Medicon Dental Sciences
Volume 4 Issue 1 January 2024
Article Type: Case Report
ISSN: 3008-2609

Use of Plasma Gel as Autologous Collagen Biostimulator with Simplified Technique: Case Report

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Received: December 23, 2023; **Published:** December 29, 2023

DOI: 10.55162/MCDS.04.064

Abstract

A bibliographic survey was carried out on PRP and plasma gel and their derivations in PUBMED and Google Scholar to date and a clinical case study was carried out in order to provide a technical and scientific basis for the use of Plasma gel as autologous facial collagen biostimulator and clinical verification of its efficiency. After carrying out this study and analyzing the clinical results, Plasma gel and PRP used as autologous collagen biostimulator improved acne scars and skin density, a simple technique with no complications. The results were evaluated clinically, by comparative photographic analysis and patient satisfaction. It was concluded that this technique proved to be efficient and safe for facial rejuvenation.

Keywords: PRP; platelet-rich plasma; plasma gel; PGRF; autologous platelets

Introduction

Skin aging is a dynamic process accompanied by phenotypic, structural and functional changes. Facial ageing is also commonly associated with wrinkles, folds, loss of volume, elasticity and laxity of the skin due to functional changes in the components of the extracellular matrix [1].

In the last two decades, the demand for minimally invasive facial soft tissue augmentation and rejuvenation procedures has increased, due to the aging of the population, and an increase in the importance of skin as a youthful appearance [2].

There is a wide range of fillers on the market, but the most commonly used fillers are temporary or semi-permanent products, which include hyaluronic acid (HA), calcium hydroxyapatite and poly-L-lactic acid [2].

The evolution of skin care towards personalized treatment requires placing greater emphasis on patient expectations. Personalized medicines offer the potential to develop therapies that meet the patient's needs to ensure the best care and response. This progress has driven researchers to develop new products that combine biological and autologous criteria [3].

Platelet-rich plasma is a safe, autologous blood product that contains a high concentration of platelets and leukocytes. Platelets, growth factors, leukocytes and plasma are fundamental fibroblast and proliferation agents. Leukocytes plasticity, reparative qualities, cross-linking between cells and ability to orchestrate diverse outcomes are receiving considerable attention in scientific research. Fibroblasts are able to migrate and proliferate in the tissue around the wound and subsequently deposit granulation tissue, which improves healing. Fibroblasts also have anti-aging benefits. Clarification of the role of leukocytes in tissue repair has led to a new ap-

proach to tissue regeneration and the formation of a new therapeutic modality, namely immuno-regenerative medicine [4].

PRP (Platelet-Rich Plasma) is obtained by centrifugation that separates the plasma, leukocytes and platelets from the red blood cells to form a clot, a red rim and a layer of plasma in a density gradient of the whole blood. Just above the red rim contains PRP (Platelet-Rich Plasma) and is suspended in a small amount of plasma to form PPP (Platelet-Poor Plasma) which contains beneficial proteins, insulin-GF (IGF) and a low number of platelets [5].

In recent years, autologous plasma preparations have been widely used in various medical situations. Numerous studies are attempting to separate platelet-rich plasma (PRP) and platelet-poor plasma (PPP), to enable valuable use of their properties [5].

PRP contains a large amount of growth factors that are vital for initiating and accelerating the wound healing process and tissue homeostasis. It has been used successfully in various aesthetic fields and skin rejuvenation [4].

Plasma gel is another plasma formulation rich in fibrin and proteins in gel state that provide volume and stability at the injection site 6. Plasma gel is suggested for soft tissue augmentation as a semi-solid, easily injectable material that generally meets the requirements of safety standards [7].

Recently, a new injectable gel based on PRGF (Plasma Rich in Growth Factors) has been developed to overcome the limitations associated with the fibrin retraction process and provide long-term shape and volume stability. This new injectable PRGF gel offers desirable mechanical properties for 3D cell growth and provides a sustained release of biologically active molecules [8].

During the follow-up period of a clinical examination study [3], 3D-topographic imaging was consistent with the rheological results as the PGRF gel was able to smoothly and naturally follow the mechanics of skin movements associated with dynamic facial expressions [3].

The production of platelet-rich plasma gel involves low-cost materials, both for collection and preparation of blood, allowing universal access to the treatment [9].

The consistency and autologous nature of the plasma gel biological filler have greater patient acceptance compared to fillers with hyaluronic acid [10].

The purpose of this study is to use plasma gel as an autologous collagen biostimulator, following scientific protocols and verifying its action in improving skin quality and acne scars through clinical evaluation of a clinical case.

Literature Review

The changes in the skin during aging, the advances in research into the molecular mechanisms that lead to these changes and the treatment strategies aimed at preventing or reversing skin aging were studied. A conclusion was reached that both intrinsic and extrinsic structural changes in aging skin, the main molecular mechanisms proposed to explain these phenotypes, and advances in treatment research on aging skin were caused by the comprehensive effect of different mechanisms, and showed the difficulty in developing an integrated theory to attach different models together. Ambiguity in the molecular mechanism of skin aging, as well as controversy in viewpoints, have slowed down the progress of therapy, although some therapeutic attempts have proven to be effective. As people's demand for aesthetics increases, more research efforts must persist to fully elucidate the molecular basis of the deteriorative changes during skin aging [1].

The main types of fillers commonly used, considering the complications associated with each of these products, were surveyed through a systematic review. The PubMed database (National Library of Medicine) was searched for various types of facial fillers, including commercial names, between January 1, 2000 and January 1, 2013. The titles of the articles were screened and only studies aimed at determining the mechanism of action and histopathology of the complications were included. As a result of the selection

criteria on biological mechanisms, 109 manuscripts were identified and the mechanisms of action of short and long-term degradable as well as permanent fillers were reviewed. Hyaluronic acid fillers, which are the most commonly used, form a fibrous capsule and induce new collagen to a limited extent. Polylactic acid and calcium hydroxylapatite are semi-permanent fillers that provide long-term restoration of tissue volume by stimulating fibroblasts and establishing a matrix of collagen and elastic fibers. Polymethylmethacrylate is the only one approved by the FDA as a permanent implant that is held in place by encapsulation, providing a structure on which the dermis can recover its original thickness. From this review, it was concluded that soft tissue augmentation products are variable and no product can be considered the most effective or ideal. An understanding of the biological mechanisms can help guide aesthetic professionals in choosing the most appropriate product from the various options available, minimizing the occurrence of complications [2].

The mechanical and biological properties of a new injectable gel based on platelet rich growth factor (PRGF) technology that has been developed to provide shape and volume stability, which can be customized into low (LVG) or high viscosity (HVG) gel forms to meet different dermatological requirements and the clinical efficacy and safety of this autologous procedure were also evaluated in this work. The methodology used was to determine the growth factor content and biomechanical properties of both gel forms and to measure the biological proliferative capacity of human dermal fibroblasts *in vitro*. Clinically, the performance of more than ten patients was analyzed using standardized macro lens photographs, 3D topographic images and ultrasound analysis of the periocular and nasolabial areas [3]. As a result, both types of gel showed similar growth factor concentrations. HVG showed a higher stiffness profile indicating its suitability for deeper tissue defects while LVG showed optimal rheological characteristics for superficial volume. Both gels showed remarkable biostability after catalytic enzyme degradation. Both forms significantly increased the mitogenic activity of dermal fibroblasts. All patients reported being very satisfied and showed excellent clinical results after one month. The overall clinical improvement was maintained for 16 weeks. At the end of the study, ultrasound examination revealed a skin regenerative effect. There were no adverse events and it was concluded that autologous platelet gels have excellent mechanical and bioactive properties and allow for moderate wrinkle reduction and efficient facial volume replacement with natural results [3].

A bibliographic survey was carried out with searches using PUBMED, The Cochrane Library and MEDLINE using the following search terms: platelet-rich plasma, leukocyte-rich platelet-rich plasma, leukocyte-poor platelet-rich plasma, platelets, plasma, fibrin, growth factors, leukocytes, mononuclear cells, monocytes, macrophages, neutrophils, lymphocytes, fibroblasts, myofibroblasts, regenerative medicines. In addition, the following terms were searched in the context of regenerative medicine: tissue regeneration, stem cells, collagen biostimulation, wound healing, burns, burn treatment, scar, scar revision, wound healing, tissue repair, keloid, hypertrophic, incision wound, with studies from 1970 to 2018. After analyzing the studies surveyed, it was concluded that there is a scarcity of data on leukocytes in PRP and for those that do exist most have presented these immune cells as catabolic, or neglected to classify them, and have not yet been fully appreciated in their critical influence on tissue regeneration. In summary, the studies have presented different, undefined methodologies, complex processing, uncertain cellular parameters, insufficient data, a lack of a translatable relationship between platelet concentrations and platelet gel supernatants along with inconsistent results. Consequently, this allowed for unfair comparisons, misinterpretation of results and provided bias. Researchers will best serve the scientific medical community by adhering to reproducible methodologies and reporting accurate clinical data. However, studies have shown clear evidence that PRP affects fibroblast proliferation and migration and that this varies according to the dose [4].

A search was made of all the definitions of PRP with the aim of finding a terminological consensus and pleading for a more serious characterization of these autologous products. In this research, the researchers were aware of the complex nature of these living biomaterials in order to avoid misunderstandings and misinterpretations. As a conclusion with the aim of seeking a terminological consensus and not playing with words, but influencing the thoughts of all researchers in the field: it is no longer acceptable to see scientific articles on these technologies where the exact content of the products tested is unclear, and their final state (activated or not). Without a better understanding of the polymorphic and adaptive nature of these products, the field of platelet concentrates may finally lose much of its credibility, showing uncontrolled contradictory results (often easily explained by the presence of leukocytes and other uncharacterized parameters), and all its potential for the future will be lost. Understanding the biomaterial or believing in the magic

of growth factors? The future of the research field depends on this choice [5].

A biomaterial for clinical practice that is autologous, safe and easy to prepare in situ has been presented in the literature. The nature of this hydrogel was based on the thermal polymerization of plasma proteins and the natural cross-linking of the fibrin network that occurs after platelet activation. Additional in vivo reports will be needed to fully characterize the functionality of this new biomaterial. Clinical studies have evaluated the efficacy and safety of this adjustable platform that could improve on the regenerative potential of current cell therapy and growth factor delivery approaches. However, the current results concluded that this new biomaterial has desirable mechanical properties for cell growth in a three-dimensional arrangement while providing a sustained release of bioactive molecules that promotes regeneration of the surrounding tissue [8].

A cost survey for autologous PRP was carried out with 18 participants over 12 weeks at the University Hospital of Rio de Janeiro, where the cost of producing Platelet Rich Plasma Gel was US$4.88 dollars per session, on average, considering the material resources in units that make up the Unified Health System. The procedure took approximately 22 minutes. They concluded that the production of Platelet Rich Plasma gel involves low-cost material resources for both blood collection and preparation, enabling universal access to treatment. The procedure requires a trained team, in a suitable location, being a safe and low-cost technology [9].

A clinical study conducted on 52 female patients with facial wrinkles (group A) and wrinkles in the orbicular region of the eyes (group B) was carried out using plasma gel. After the plasma gel injection treatment, some patients reported some side effects, such as transient mild pain, burning sensation, erythema and edema at the injection site, which disappeared spontaneously within a few hours. No patient reported any fibrosis, irregularity, hardness or lumps at the injection site at any time. They showed significant clinical improvement immediately after the plasma gel injection, which was maintained until the end of the 3-month follow-up period. This finding was confirmed by the significant reduction in the mean values of the Wrinkle Severity Scale in group A and the Eye Orbicular Wrinkle Rating Scale in group B, and significant improvement in skin homogeneity and texture in both groups and concluded that autologous injection of platelet-poor plasma gel appears to be technically cost-effective, safe, well-tolerated and minimally invasive, producing significant benefits in the correction of static facial wrinkles and eye orbicular regions [11].

A thorough search using PubMed, Google Scholar and the Cochrane Library including articles published only in English from 2000 to 2015 was performed using keywords such as platelet-rich plasma, PRP, skin rejuvenation, skin aging, skin, platelet-rich plasma therapy and yielded a total of ten articles that were retrieved and included for analysis. Eight studies showed improvement in skin wrinkles. The other two studies reported improvements in the nasolabial fold. Clinical assessments were based on patient satisfaction or feedback questionnaire, pre- and post-treatment photography and skin biopsy. The results showed a significant improvement in the appearance, elasticity, texture and homogeneity of the skin and that PRP therapy is an effective and safe treatment for skin rejuvenation, with no significant difference in the different PRP preparation and injection techniques [12].

A critical analysis of the success of PRP in the field of dermatology, with specific attention to the role of PRP in hair restoration was proposed. Where possible, meta-analyses were used to evaluate the efficacy of PRP. In patients with androgenetic alopecia (AGA), 3 monthly PRP injections (1 session administered each month for 3 months) exhibited greater efficacy compared to placebo, as measured by the change in total hair density (hair/cm2) over the treatment period (mean difference: 25.61, 95% CI: 4.45 to 46.77; P = 0.02). The studies included in the meta-analysis used a half-head model, which may have influenced the results due to the effects that PRP can induce. Controlled studies suggest that 2 to 4 PRP sessions combined with traditional therapies and procedures can help minimize acne scars and burns, improve aesthetic results and decrease recovery time. However, data for these indications are lacking and are less robust in randomized study models. In conclusion, to achieve an improvement in hair restoration in patients with mild AGA, initial 3-month PRP injections should be administered. Only after the completion of rigorous, randomized, controlled studies can effective PRP protocols be standardized and launched for the treatment of dermatological conditions such as acne scars, facial burns and skin aging [7].

A clinical case was carried out on a 52-year-old woman who presented with facial ageing changes, such as loss of volume in the zygomatic bones, nasolabial lines and fine lines around the eyes and forehead. The patient was advised on hyaluronic acid fillers, botulinum toxin treatments and radiofrequency or CO2 laser skin tightening. But she was unwilling to undergo any of these procedures. After refusing the previously proposed treatments, she was advised on platelet-rich plasma (PRP) injections for fine lines and plasma gel fillers to add volume to the zygomatic prominences and nasolabial lines. She agreed to this considering the low cost and the plasma gel being an autologous product, therefore without immunogenic potential, and advised on the duration of the effects of this procedure up to 3-6 months with a touch-up procedure in 2-3 months. Immediately after the PRP treatment, the void over the zygomatic and nasolabial lines immediately showed more volume and a filling effect; the patient was presented with her result regarding the improvement of the fine lines over 3 to 4 weeks due to the new production of collagen by the PRP. At the 1-month follow-up and after 3 months, after evaluating the patient, she showed considerable improvement in the general texture of the skin, sagging and the filling effect of the bio-filler was maintained at up to 60% to 70% of the original volume [10].

An experimental analytical study was conducted over a period of 2 years with 40 patients. They conducted a split-face design in which the right side of the patient's face was the study side where autologous PRP was injected into each scar after subcision was performed. The left side of the face was the control side where only the subcision was performed. Digital photographs were taken at each session. After analysis, the side that used PRP and subcision showed greater improvement (32.08%) in post-acne scars when compared to subcision alone (8.33%). Rolling acne scars responded best (39.27%) followed by box-type scars (33.88%); concluding that platelet-rich plasma and subcision acted synergistically to improve the appearance of acne scars [13].

A growing approach to the use of PRP is coming from Asia where doctors are combining PRP with fillers for injection into the face. They monitored 75 Asian participants over two years, with an average age of 43.5 years, whose patients were injected with a dermal filler based on HA mixed with PRP. Six months after the last injection, 100% of the participants had improved. Six months later, 97.3% of the participants had maintained the improvement from the initial baseline, and 90.7% felt much better or a little better up to two years after the injection. There was a low incidence of complications [14].

Twenty women with a clinical diagnosis of aging skin symptoms were treated with PRGF-gel. The participants received an individualized regimen depending on their therapeutic needs. At the end of the follow-up period, the analysis of clinical performance was evaluated by standardized macrophotographs, together with clinical and patient data with results based on their initial expectations. The patients reported being very satisfied after treatment with PRGF-gel in terms of improved reduction of wrinkles and fine lines and improved sagging (overall satisfaction of 8/10). After clinical evaluation pre/post-photography, an improvement of 2.5/3 was observed and the patients showed remarkable facial rejuvenation due to the soft tissue augmentation effect that translated into smoothing of the surface texture and recovery of tone, concluding that although additional randomized clinical trials should be carried out, this study provided preliminary data supporting the use of PRGF-gel for restoration of facial volumization [15].

An experiment with autologous plasma gel was carried out to inject in laryngoplasty and overcome the potential disadvantages of using foreign materials and autologous fat or collagen; and to test this new injection material, a plasma gel, and discuss its clinical efficacy. In the research, 2 mL of blood was used, the platelet-poor serum layer was collected and heated to 100°C for 12 min to form a plasma gel. The plasma gel was then injected into a target site; its safety and efficacy were evaluated in 30 rats. They also conducted a phase I/II clinical study of laryngoplasty with plasma gel injection in 11 patients with unilateral vocal fold paralysis. Results: The plasma gel was semi-solid and easily injectable. It is important to note that the plasma gel maintained the same consistency for up to 1 year in a closed bottle. However, exposure to ambient air caused the plasma gel to disappear within 1 month. In the animal study, the autologous plasma gel remained in situ for 6 months with minimal inflammation. In the clinical study Woo H S et al (2013) showed that vocal fold paralysis was well compensated with the plasma gel in all patients within two months of injection without significant complications. Jitter, brightness, maximum phonation time (MPT) and mean vocal handicap index (VHI) also improved significantly after plasma gel injection. However, as the injected plasma gel was gradually absorbed, 6 patients required another injection, while the gel remained in place in 2 patients. Conclusion: Plasma gel injection laryngoplasty may be a useful and safe treatment option for

temporary vocal cord paralysis [3].

The efficacy and safety of acne scar subcision combined with plasma gel injection versus scar subcision combined with platelet-rich plasma (PRP) injection for post-acne atrophic scars was studied and compared. Scar subcision was performed first on both sides of the face and plasma gel injection was performed on the right side and PRP injection was performed on the left side. The sessions were carried out monthly for 4 months and the follow-up period was 6 months. The results of this follow-up were verified and there was a significant improvement (p=0.035) in the scars on the subcision-gel-side one month after the 1st treatment session. However, with the following sessions, there were no significant differences between the two sides. Finally, at the follow-up visit 6 months after the end of the treatment course there was a significant difference between the 2 sides of the face in favor of the gel-subcision side, concluding that subcision combined with autologous plasma gel injection is a successful technique for post-acne atrophic scars [16].

The in vitro effects of two commonly used local anesthetics (xylocaine* and Naropin*) on the functionality of PRP were analyzed. It was also investigated whether the quantity and quality of PRP passed through the smallest commercially available needle would influence the PRP. After the preparation of PRP from 9 healthy volunteers, platelet aggregation capacity was assessed by aggregometry assays and growth factor release was determined by ELISA after platelet activation. Platelet activation status, reactivity and stability were also assessed by flow cytometry using the expression marker P-selectin. The results obtained were that the association of local anesthetics with PRP injections resulted in a significant decrease in platelet functionality, as assessed by their ability to aggregate, but local anesthetics did not interfere with the release of growth factors and the different sizes and calibers of needles tested for PRP injections did not influence platelet functionality. Concluding that the use of local anesthetics to prevent pain during PRP injections may compromise the therapeutic potential of PRP. These results suggest the careful use of local anesthetics or limiting their use whenever possible [17].

A new method of autologous filler material derived from cultured dermal fibroblasts and plasma gel has been described in a clinical case report. The plasma gel, which is the bio-skeleton of the filler, was prepared from the patient's plasma, which provides a dense framework with a three-dimensional configuration of dermal fibroblasts. Although the plasma gel provides an immediate volume effect, the fibroblasts synthesize proteins from the extracellular matrix to promote skin rejuvenation. The filling effect occurred immediately after the first injection and persisted for 12 months after the third injection, without any complications. The long-term result of the case presented was promising for the concept of developing an autologous biological filler [18].

A randomized study was conducted in which the authors compared the efficacy of fractionated CO2 as monotherapy, another group with microneedling monotherapy and another with PRP monotherapy with intradermal injection in post-acne scars. They concluded that monotherapy with CO2 and microneedling was significantly more effective than monotherapy with PRP and concluded based on their results that the use of PRP as monotherapy for acne scars is still debatable [19].

A randomized study carried out for the treatment of scars included 90 patients separated into three treatment groups. One group received microneedling, another group received intradermal PRP, and the third group was treated with alternating microneedling and intradermal PRP. Although improvement was observed in all groups, combined treatment was associated with the highest mean improvement score, followed by microneedling, then PRP. Patient satisfaction was significantly higher in the combination group. In the histological analysis, the combined treatment produced a more developed dermal thickening with crystal network compared to the single treatment modalities [20].

Although periorbital aging is an aesthetic concern, it is usually the first sign of aging and can cause immense psychological suffering. All available minimally invasive treatments have limitations. PRP can be used to treat aesthetic problems in the periorbital regions such as wrinkles, pigmentation, erythema, loss of skin elasticity and volume. Despite the number of treatments and options available ranging from topical to lasers, PRP is emerging as a promising treatment for this difficult-to-treat condition. They found that skin fibroblasts in PRP secrete endogenous hyaluronic acid in high concentration leading to a significant improvement in skin quality and a decrease in the signs of skin aging. The decrease in melanin production is attributed to the presence of TGF β giving the skin a light-

ening appearance. PRP leads to increased collagen production inducing mild inflammation leading to an improvement in tear trough deformity [21].

A comprehensive literature review was carried out on the use of platelet-rich plasma in aesthetic and regenerative medicine and its therapeutic applications of PRP including various methods for its clinical implementation in conditions related to aesthetic and regenerative medicine including wound healing, skin and facial rejuvenation, hair restoration, hand rejuvenation and musculoskeletal regeneration were reviewed and concluded that PRP treatment has shown a bright future for safe and efficient cosmetic intervention. However, more studies are needed to better understand the limitations and benefits in the clinical phases associated with the aesthetic use of PRP [22].

PRP has 7 fundamental proteins: platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and adhesive proteins - fibrin, fibronectin and vitronectin. PDGF is a glycoprotein that arises from the degranulation of platelets at the site of injury. It activates cell membrane receptors on the target cell which, in turn, develop high-energy phosphate bonds, which activate signal proteins to initiate specific activity in the target cells. These specific activities include mitogenesis, angiogenesis and macrophage activation. TGF-β is secreted by platelets as well as macrophages and acts as an antiproliferative factor in normal epithelial cells. It acts as paracrine and autocrine in nature. The target cells for TGF-β are fibroblasts, bone marrow stem cells and pre-osteoblasts. According to the authors, most current PRP preparation methods use calcium and bovine thrombin to initiate the formation of the PRP gel. Very rare cases of bleeding have been reported with bovine thrombin. Unfortunately, the use of bovine thrombin has been associated with the development of antibodies against human coagulation factors V, XI and thrombin, resulting in a risk of potentially fatal coagulopathies. Alternative agents for PRP activation, such as autologous human thrombin or synthetic peptides, such as the thrombin receptor agonist peptide-6, are now available to counteract this side effect. Treatment with autologous PRP is generally considered safe in appropriately selected patients. Potential candidates for PRP treatment should undergo a pre-treatment hematological evaluation to rule out possible coagulopathies and platelet function disorders. Anemic patients and those with thrombocytopenia may be unsuitable candidates for PRP treatment. Other possible contraindications include hemodynamic instability, severe hypovolemia, unstable angina, sepsis and therapy with anticoagulants or fibrinolytics [23].

A simplified single centrifugation technique and a simple, disposable system for PRP preparation have been published. They used the Gravitational Platelet Separation System, in which after centrifugation the PRP and PPP are separated by gravitational weight, and when PRP is used in soft tissue, there is no need for exogenous activation (with CaCl2 or thrombin), as collagen is a natural activator of PRP [24].

A study to explore the clinical value of CO2 matrix laser combined with platelet-rich plasma (PRP) was carried out with a total of 81 patients with acne scars between December 2018 and October 2019, randomly divided into an observation group (GO, n = 39) and a control group (CG, n = 42). Patients in the GO group were treated with CO2 dot matrix laser combined with PRP, and those in the GC group were treated with CO2 dot matrix laser alone, in order to observe the clinical results in both groups. According to the experimental analysis, compared to the GC group, CO2 dot matrix laser combined with PRP can more strongly improve clinical efficacy in patients, shorten scab formation time and peeling time, contribute more effectively to scar repair, comfort, skin condition, psychological state and satisfaction, and reduce pain. Subsequent follow-up results also showed that patients in the Observation Group (OG) had a better quality of life. The matrix laser combined with PRP was an independent protective factor. They concluded that the CO2 matrix laser combined with PRP can strongly improve the scar repair effect, psychological state and quality of life of patients with acne vulgaris scars, so it is worth popularizing in clinical practice [25].

Because PRP is obtained from a small sample of the patient's own blood, which is centrifuged to separate the platelet growth factors from the red blood cells, this concentration of platelets triggers the rapid growth of new bone and soft tissue and very little risk because the healing process is natural and accelerated by PRP. Autologous PRP is a relatively new biotechnology that has shown promise in stimulating and accelerating soft tissue and bone healing. The effectiveness of this treatment lies in the local delivery of a wide range of growth factors and proteins, mimicking and supporting physiological wound healing and tissue repair processes. Accelerated heal-

ing is a goal we have been pursuing in the medical field and now we have a treatment that activates the natural healing process. PRP is a very promising biotechnology [26].

For the treatment of melasma, the two-spin centrifugation method was used to obtain the PRP and PRP injections were administered for six sessions. This study found significant reductions in melasma after PRP injection. TGF-β1 and PDGF present in PRP could lead to a reduction in melasma. TGF-β1 decreases melanogenesis by delaying regulated kinase activation via extracellular signaling and thus inhibiting melanin synthesis in a dose-dependent concentration. PDGF can accelerate neogenesis, collagen synthesis and ECM formation, leading to a favorable microenvironment in the dermis [27].

[28] A vast bibliographic survey from 2000 to 2020 was carried out in order to provide a lean review of the current evidence on the usefulness of PRP in medical and aesthetic dermatology with a focus on preliminary applications. More studies reported favourable results, using PRP as a convenient and biocompatible therapeutic option that not only produced clinical improvement in multiple dermatological diseases, but also improved or minimized many post-procedural adverse effects. This review reinforced the need for robust, randomized and controlled studies to better elucidate the usefulness of these treatments. Reinforcing the need for standardization in future research so that emerging uses for PRP in dermatology can be shared and improved through high-quality clinical application methodologies.

Clinical Case

A 28-year-old patient whose main complaint was sagging skin, spots and acne scars on her face. Three sessions of plasma gel enriched with PRGF (plasma rich in growth factors) were carried out, with a 30-day interval between sessions, and the patient was followed up for 6 months.

Twelve 3ml vacuum tubes were collected with 3.8% sodium citrate anticoagulant per vacuum collection, totaling 36 ml of blood. After collection, the tubes were placed in a centrifuge and rotated at 1800 rcp for 6 minutes to separate the plasma from the red series. The plasma was divided into three phases, the two upper parts known as poor plasma (PPP) were aspirated and placed in a dry white tube without assets for storage and the part closest to the red rim known as platelet-rich plasma (PRP) aspirated and stored in another white tube without assets for concentration of the PRP assets being known as Plasma rich in growth factors (PRGF), as shown in Figure 01.

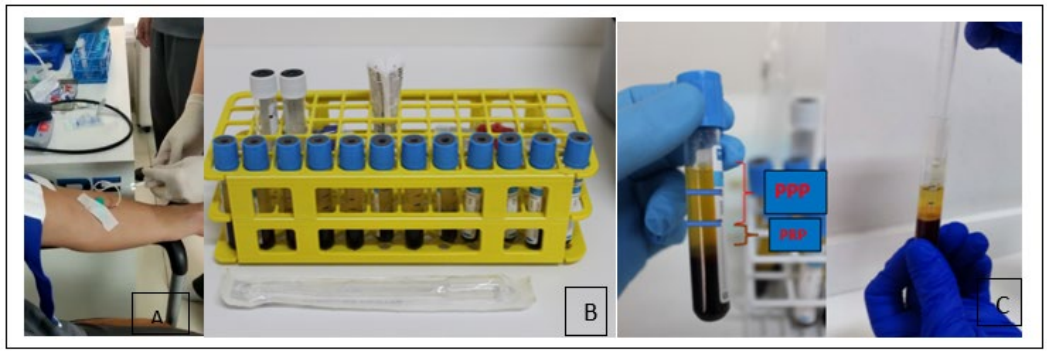

Figure 1: A. Image of venipuncture; B. Image of the collection tubes with sodium citrate after centrifugation; C. Image of tube marked with fraction separations and aspiration of fractions to separate them.

In the white tube with PPP, three 3ml syringes were aspirated with 2.5ml of poor plasma in each syringe and placed in the heating machine at 90° C for 12 minutes to densify it into a gel known as plasma gel. After cooling, each syringe was mixed with 0.5ml of plasma rich in growth factors (PRGF), totaling three syringes with a total volume of 3 ml in each.

The patient's skin was cleansed with 2% degerming digluconate and then with 70% alcohol, a single perforation was marked and 4.5 ml were placed on each side of the face using a 22G X70 mm cannula at points that required skin improvement.

After placing the plasma gel, mesotherapy was carried out using a dermopigmentation pen (Aston) (Figure 02) with a plasma solution rich in growth factors (PRGF) on the entire face and neck and finished off with a soothing mask with liquid PPP actives.

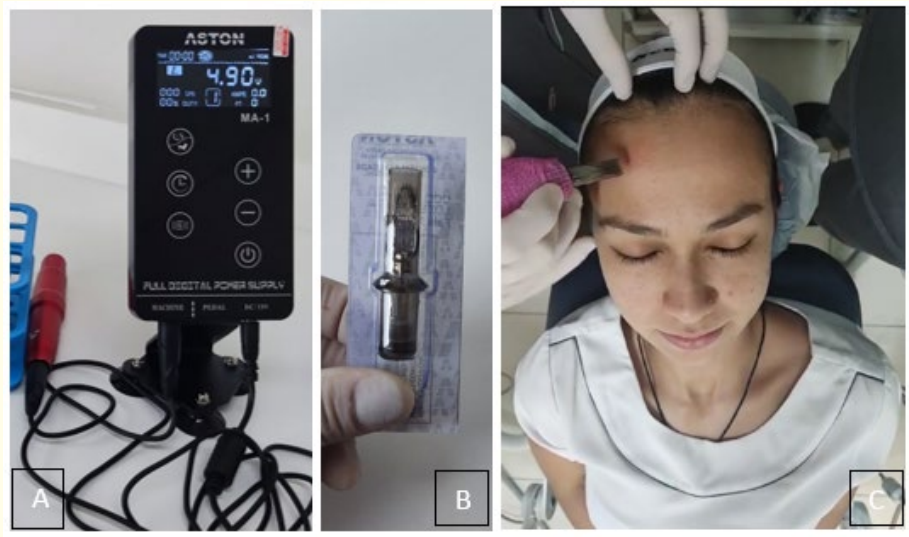

Figure 2: A. Aston mesotherapy pen; B. Disposable mesotherapy pen cartridge that aspirates and microinjects PRGF; C. Patient receiving mesotherapy.

Three sessions of this protocol were carried out with an interval of around 30 days each. After the last session, final photos were taken and a clinical evaluation of skin improvement and patient satisfaction was carried out (Figure 03).

After 90 days, a clinical evaluation and photographic analysis were carried out and showed an improvement in skin firmness, an improvement in acne scars and patient satisfaction.

Figure 3: A and C. Initial photos of the patient during the first session; B and D. Final photos after the third session, around 90 days after the first photo.

Discussion

Skin aging is multifactorial and constant [1], but due to the increased demand for aesthetic procedures in the search for treatments that slow down this process and improve aesthetic appearance, medicine and the aesthetic field are always looking for new treatments to offer to a market that is constantly growing [2, 21, 22].

The periorbital region around the eyes is usually the area that suffers the first signs of aging [21] and all available minimally invasive treatments have limitations. PRP can be used to treat aesthetic problems in the periorbital regions such as wrinkles, pigmentation, er-

ythema, loss of skin elasticity and volume. Despite the number of treatments and options available ranging from topical to lasers, PRP is emerging as a promising treatment for this difficult-to-treat condition [23]. Skin fibroblasts in contact with PRP secrete endogenous hyaluronic acid in high concentration, leading to a significant improvement in skin quality and a reduction in the signs of skin ageing. The decrease in melanin production in the skin is attributed to the presence of TGF-β giving the skin a lightening appearance. PRP leads to increased collagen production inducing mild inflammation leading to an improvement in tear trough deformity [21].

To delay ageing, hyaluronic acid fillers, which are the most commonly used, form a fibrous capsule and induce new collagen to a limited extent, and these artificial soft tissue augmentation products are variable and no product can be considered the most effective or ideal [2]. Some patients, knowing this, refuse to undergo these artificial fillers and seek more natural treatments for facial rejuvenation, such as PRP [10]. Based on this context, the patient in this study also preferred to start her aesthetic treatments with a more natural therapy such as Plasma gel for skin improvement and collagen stimulation.

In aesthetic treatment, no single therapy can delay and improve appearance for a long period, which is why the use of combined therapies [16, 25] such as CO2 laser, microneedling and PRP has been one of the most promising treatments for improving and rejuvenating the skin [19] and not just a single treatment such as the use of fillers, which when not properly indicated can lead to complications [2].

Several studies have compared the efficacy and safety of the use of plasmagel and PRP in the treatment of atrophic acne scars [13, 16, 20], even in the clinical case carried out in the present study one of the complaints was acne scars, the subcision technique combined with autologous plasma gel injection [13, 16] and treatment with alternating microneedling and intradermal PRP [20] were successful techniques for post-acne atrophic scars, although some authors based on their results indicate that the use of PRP as monotherapy for acne scars is still debatable [19].

Several studies with clinical cases [10, 11, 13], some using PRP compared the use of plasma gel in high or low consistency [3], both consistencies showed performance in the release of growth factors, in the clinical case of the study, the dense form of the gel and liquid in microneedling were used, achieving good results. Clinical cases seeking skin improvement and facial rejuvenation [5, 4, 21, 26], others hair restoration [7], acne scar treatments [13], hand rejuvenation [16], melasma [27] and musculoskeletal regeneration were reviewed and concluded that PRP treatment has shown a bright future for safe and efficient cosmetic intervention [23].

Many studies using PubMed, Google Scholar and the Cochrane Library [21, 26] containing keywords such as: platelet-rich plasma, PRP, skin rejuvenation, skin ageing, skin, platelet-rich plasma therapy showed a significant improvement in the appearance, elasticity, texture and homogeneity of the skin, showing that PRP therapy is an effective and safe treatment for skin rejuvenation, with no significant difference in the different techniques for preparing and injecting PRP [12].

The production of platelet-rich plasma gel, which uses low-cost material for both blood collection and preparation, allows universal access to treatment [9]. The consistency and autologous nature of the biological filler plasma gel are more acceptable to patients than fillers such as hyaluronic acid [10] and have a low level of complications with a high level of patient satisfaction with the results [14, 15, 18].

The study conducted [11] on 52 female patients with facial wrinkles reported some side effects of the plasma gel injection, such as transient mild pain, burning sensation, erythema and edema at the injection site, which disappeared spontaneously within a few hours and no patient reported any fibrosis, irregularity, hardness or lumps at the injection site at any time. In the clinical case carried out in this study, similar symptoms were obtained, with no post-procedure intercurrence.

During the application of PRP, the treatment is bearable and the use of local anesthetics to prevent pain should be avoided, as they can compromise the therapeutic potential [17]. These results suggest the careful use of local anesthetics or limiting their use whenever possible [17]. Treatment with autologous PRP is generally considered safe in appropriately selected patients. Potential candidates for

PRP treatment should undergo a pre-treatment hematological evaluation to rule out possible coagulopathies and platelet function disorders [23].

Plasma gel, being the bio-skeleton of the filler and prepared from the patient's plasma, provides a dense framework with a three-dimensional configuration of dermal fibroblasts [18]. Thus, a growing approach to the use of PRP is coming from Asia where doctors are mixing PRP with HA (hyaluronic acid) fillers for injection for dermal filling with results with a high level of satisfaction and maintenance of improvement in skin and volume of 90.7% after a two-year follow-up [14].

Because PRP is obtained from a small sample of the patient's own blood and is centrifuged to separate the platelet growth factors from the red blood cells, this concentration of platelets results in the local delivery of a wide range of growth factors and proteins, mimicking and supporting physiological wound healing, repair of tissue processes, relatively a biotechnology that has shown promise in stimulating and accelerating the healing of soft tissues and bones [23]. Some studies show the need for a single centrifugation cycle [24], as in the present study, although other studies show the use of two centrifugation cycles to separate the PRP [27]. Due to the lack [4, 5, 21, 26] of standardization of protocols for obtaining and processing PRP and its derivatives, this may be the reason why this method is not yet used as the first choice in aesthetic medicine. Understanding the biomaterial or believing in the magic of growth factors? The future of the research field depends on this choice [5].

The search for treatments that slow down the aging process and improve aesthetic appearance means that medicine and the aesthetic field are always looking for new treatments to offer to an ever-growing market [2, 21, 22] and plasma gel and PRP, being autologous, are technically very cost-effective, safe, well tolerated and minimally invasive, producing significant benefits in the correction of static facial wrinkles and regions of the orbicularis oculi [11]. All the properties of plasma gel were verified during the clinical study in this study and it was verified its efficiency as a collagen biostimulator, using a simplified centrifugation process and a protocol that can be used as a standard, which is easy to reproduce and can be used on a large scale.

Conclusion

After the clinical study using plasma gel as an autologous collagen biostimulator following the scientific protocols, it was found that there was an improvement in skin quality and a reduction in acne scars after 90 days of patient follow-up.

Conflicts of Interest and Financial Disclosure

Resende Marcela declares no conflict of interest and financial disclosure.

Borges Kely Pereira declares no conflict of interest and financial disclosure.

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Volume 4 Issue 1 January 2024