% erythema, and 7% nodule formation after PLLA injections, with no nodule occurring after IPL. - During treatment with IPL, 12% of patients reported mild discomfort. - 86.7% of patients reported at least mild effects on facial rejuvenation with the PLLA + IPL combination, with 64.4% reporting good to excellent effects.	The combination of PLLA with IPL in facial rejuvenation is effective and safe.
Masveyraud, 2011	- The corrective effect was considered satisfactory by 91% of patients. - Delayed adverse reaction was present in 4.7% of patients. - Palpable and non-visible subcutaneous indurations were reported in 3.7% of patients. - 1% had multiple, deep and imperceptible nodules that can be	Injectable PLLA is a volumizing agent that allows for a correction of the natural aging process with few adverse effects.

	classified as granulomas.	
Narins, 2010	- The injectable PLLA significantly improved the mean scores of the wrinkle assessment scale in all evaluated periods. - Improvements with injectable PLLA (up to month 25) were significantly greater than with human collagen at month 3 and 13 post-treatment. - Mild to moderate adverse effects have been reported in the long term.	Injectable PLLA is well tolerated, effective and long-lasting (up to 25 months) for the correction of wrinkles in the nasolabial fold.
Palm, 2010	- The most common adverse effects was the formation of nodules (8.5%). Almost all nodules were palpable and only one was visible. - Overall, patients were satisfied, with 55% rating their correction from good to excellent. - 75% of patients, who performed 5 or more sessions, rated their correction from good to excellent. - 68% of patients would undergo the procedure with injectable PLLA again.	- PLLA is used to reverse the signs of aging, gradually correcting volume loss. - Patients should be aware of possible adverse reactions during treatment. Nodule formation is low, with most patients showing good to excellent correction.

Risk of bias assessment

The risk of bias assessment provides a qualitative synthesis of the studies. In this systematic review, the Cochrane Collaboration tool revealed that the three RCTs included had a low risk of bias in participant random sequence generation and a high

risk of bias in participant allocation concealment. A low risk was also attributed to performance bias (blinding of participants and professionals), detection bias (blinding of the outcome assessor), attrition bias (incomplete result data), reporting bias (selective reporting) and other bias (Figure 2) (Brandt, 2011; Bravo and Carvalho, 2021; Brown, 2011; Chen, 2015; Fabi and Goldman, 2021; Masveyraud, 2011; Narins, 2010; Palm, 2010).

DISCUSSION

Systematic reviews published in the area of facial cosmetics are scarce (Stojanovič and Majdič, 2019; Cunha et al., 2021). The literature brings together a range of in vitro and in vivo studies related to PLLA applications (Bravo and Carvalho, 2021; Ray and Ta, 2020). However, this is the first study to systematically synthesize the available evidence on the use of Sculptra® for facial rejuvenation.

The eligible studies for this investigation evaluated the use of Sculptra® for the treatment of facial sagging, correction of nasolabial wrinkles, middle third volumization or general facial aging. In all these treatment purposes, Sculptra® proved to be effective, long-lasting and safe, stimulating collagen production and improving the appearance, quality, volume and thickness of the skin (Brandt, 2011; Bravo and Carvalho, 2021; Brown, 2011; Chen, 2015; Fabi and Goldman, 2021; Masveyraud, 2011; Narins, 2010; Palm, 2010). Although the focus has been on the application of injectable PLLA to the face, several studies show that this substance can be recommended for the treatment of sagging skin

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in other body regions (Hart et al., 2015). PLLA is also a promising method in areas such as the neck, cleavage, hands, arms, abdomen and buttocks, improving body contour and appearance in a safe and lasting way (Jabbar et al., 2017; Haddad et al., 2019). This is likely due to the stimulation of collagen production, which triggers a gradual restoration of volume (Kim et al., 2019a; Haddad et al., 2019). More studies are needed to understand these effects.

The use of injectable fillers in soft tissue, including calcium hydroxyapatite, hyaluronic acid and PLLA, has grown exponentially in recent years (Kontis et al., 2018). The increasing popularity of these minimally invasive procedures is understandable, as they allow the correction of volume and contour of the face with signs of aging in a non-surgical manner and with good durability (Bass, 2015). Some included studies chose to compare Sculptra® to human collagen. This is because human collagen is an immunologically inert product with well-established efficacy and safety, not requiring a hypersensitivity test prior to treatment (Baumann et al., 2020). However, its durability is inferior to the other injectable fillers mentioned above. As expected, in all studies whose control was human collagen, Sculptra® showed better efficacy in correcting nasolabial wrinkles, with a prolonged effect and with minor adverse effects (Brandt, 2011; Brown, 2011; Narins, 2010).

The proper technique for the preparation and application of the injectable PLLA are critical factors for optimizing the results. This includes product reconstitution and hydration, application to specific areas under lo-

cal anesthesia and post-procedure recommendations. Although a product reconstitution time of 24 to 72 hours before application is recommended, there are current studies that propose an immediate reconstitution (Bravo and Carvalho, 2021; Baumann et al., 2020). A study included in this systematic review demonstrated the efficacy and safety of immediate reconstitution of Sculptra®. A prospective study with 26 patients who used this product with the purpose of biostimulating collagen in the face concluded that its immediate reconstitution proved to be safe, with a very low rate of adverse effects (Bravo and Carvalho, 2021). The advantage of this technique is the reduction of clinical time and product loss. However, well-designed randomized clinical trials must be performed to support these conclusions.

PLLA must be injected supraperiosteally in areas with bone support or in the subcutaneous tissue when there is no bone structure (Vleggaar et al., 2014; Lorenc, 2012). For supraperiosteal and subcutaneous application, the depot application and fan-retroinjection technique, respectively, are the most appropriate (Lorenc, 2012). The included articles corroborate these concepts (Brandt, 2011; Bravo and Carvalho, 2021; Brown, 2011; Chen, 2015; Fabi and Goldman, 2021; Masveyraud, 2011; Narins, 2010; Palm, 2010). Intradermal injections should be avoided as they are associated with an increased risk of developing papules or nodules (Lorenc, 2012).

The Sculptra® treatment continues until the patient is satisfied with the result. The number of sessions varies, but usually after 3 to 5 sessions satisfactory

results can be verified (Vleggaar et al., 2014). The "treat, wait and evaluate" rule is considered a good strategy to guide planning the number of sessions. Usually, it is recommended to schedule a reassessment for a possible new session between 4 and 6 weeks after the previous one (Xiong et al., 2020). Maintenance treatment is usually performed one year after starting treatment and requires fewer applications (Vleggaar et al., 2014). In the included studies, the number of sessions and the interval between sessions were quite heterogeneous (1-12 sessions; 14-121 days interval), which is a limitation of this review (Brandt, 2011; Bravo and Carvalho, 2021; Brown, 2011; Chen, 2015; Fabi and Goldman, 2021; Masveyraud, 2011; Narins, 2010; Palm, 2010).

Cutaneous injection procedures usually cause some discomfort, erythema, edema or hematoma usually self-limiting (Werschler and Weinkle, 2005). Injectable PLLA has been used for decades and is usually associated with minor adverse effects, being considered a safe substance (Alijotas-Reig et al., 2009; Bartus et al., 2013). The authors presented in this systematic review contribute positively to this definition of safety. However, although uncommon, more serious adverse effects have been reported. Papules, nodules and granulomas are the most frequent effects in clinical situations. Non-inflammatory papules and nodules have a good prognosis and easy resolution, while inflammatory nodules and granulomas can become chronic and difficult to resolve (Alijotas-Reig et al., 2009; Bartus et al., 2013). Due to PLLA microparticles, the most common adverse effect is papules and nodules,

being caused by the material accumulation with inadequate reconstitution. Its frequency can be minimized with good behavior in the application technique and massage protocols (Narins et al., 2010; Palm et al., 2010).

As discussed earlier, injectable PLLA alone is able to provide good results in facial rejuvenation. Despite this, in the last decade there has been evidence of the association of PLLA with other cosmetic procedures (Friedmann et al., 2014). Our systematic review evaluated the retrospective study, where 90 patients were treated with Sculptra® associated with intense pulsed light immediately before and 6 days after treatment (Fabi and Goldman, 2021). Facial aging involves the interaction of numerous simultaneous factors, thus, it is convenient that patients need different and concomitant therapeutic modalities (Cotofana et al., 2016). The treatment of photodamage contributes substantially to the facial rejuvenation and intense pulsed light is usually indicated for this purpose (Friedmann et al., 2014). When combined with Sculptra®, patients seeking skin photorejuvenation can also obtain improvements in skin sagging and facial volume (Fabi and Goldman, 2021). There are also reports of injectable PLLA associated with the application of micro-focused ultrasound and other injectable facial products, specifically hyaluronic acid, calcium hydroxyapathy and neurotoxins (Friedmann et al., 2014; Lorenc et al., 2014). The combination of these three injectables for the purpose of facial rejuvenation was also described in the series of this study, providing effective and lasting results and corroborating the pre-existing literature.

Although this investigation has an unprecedented contribution, some limitations are evident. Initially, the small number of clinical studies on the application of Sculptra® for facial rejuvenation makes the results of the systematic review biased. Furthermore, among the clinical studies, only three were randomized clinical trials, and therefore, subject to assessment of the risk of bias using the Cochrane Collaboration tool. Despite this, their quality was considered good, with low risk of bias in all domains, except in the domain of concealment of the participants' allocation.

CONCLUSIONS

This systematic review shows that the use of Sculptra® for facial rejuvenation is effective, safe and long-lasting. The correction of sagging skin, volume and facial contour occurs through a local tissue reaction, which promotes a gradual neocollagenesis and a consequent volume restoration. Despite the clinical relevance of this investigation, limitations were observed. Thus, it is suggested to performed well-designed and high-quality randomized clinical trials for future investigations.

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