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Biosafe Technique–Facial Biostimulation with 10% Polymethylmethacrylate Technical Note

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ABSTRACT

Among the different types of biostimulators used in the global market, polymethylmethacrylate (PMMA) biostimulation has been considered the most effective in truly stimulating clinically visible neocollagenesis.Many histological and clinical studies have also proven the product's safety, in addition to its efficacy.The described technique proposes the use of 10% PMMA for the treatment of skin flaccidity caused by the aging process at different degrees. This publication suggests a standardization in five pre-determined regions that most frequently require the clinical effect of neocollagenesis and reviews the ideal anatomical plane and vascular risk zones to enhance the safety of product application.The proposed nomenclature refers to the safety of the product and the suggested protocol, supported by nearly 40 years of use in medicine.

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Introduction

According to the annual statistics released by The Aesthetic Society, a total of 1,857,339 soft tissue filler procedures were performed in the United States in 2021, representing a 29% increase compared to 2011 (over 10 years of research) [1-12]. Among these procedures, there are two distinct types: true fillers (the most common composed of hyaluronic acid) and those considered "biostimulators" for inducing neocollagenesis or stimulating the extracellular matrix through direct or indirect fibroblast stimulation [13-18]. Used as collagen production inducers, their effect combines rejuvenation and beautification, as collagen is the body's main structural protein, responsible for dermal densification, which clinically translates into firmness and improved texture.

Currently, several products are used as biostimulators in the market, which can be broadly divided into absorbable and non-absorbable types [8]. Among the absorbable ones, polylactic acid, calcium hydroxyapatite, polycaprolactone, and polydioxanone stand out as safe options for neocollagenesis [1-4,14,15,17-20].

The current debate revolves around the true ability of absorbable products to induce clinically significant collagen formation. This is because the entire chain of cellular reactions leading to neocollagenesis takes time to occur, often requiring weeks or even months for the initial collagen production. Furthermore, this newly formed collagen must undergo a remodelling or maturation process to become a type able of improving flaccidity and texture of skin treated with biostimulators [21-27].

Additionally, the physical effects of neocollagenesis require a substantial amount of collagen, making it necessary to achieve a more robust production of this structural protein for significant clinical outcomes.

Among non-absorbable options, PMMA stands out for its potency, long-lasting results, and sustained neocollagenesis, which has been clinically and histologically proven by extensive literature [27-34]. PMMA is a synthetic, biocompatible, inert, non-allergenic, and particulate polymer that has been used in several medical fields, such as medical implants, orthopaedics, and suture materials, for over four decades [6,10]. It remains biologically inert and has been approved for use in Brazil by ANVISA. Its safety is directly linked to a correct injection technique, the quantity used, and an understanding of the product's behaviour over time.

Microparticles induce a controlled tissue inflammation with the recruitment of neutrophils and macrophages, along with the release of cytokines by resident cells at the application site. Subsequently, macrophages become activated, leading to the attraction and differentiation of myofibroblasts and fibroblasts, which begin collagen production approximately one week after application. This process provides structural support and generates new collagen fibers at the injection site. Over the following months, the collagen undergoes a remodeling process, eventually maturing into stable collagen with a slow turnover rate of approximately 15 years [34].

This study proposes a facial biostimulation technique using 10% polymethylmethacrylate (PMMA) through a method called BIOSAFE. The name suggests a safe biostimulation approach, taking into account the risk areas described in this study while adhering to technical guidelines, including smooth cannula gliding, high gauge, delicate maneuvers, small boluses of product evenly distributed across the treatment area, and a uniform and homogeneous product dispersion.

Materials and Methods

Indications

The indications for the procedure include facial flaccidity of varying degrees, as classified by the Facial Laxity Rating Scale (FLR), fine wrinkles in lateral facial regions, medial facial ptosis with evident nasolabial and labiomental folds, and facial ptosis leading to the formation of jowls and aesthetic alterations of the mandibular line [35]. Patients are photographed following a standardized aesthetic photography protocol to ensure better clinical evaluation of the results [36].

Technique

The product used is LINNEA SAFE 10%, a gelified suspension containing 10% PMMA particles dispersed in an aqueous medium. Its viscosity is optimized by the suspending agent hydroxyethylcellulose, along with methylparaben, propylparaben, and water for injection.

The product is supplied in a box containing ten 1 ml syringes. One box is used per side, following a standardized approach of 5 ml per side. However, individualized treatment is crucial, as it depends on the degree of flaccidity, expected results, therapeutic proposal, and the patient's budget approval.

The use of a 1 ml syringe facilitates the homogeneous distribution of the product and the precise injection of small aliquots. The standardized injection volumes—0.1 ml per line and 1 ml per fan pattern—ensure an even and adequate distribution of the material.

Marking

The treatment areas marked include the temporal, zygomatic (lateral and medial), preauricular, jaw angle, and lateral chin regions, as shown in Figure 1.

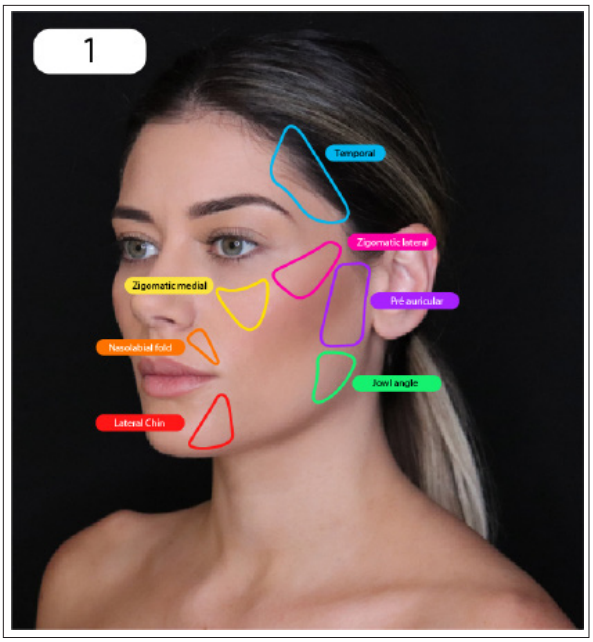


Figure 1: Legend: Facial Regions for BIOSAFE Treatment

Three entry points are marked, as described in Figure 2.

1. Zygomatic arch, 3 cm anterior to the pretragal line.
2. Anteroinferior chin line, 1 cm lateral to the gnathion.
3. Most distal point of the nasolabial fold.

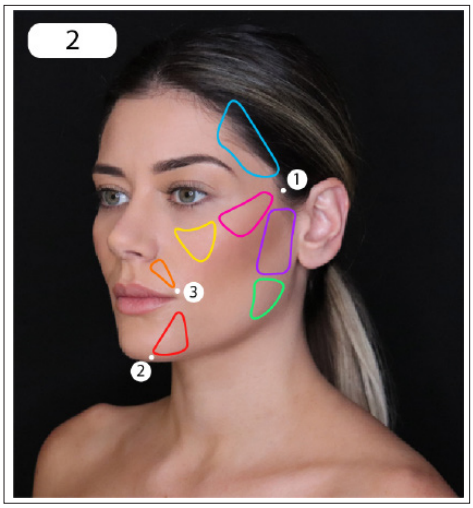


Figure 2: Legend: Entry Point Marking Regions

Application

The entry points are infiltrated with 0.1 to 0.2 ml of 2% lidocaine with a vasoconstrictor for anesthesia. The entry punctures are made using a 21G needle. From each entry point, the described technique recommends 10 lines per fan pattern, 0.1 ml per line, 1 ml per fan, 5 fans per hemiface with a total of 10 ml per face. A 22G x 70 mm cannula should be used for the prescribed retroinjections.

The suggested quantities are detailed in Table 1 and Figure 3.

Table 1

Injected region	Volume
Temporal	1 ml
Zygomatic	1 ml
Preauricular	1 ml
Jaw angle	1 ml
Nasolabial fold	0.5 ml
Lateral chin	0.5 ml
TOTAL	5 ml per side

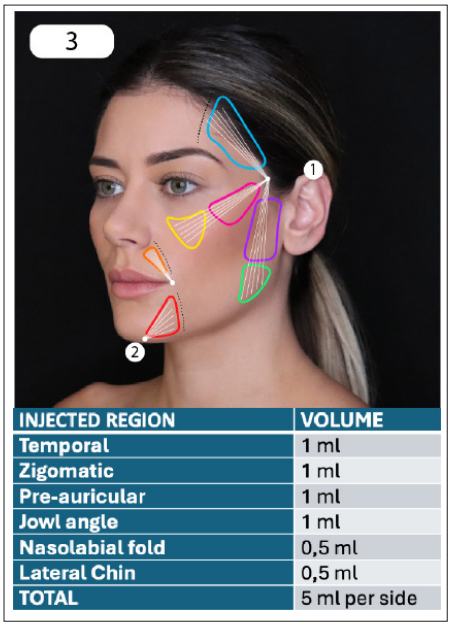


Figure 3: Legend: Quantity Injected Per Treated Facial Region

The recommended treatment areas for the BIOSAFE technique correspond to regions that experience volume loss due to aging and the inferomedial tissue descent caused by gravity over time.

With the exception of the nasolabial fold and the lateral chin region, which also undergo significant volume loss, the areas that require the highest product volume are lateral to the functional ligament line [37]. This imaginary line marks the transition between the "mobile face" and the "fixed face" (Figure 4).

Figure 4: Legend: Transition between the mobile face and the fixed face, marked by an imaginary ligament line that traces the sequence of ligaments separating these two facial zones. From top to bottom temporal ligament adhesions, lateral orbital thickening, zygomatic ligament, masseteric cutaneous ligament and mandibular ligament.

Starting from each entry point, each treatment area should be marked and divided into five equidistant lines to ensure homogeneous coverage. Each injection line should receive a total of 0.2 ml.

1 ml syringes should be used to deposit 0.02 ml aliquots per bolus, along the retroinjection lines (Figure 5).

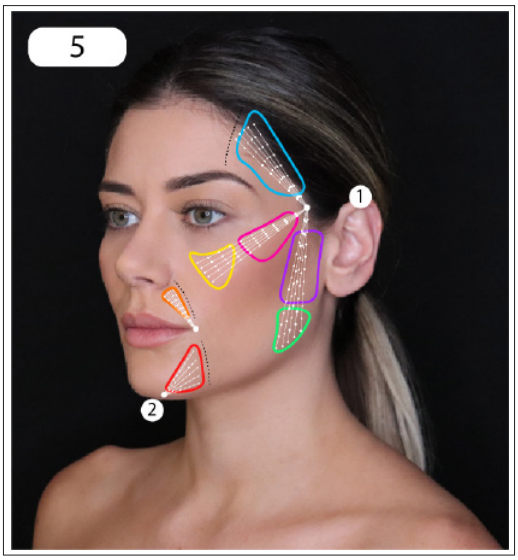


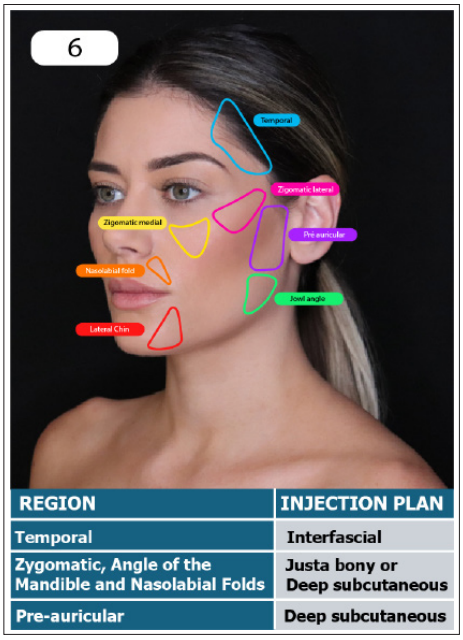
Figure 5: Legend: Injection Volume Per Aliquot, Per Line, and Per Region

The injection plane for the BIOSAFE technique varies depending on the region. In the temporal Region, the interfascial plane is the most appropriate because it's a closed compartment, reducing the risk of product migration to the cheek [38]. Additionally, the risk of intravascular injection is lower due to the scarcity of blood vessels in this plane. A more superficial injection in this area could lead to visible nodules, given the thin subcutaneous tissue.

In the zygomatic, jaw angle, and nasolabial fold regions, the juxta-osseous or deep subcutaneous plane can be used, depending on the patient's skin thickness. In patients with thicker soft tissue, the deep subcutaneous plane may be selected, making the product more visible and enhancing both volumetric and skin texture improvement effects. In slimmer patients, a deeper injection plane

should be chosen to create a subtler volumetric effect and a more natural aesthetic result.

In the preauricular and lateral chin regions, the deep subcutaneous plane is recommended. In the preauricular region, the parotid gland is located deep to the parotid fascia, just below the subcutaneous layer. In the lateral chin region, the Depressor Anguli Oris muscle lies directly beneath the subcutaneous layer. Additionally, this plane is easier to access.



REGION	INJECTION PLAN
Temporal	Interfascial
Zygomatic, Angle of the Mandible and Nasolabial Folds	Justa bony or Deep subcutaneous
Pre-auricular	Deep subcutaneous

Figure 6: Legend: Injection Planes for Each Facial Region.

The cannula should glide using light and smooth movements. If an obstacle is encountered, the injector should slightly shift the cannula laterally, finding a path free of adhesions. Typically, these obstacles are connective tissue septa through which blood vessels pass, representing a higher risk of vascular injury [39]. It's recommended to stop the injection near the entry point to avoid product accumulation in that area.

Video: Biosafety Technique for Facial Bio-Stimulation

https://vimeo.com/829928589/779cea6dba?share=copy

Immediately after injections, a gentle massage is performed in the treated areas to help with product distribution. Patients should continue this daily for the next 7 days. Small adhesive dressings are placed on the entry points and should be kept for 24 hours to prevent contamination. Mild to moderate analgesics are prescribed, along with medium-potency corticosteroids to minimize the initial oedema, which is common in the first few days.

A 3-month interval is advised before subsequent applications to assess the clinical response, including new collagen formation and the volumetric effects of the procedure. Two to 3 sessions are usually enough for treating skin flaccidity and volume restoration. Annual evaluations and clinical and aesthetic management are recommended to determine the need for additional applications, considering the ongoing nature of the aging process.

Results

The patients included in this report underwent three sessions of the BIOSAFE protocol, meeting the inclusion criteria. A detailed anamnesis was conducted during the medical consultation to rule out any clinical signs or symptoms that would contraindicate aesthetic procedures. Figure 7 presents the results of three patients treated with three BIOSAFE sessions, performed at two-month intervals. The "after" photo was taken one year after the first session. A significant improvement in skin flaccidity and overall skin quality was observed progressively with the sessions.

No cases of infection, nodules, ischemia, or other relevant adverse effects were reported. Only mild pain, bruising, and localized swelling were observed, which subsided within four days after each session.

Figure 7: Legend: Results of Patients Treated with Three BIOSAFE Sessions at Two-Month Intervals

Discussion

The aging of tissues during the senescence process is due to multiple factors, including mitochondrial damage, hormonal senescence, oxidative stress, and sun damage to the skin. These changes lead to the downward and inward displacement of facial tissues, accentuating natural folds and depressions such as the nasolabial and labiomental sulcus. Additionally, they alter fat distribution, modify the facial contour, and highlight fine wrinkles, which demonstrate the loss of structural dermal support due to the depletion of collagen, elastin, and hydration.

The use of biostimulators for treating facial skin flaccidity has been used in facial and body aesthetics in recent years. Their ability to stimulate cellular activity enhances the production of collagen and elastin, restoring the skin's structural support while improving texture and glow. As a secondary effect, this also results in firmer skin, reducing visible signs of facial flaccidity.

Absorbable synthetic polymers, such as poly-L-lactic acid, calcium hydroxyapatite, polycaprolactone, and polydioxanone, gradually degrade over time lasting around 14 to 24 months, depending on the product. During their time in the tissues, these materials chemically and physically stimulate collagen and elastin-producing cells, leading to collagen deposit, which improves skin firmness. Their biological performance has been extensively validated in the scientific literature, as have the potential complications associated with their use [15-21]. Although these products effectively provide temporary results, their limited longevity requires reapplication approximately after one year to maintain their effects.

The aesthetic market is in constant search of longer-lasting and more effective products with durable biological performance, cost-effectiveness, safety, and efficacy. The search for the ideal product is ongoing, with three key criteria standing out in this pursuit: biological performance, efficacy and longevity.

A current concern is the actual ability of absorbable products to induce the formation of clinically significant collagen. Since the entire cellular reaction cascade that leads to neocollagenesis takes weeks or months to begin, the initial collagen production is slow. Furthermore, this collagen must undergo a remodelling or maturation process to transform into type I collagen, which is the primary contributor to improved skin flaccidity and texture when using biostimulators. Additionally, for the physical effects of neocollagenesis to be visibly significant, a greater amount of collagen is required, with the need of a more robust production of this structural protein to achieve clinically relevant outcomes.

Polymethylmethacrylate (PMMA) stands out among non-absorbable biostimulators due to its potency, long-lasting results, and sustained neocollagenesis, evidenced both clinically and histologically. Several studies have confirmed its histological action and positive clinical effects [27-34]. PMMA microspheres, with a 40-micrometer diameter, were developed in the 1980s when the aesthetics industry sought a soft tissue filler with greater durability than bovine collagen, which was widely used at the time but had only temporary effects. PMMA-based products were marketed in Europe from 1994 to 2002, introduced in Brazil in 1996, and launched in China in 2002 under the name Artecoll [40]. In the United States, they began to be used from 2006, now under the brand Bellafill [41].

In Brazil, advancements in production and filtration technology resulted in a more homogeneous and purer product, meeting regulatory requirements. Currently, two products are approved by ANVISA: Linnea Safe® (Lebon Laboratory, Porto Alegre, Brazil) and Biossimetric® (MTC Medical) [42]. However, Linnea Safe® leads the national market share and is considered the industry benchmark in technology and quality. Although all PMMA microspheres used today are uniform in size and free of impurities, their surface still provides sufficient roughness to allow macrophage adhesion [43].

In 2006, Lebon Laboratory became the first Brazilian company to manufacture PMMA with 40-micrometer microspheres, adopting advanced technology and strict quality control standards. Initially marketed as New Plastic, the product was later renamed Linnea Safe®. In 2014, Linnea Safe® was the only product approved by the Ministry of Health for sale in Brazil due to its purity and consistency in particle size.

The product chosen for this study uses hydroxyethyl cellulose (HEC) as a gel carrier instead of carboxymethylcellulose (CMC). HEC is a cellulose derivative widely used in pharmaceutical formulations, just like CMC. However, HEC can retain more moisture than CMC, depending on experimental conditions. This is one of the key differences between the two and a primary reason why HEC was selected for the pharmaceutical development of Linnea Safe® [44]. HEC is absorbed within the first week, leaving the PMMA microspheres clustered and fixed at the injection site. In one week, macrophages begin to invade the outer edges of most microspheres and, after three months, all microspheres become anchored in the tissue by two or three macrophages. At this stage, fibroblasts migrate into the extracellular matrix, producing collagen and forming capillaries for nutrition and tissue renewal. At nine months, most macrophages disappear or undergo apoptosis, while fibroblasts, collagen fibres, and capillaries fill the spaces between the microspheres. Histological studies show that after ten years, all microspheres are interwoven with fibroblasts, collagen fibres, arterioles, and small veins, transforming the injected PMMA into a "living implant" that is well integrated into the tissue [1].

In 2016, Costa E et al. published a study aimed at analyzing the size of PMMA microspheres in three products commercialized in Brazil and comparing their size homogeneity [45]. The study found that Linnea Safe® had a greater particle size uniformity compared to the other two analyzed products. In the histological analysis, the authors observed connective tissue deposit between the microspheres after 15 days. By 30 days, the cellular reaction was non-granulomatous, with a predominance of mononuclear infiltrate, muscle tissue reorganization, and increased collagen depositi between the microspheres. These findings were similar to previous studies by Lemperle and Jesus [11,46]. The authors concluded that Linnea Safe® PMMA behaved as a stable biomaterial, preventing phagocytosis and product migration, resulting in localized and controlled inflammation. For these reasons, Linnea Safe® was chosen as the preferred product for the protocol.

In 2008, Piacquadio, Smith, and Anderson (17 PMMA cases) also compared different PMMA formulations and found significant morphological differences, particularly in microsphere size [47]. The authors concluded that these morphological differences led to different clinical outcomes, directly impacting product safety. They also warned that seemingly similar products may differ significantly in terms of quality and safety.

Other protocols for biostimulation with PMMA have already been published, recommending the use of the product at 30% dilution with saline solution [48]. However, the current recommendation is to use particulate products in their original formulation, without modifications, since untested alterations may lead to changes in the physicochemical parameters of the formulation, such as pH value, electrostatic characteristics, and viscosity, potentially causing unforeseen effects and inadequate patient responses, ultimately compromising its efficacy and safety.

Furthermore, in Lemperle's 2010 publication on the mechanism of action of PMMA microspheres, the author demonstrated histologically the importance of keeping the spheres suspended in a gel or aqueous vehicle that ensures their proper physical separation during the physicochemical processes that occur in the first few days after injection [11]. According to the author, such separation is crucial for the microspheres to properly fulfil their histological role without gathering. Excessive particle aggregation, which could be caused by dilution with saline solution or other liquid mediums, resulting in product adulteration, may predispose patients to nodule formation due to product accumulation (Figure 8).

Figure 8: Legend: Well-Distributed Spheres in a Gel Vehicle. Spheres Adhered in a Gel + Water Vehicle, Showing Mixture Heterogeneity

Both biostimulation effects occur with the BIOSAFE protocol: volumizing effect and skin flaccidity improvement. The volumizing effect results from the of endogenous tissue formation around the PMMA microspheres, which gradually replace the carrier gel over time. In his histological studies, Lemperle reported that 80% of the carrier gel, specifically bovine collagen, in the PMMA-based product studied at the time (Artefill) was replaced within 1 to 3 months by autologous tissue,as shown in Figure 8 [38]. Although there is no data in the literature regarding an equivalent replacement for the 10% PMMA formulation, it's estimated that a similar volumetric substitution occurs, given the clearly noticeable clinical effects. The effect of skin surface improvement, clinically observed as a reduction in skin flaccidity and fine wrinkling, occurs due to endogenous collagen production, which has been extensively documented in the literature through histological analyses (Figure 9) and clinical studies [1,2,3,5,8]. Additionally, there is intense vascularization of the newly formed tissue, which ensures long-term nourishment and maintenance (Figure 10).

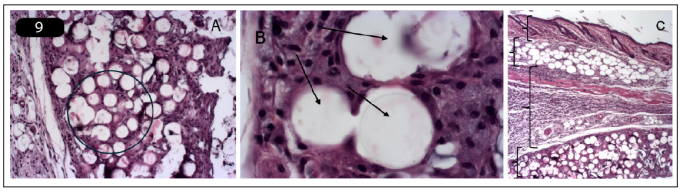


Figure 9: Legend:

A: PMMA Particles Surrounded by Cellular Infiltrate (Black Circle)

B: Detailed View of each Microsphere Encapsulated by Cellular Infiltrate

C: Skin Layers from Superficial to Deep: Dermis, Hypodermis, Large Cellular Infiltrate, and 10% PMMA Microspheres

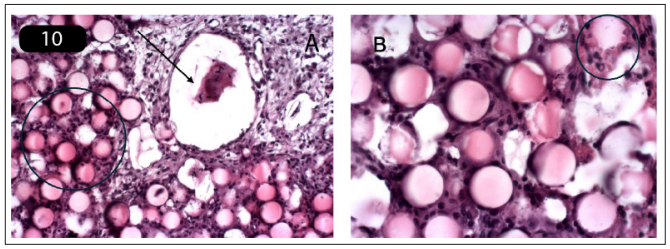


Figure 10: Legend

A: Blood Vessel (Black Arrow)/Haemacious – Highly Vascularized Tissue (Black Circle)

B: Highly Vascularized Tissue Rich in Red Blood Cells (Black Circle)

Regarding the injection technique, some considerations about vascular risk are important and related to the safety of the BIOSAFE protocol. Near the entry point at the zygomatic arch, the transverse facial artery travels inferiorly along the lower margin of the zygomatic arch. Superior to it, the zygomatic-orbital artery travels more superficially in the subcutaneous tissue. It's important to insert only the bevel of the needle in order to avoid vascular injury and hematomas at this entry point.

Lateral to the chin entry point, branches of the submental and horizontal mental labial arteries travel within the subcutaneous tissue. Similarly, it's recommended to make the entry point in a superficial plane. In the nasolabial entry point region, the facial artery travels in an ascending and oblique path towards the inner corner of the eyes. In this area, it's located in an intermediate plane, making it equally important to establish the entry point in a superficial plane to avoid unnecessary hematomas.

Regarding the trajectories of retro-injections in the temporal region, it's important to highlight that the frontal branch of the superficial temporal artery runs along the posterior surface of the superficial temporal fascia, a very thin tissue layer that is firmly adhered to the subcutaneous tissue. It's essential to feel the deeper, firmer, and more mobile deep temporal fascia and reach a gliding plane where the blunt tip of the cannula can rest and move smoothly. After emerging 1 cm above and anterior to the tragus, from the superior pole of the parotid gland, the frontal branch moves anteriorly, following an oblique trajectory towards the forehead, positioning itself approximately 2 cm above the eyebrows. Once again, ensuring the smooth passage of the cannula along this path while maintaining the anatomical plane is crucial to prevent vascular injury and embolization. This is particularly important considering that the frontal branch of the superficial temporal artery anastomoses with branches of the supraorbital artery in its ascending path along the forehead, which poses a risk of amaurosis in the event of retrograde injection of the product [49].

Regarding retro-injections in the lateral and medial zygomatic region, a risk area is located 1 cm lateral and 1 cm inferior to the exocanthion, which is the emergence point of the zygomaticofacial pedicle [50]. This pedicle exits the skull through the zygomaticofacial foramen in the zygomatic bone. The zygomaticofacial artery is a branch of the lacrimal artery, which

itself is a direct branch of the ophthalmic artery. Embolization of this vessel, with retrograde migration of the filler into the trunk of the ophthalmic artery, could lead to amaurosis due to obstruction of the central artery of the retina.

Another risk area is the preauricular region, which corresponds to the anatomical location of the parotid gland. Caution must be taken in this region to maintain the correct anatomical plane of injection and avoid injecting into the parotid gland. The subcutaneous plane in this area is rich in connective septa, making cannula progression less smooth. However, if the injection is in a deeper plane within the parotid gland, the cannula's movement becomes significantly more rigid, preventing smooth gliding and indicating an incorrect plane.

Another point of caution is the transverse facial artery, which follows an oblique trajectory from lateral to medial and superior to inferior. It's always located below the zygomatic arch, specifically between the arch and Stensen's duct, forming a linear path connecting the tragus to the oral commissure. For most of its course, it runs in a deep subcutaneous plane, becoming more superficial approximately 3.5 cm below and lateral to the exocanthion.

Regarding the risk of nerve injury, the fronto-temporal branch of the facial nerve travels between the superior attachment of the ear and the outer corner of the eyebrows, crossing the zygomatic arch approximately 2 cm from the lateral end of the eyebrows. In this region, it's located in a subcutaneous plane, which is particularly thin, making it especially susceptible to injury. The marginal mandibular branch of the facial nerve runs along the lower margin of the jaw, crossing it slightly lateral to a vertical line extending from the oral commissure. Therefore, it lies outside the treatment area proposed by this technique.

Conclusion

The authors describe a facial biostimulation technique using a PMMA-based product called BIOSAFE, specifically referring to a product available in the Brazilian market: Linnea Safe®. They highlight the reasons for choosing this product and propose technical safety manoeuvres to achieve effective and safe clinical results. The study presents another option for long-lasting facial biostimulation, as the aesthetic market is becoming increasingly demanding and currently seeks more effective and longer-lasting procedures.

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