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Research Article

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Facial Skin Changes Produced by Treatment with Autologous Platelet Concentrate

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Abstract

Background: *The tireless search for therapeutic options that alleviate the signs of skin aging is a challenge for the aesthetic practitioner.*

Objective: *To evaluate the efficacy and safety of autologous platelet concentrate (APC) in the treatment of facial cutaneous aging (FCA).*

Method: *Between March 1, 2017 and March 31, 2021 at the "Hermanos Ameijeiras" hospital, a randomized, single-center, double-blind and controlled clinical trial was carried out in 164 patients with FCA. A group treated with APC was compared to another treated with fresh autologous plasma (FAP). The treatment was applied monthly for 1 year.*

Results: *Three months after the end of the treatment, there were significant differences between the patients treated with APC compared to those treated with FAP in terms of improvement in the texture, tone, elasticity, hydration, pores, homogeneity of the skin, the global aesthetic improvement scale (GAIS) and degree of satisfaction ($p < 0.001$). All adverse events were of mild intensity, did not imply changes before the intervention and were completely resolved.*

Conclusions: *The autologous platelet concentrate proved to be effective and safe in reducing the signs of skin aging, associated with a high degree of patient satisfaction.*

Introduction

The aging of the skin represents an insidious, multifactorial, progressive and degenerative process, of an inevitable and practically irreversible course [1,2]. Platelets play a vital role in initiating hemostasis and wound healing. In response to tissue and vascular damage, a platelet plug is formed, with the subsequent release from its alpha granules of more than 30 biologically active proteins, however, the results of their action on skin rejuvenation is a field in the that there is still much to investigate [3, 4].

Objectives

The primary objective was to evaluate the efficacy and safety of autologous platelet concentrate in the treatment of facial skin aging and the secondary objectives were: 1) to evaluate the clinical response to treatment, 2) to evaluate the type and intensity of adverse events that occur and 3) describe the degree of patient satisfaction.

Method

A prospective, randomized, double-blind and controlled phase III clinical trial was carried out at the Hospital Clínico Quirúrgico: "Hermanos Ameijeiras", in the period between March 1, 2017 and March 31, 2021. 164 were included patients, who were assigned to two different therapeutic groups: group A intradermal administration of autologous platelet concentrate (APC) and group B intradermal administration of fresh autologous plasma (FAP). Each group consisted of 82 patients. In both groups the treatment was applied monthly for 12 months. Three months after the end of the treatment (month 15), the response to it (final evaluation) was evaluated, comparing the current state of the lesions with the initial state; for this, the patient had to attend the scheduled consultation. Throughout the study there was a rigorous control of ad-

verse reactions that may have occurred, including hematology and clinical biochemistry.

Inclusion criteria

Patients between 20 and 60 years of age, of any sex and skin phototype, skin photoaging grade II to IV according to Glogau's classification [5], normal complementary tests (hemogram with differential, coagulogram, blood chemistry and serology for HIV, hepatitis B and C), with signed informed consent. Exclusion criteria (table 1).

Table 1. Exclusion criteria and their relationship with the time limits to perform the procedure.

Criteria	Time limits
Congenital or acquired coagulation disorders.	Prior and simultaneous to the procedure.
Bone marrow aplasia.	Prior and simultaneous to the procedure.
Prone to forming keloids.	Before the procedure.
Cardiovascular or pacemaker, neurological, liver, kidney, endocrine or immunological diseases, decompensated.	Simultaneous to the procedure.
Severe psychiatric disorder or other limitation that prevents the patient from giving his informed consent or makes his evaluation difficult.	Simultaneous to the procedure.
Pregnancy or breastfeeding	Simultaneous to the procedure.
Herpes simplex infection and / or other septic foci.	Simultaneous to the procedure.
Hormonal treatment (estrogens, progesterone, hormonal contraceptives).	One year before the procedure.
Treatment with anticoagulants, antifibrinolytics, macrolides, terfenadine, cimetidine, amiodarone, fluoxetine, NSAIDs, or corticosteroids.	One month prior to the procedure.
Application of topical retinoids, aesthetic treatments in the region to be treated, including lasers, intense pulsed light, chemical peels, mesotherapy, carboxytherapy or others.	Three months prior to the procedure.
Fillers in the region to be treated.	One year prior to the procedure.
Active neoplastic diseases or during the follow-up period	Five years post-healing prior to the procedure.
Inadequate photoprotection.	Unlimited

Elimination criteria

Patients who wish to abandon the study, presence of an adverse event and / or complication that prevents continuing with the treatment, or patients who have missed a treatment session.

Procedures

Once the patients gave informed consent, the included subject's registry template and the investigator's internal registry were filled out. All information on the included patients was compiled in the data collection notebook. The blood was extracted (500 milliliters), then the APC or FAP were obtained with the Rotixa centrifuge (221 mm radius) according to international standards [6]. To obtain the APC, a first light centrifugation was performed of the whole blood in the plastic bag for 3 minutes at 2800 rpm at 22 oC, with a centrifugation force of 2000 g, in this way 250 ml of red blood cells and 250 ml of PRP were obtained; then a second weighted centrifugation was carried out on the PRP in the plastic bag for 5 minutes at 4500 rpm at 22 oC, with a centrifugation force of 5000 g. Once the heavy centrifugation had been carried out, the supernatant plasma was transferred through the tubes that have the plastic bags for blood collection and only 10 ml were left and it is in said volume that by shaking the platelets that were deposited in the cell were re suspended bottom of the bag as results of the centrifugation procedure. To obtain the FAP, a single heavy centrifugation was performed on the plastic blood bag containing 500 ml of whole blood for 7 minutes at 4500 rpm at 4 oC, with a centrifugation force of 5000 g to obtain 250 ml of globules and 250 ml of fresh plasma of which we only take 10 ml to be administered to the patient in the area to be treated. Subsequently, the red blood cells were returned to the patients and lastly, a microinjection of 10 milliliters of APC or FAP was performed, distributed throughout the facial area. Asepsis and antisepsis of the facial area were performed. Subsequently, with a 27G × 16 mm hypodermic needle and 1 ml syringes, intradermal injections of approximately 1.5 ml were administered at a distance of 1.5 to 2 mm between each application area (point-to-point, fan, back trace and nap page).

Variables Related to The Response to Treatment

The response to treatment was evaluated by two specialists in dermatology, with teaching and research categories between auxiliary and holder, scientific degree between master and doctor of medical sciences, and between 20 and 40 years of experience, who did not know the therapeutic modality used. The final result was evaluated using the global aesthetic improvement scale (GAIS) (Table 2) [7] and by means of the dermatological physical examination which evaluated the post-treatment evolution of the following variables: texture (smooth, rough), tone (normal or decreased) and elasticity (normal or decreased). Hydration was measured with a corneometer; it can be normal or decreased. The homogeneity of the skin and the dilation of the pores were evaluated by photographic examination with the FotoFinder® (Adonia) for the analysis of the skin.

Table 2. Global aesthetic improvement scale (GAIS).

Evaluation		Degree of improvement
1	Total answer.	Patient with exceptional or much better improvement (excellent corrective result, total disappearance of the lesions).
2	Marked partial response.	Patient greatly improved or considerably better (marked improvement in appearance, but not completely optimal, reduction of lesions by ≥ 50% and <100%).
3	Slight partial response.	Improved or somewhat better patient (appearance slightly better than initial condition, but needs more treatments, <50% lesions decrease).
4	Non-response	No change (the same number and size of lesions as at the start of treatment).
5	Progression.	Worse (increased number or size of lesions).

Adverse events.

Adverse events reported in the reviewed literature are pain, edema, and ecchymosis at the microinjection site [3, 4].

Classification of adverse events (Table 3) [8].

Degree of Satisfaction of Patients to Treatment.

The degree of satisfaction (PSSS) of the patients with the treatment was evaluated taking into account what was reported by the patient according to the scale (Table 4) [9].

Table 3. Intensity scale of adverse events.

Intensity	Characteristics
Mild	if the adverse event subsided without treatment.
Moderate	if treatment was required, but the adverse event subsided with it.
Serious	if he required hospitalization or did not yield to treatment.
Very serious	if it endangered the life of the patient, if it caused sequelae or disability.

Table 4. Scale of the degree of patient satisfaction.

Evaluation		Degree of satisfaction
1	Very bad.	I did not get any improvement and the treatment caused me multiple discomforts (inflammation, bruising and pain).
2	Bad.	I did not get any improvement, but the treatment did not cause me any discomfort.
3	Regular.	The improvement was little.
4	Good.	The improvement was noticeable, but not total.
5	Very good	The improvement was complete with minimal discomfort.

Bioethical considerations

The protocol was submitted for the consideration and approval of a Review and Ethics Committee for Clinical Research created for this purpose, which evaluated it from an ethical point of view. Additionally, this protocol was submitted to the scientific and methodological review and approval by the Institutional Scientific Council of the "Hermanos Ameijeiras" Surgical Clinic Hospital.

Statistical Methods Used

The medical records of the patients included in the study were stored in the Department's file. With the information gathered, a Microsoft Office version XP database in Excel format was prepared, which was exported to the SPSS version 21.0 system for analysis. No intermediate statistical analyzes were carried out, only the one corresponding to the end of the study. To summarize the information of the study sample, the arithmetic mean, standard deviation and minimum and maximum value for all quantitative variables were used, the assumption of normality of the data was verified through the Kolmogorov Smirnov test. For all qualitative variables, absolute numbers and percentages were calculated. To find an association between the groups in the epidemiological and clinical variables, the student's t-test was used for the age variable for independent samples and the Pearson Chi-square test for the rest of the variables, and in the event that more than 25% of the cells presented values below 5, the Fisher test was used. To find an association between qualitative variables (degree of aesthetic improvement and degree of satisfaction) before and after treatment, the signs test was used in variables with two categories and the Friedman test with more than two categories. Pearson's Chi-square test was used to search for an association between the qualitative

variables (degree of photodamage and degree of satisfaction) after treatment between the groups. To find an association between the quantitative variables (pores and homogeneity) before and after the treatment, the student's t test was used for paired samples. To find an association between the quantitative variables (degree of aesthetic improvement and degree of satisfaction) after treatment with respect to the groups, the student's t test was used for independent samples. The Kappa coefficient was used to evaluate inter-observer agreement in the dermatological evaluation. In all hypothesis tests carried out, a significance level $\alpha = 0.05$ was used.

Sample's size calculation

The sample size was calculated using the C4-Study Design Pack computerized program. (C4- SDP) for sample size calculation (CTM). Version 1.1® Glaxo Wellcome. SA; [10] considering the following values: percentage of success reported in the literature 70%, percentage of success in the current study of 80% and a difference of 10% in the group under study. With an alpha error of 0.05, a power of 80% and covering a loss of 5% of patients, it was necessary to have 164 subjects in total, 82 for each treatment group.

Results

The age of the patients showed a global mean of 45.2 years with values between 25 and 58 years, and a predominance between 30 and 49 years. The female sex resulted in a higher proportion (86.6%) in the study, with a distribution of 85.4% in group A and 87.8% in group B. Phototype II (69.5%) prevailed in the study. study, with distribution of 70.7% in group A and 68.3% in group B. The age of the patients showed a global mean of 45.2 years with values between 25 and 58 years, and a predominance between 30 and 49 years. Phototype II (69.5%) prevailed in the study, with a distribution of 70.7% in group A and 68.3% in group B.

Physical examination showed significant changes in skin texture, tone and elasticity in the group treated with APC ($p < 0.001$); however, the same did not occur in the group treated with FAP in relation to these same parameters. The corneometric analysis showed a significant improvement in skin hydration in the group treated with APC ($p < 0.001$), while this did not occur in the group treated with FAP ($p = 0.352$). The difference between both groups was significant after treatment ($p < 0.001$) (Table 5).

Table 5. Modifications of skin parameters.

Parameters		APC (n = 82)					FAP (n = 82)				
		Before		After			Before		After		
		n	%	n	%	p*	n	%	n	%	p*
Texture	Smooth	0	0	82	100	0,000	0	0	12	14,6	0,851
	Rough	82	100	0	0		82	100	70	85,4	
Tone	Normal	3	3,6	81	98,7	0,000	6	7,3	7	8,5	0,987
	Diminished	79	96,3	1	1,1		76	92,7	75	91,5	
Elasticity	Normal	4	4,8	77	93,9	0,000	8	9,7	10	12,2	0,457
	Diminished	78	95,1	5	6,1		74	90,2	72	87,8	
Hydration	Normal	1	1,1	82	100	0,000	2	2,4	13	15,8	0,352
	Diminished	81	98,8	0	0		80	97,6	69	84,1	

* Signs test

According to the global scale of aesthetic improvement, there were significant changes after treatment with APC ($p = 0.001$). Seventy-eight patients (95.1%) achieved a total response. Three patients (3.6%) achieved a marked partial response. One patient (1.2%) achieved a mild partial response. After treatment with FAP, there was only a slight partial response in 12/82 (14.6%) patients ($p = 0.453$). The response was higher in the group treated with APC compared to the group treated with FAP ($p < 0.001$) (Table 6). Skin analysis using the Adonia software with FotoFinder® showed significant improvement, both from the photographic and statistical point of view in relation to the enlarged pores and homogeneity in the group treated with APC ($p < 0.001$), (Figure 1A, 1B and 2A, 2B); while there was no photographic or statistical improvement in relation to dilated pores ($p = 0.957$) and homogeneity ($p = 0.921$) in the group treated with FAP The difference between both groups after treatment was significant ($p < 0.001$) (Table 7).

Table 6. Modifications of Global aesthetic improvement scale (GAIS).

	APC (n = 82)		p*	FAP (n = 82)		p*
	n	%		n	%	
Total answer.	78	95,1	0,001	0	0	0,453
Marked partial response.	3	3,6		0	0	
Slight partial response.	1	1,2		12	14,6	
Non-response	0	0		70	85,4	

*Chi cuadrado

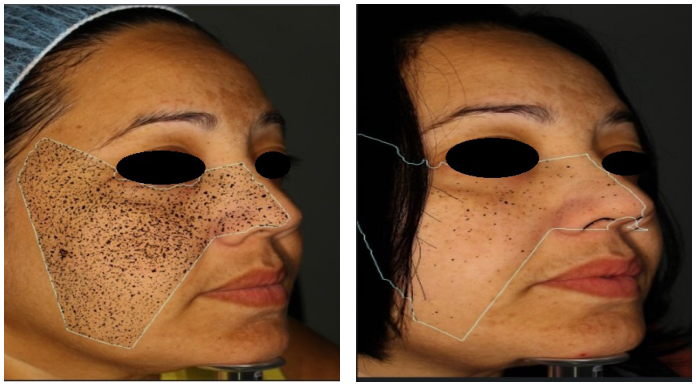

Figure 1A and 2A. Before the treatment.

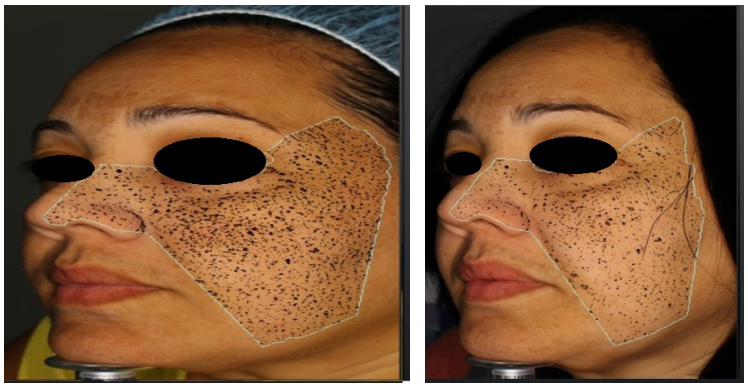

Figure 1B and 2B. After the treatment.

Table 7. Photographic analysis of the pores and homogeneity of the skin using the FotoFinder Adonia®.

Parameters	APC (n = 82)			FAP (n = 82		
	Before	After	p*	Before	After	p*
	Arithmetic average	Arithmetic average		Arithmetic average	Arithmetic average	
Enlarged pores	69,5	14,8	0,000	64,9	62,2	0,957
Non-homogeneity	61,2	16,3	0,000	62,1	59,7	0,921

All patients in both groups reported some adverse event (pain, edema or ecchymosis), which were of mild intensity, did not imply changes before the intervention and were completely resolved. Pain occurred in both groups during the procedure and disappeared immediately after completion of the procedure (100%). Although the edema lasted only 2 to 3 days, it was higher in frequency in the group that received APC (100%) compared to the group that received FAP (2.4%) (p = 0.000). Ecchymoses occurred in both groups at the puncture sites (14.6% in group A and 15.8% in group B), were infrequent and of short duration (five to seven days duration) (Table 8). Of the 82 patients treated with APC, 61 patients (74.4%) reported a very good degree of satisfaction, 17 patients

(20.7%) good and 4 patients (4.9%) fair, because they achieved evident improvement with respect to to its initial condition. Of the 82 patients treated with FAP, 73 patients (89.1%) reported a fair degree of satisfaction and 9 patients (10.9%) poor, because they did not achieve evident improvement with respect to their initial condition (Table 9).

Table 8. Adverse events.

ADVERSE EVENTS		APC (n = 82)		AFP (n = 82)	
		n	%	n	%
Type	Pain	82	100,0	82	100,0
	Edema	82	100,0	2	2,4
	Ecchymosis	12	14,6	13	15,8
Duration	Less than 7 days	82	100,0	82	100,0
Intensity	Slight	82	100,0	82	100,0
Attitude	Unchanged	82	100,0	82	100,0
Result	Resolved	82	100,0	82	100,0

Table 9. Degree of patient satisfaction.

	APC		AFP		p*
	n	%	n	%	
Bad	0	0	9	10,9	0,003
Regular	4	4,9	73	89,1	
Well	17	20,7	0	0	
Very good	61	74,4	0	0	

*Chi cuadrado

Discussion

Most people want to "die old looking young," and they don't spare any sacrifices to do so. They want to "buy many more years of life" (with quality of life, for the record), without paying the price of the extra time that this entails. To "rejuvenate" their skin, people try to prevent, postpone, or reverse the signs and symptoms of skin aging by consuming "dreams packaged in dream packages [11].

Maisel-Campbell AL et al conducted a systematic review looking for prospective trials and case series with 10 patients or more, from the start of the use of platelet-rich plasma (PRP) until March 2019, to evaluate the evidence on its safety and effectiveness in reducing the visible signs of aging. Twenty-four studies were included, including 8 randomized controlled trials, representing a total of 480 patients. According to the global evaluation of the doctors, it was shown that injectable therapy induces an improvement in the appearance, texture, pigmentation and fine lines of the skin, with adequate safety and a high degree of patient satisfaction. They found heterogeneity in the preparation and administration of the PRP and the lack of standardization in the outcome measures as a limitation. They recommended more high-quality trials with sufficient follow-up to optimize treatment regimens [12].

Gawdat HI et al published a study comparing the efficacy and safety of PRP with pre-made growth factors (mixture of epidermal growth factor, insulin-like growth factor-1, basic fibroblast growth factor, thioredoxin, tripeptide of copper-1, multivitamins, amino acids and minerals) in skin rejuvenation. They included 20 adult women with Fitzpatrick skin types III-IV and Glogau photoaging types II and III, who underwent split face therapy in which each side was randomized to treatment by pre-fabricated growth factors (area A) or autologous PRP (area B). All patients received six sessions with an interval of 2 weeks. The evaluation was carried out using the Global Aesthetic Improvement Scale (GAIS) and optical coherence tomography (OCT). The patients were followed for 6 months. Both procedures produced a significant improvement with respect to the evaluation of GAIS (skin turgor and general vitality) and OCT (epidermal and dermal thickness) ($p < 0.05$). A significant negative correlation was detected between patient age, sun exposure, and GAIS. Burning sensation was significantly higher in area A. Patient satisfaction was significantly higher in area B. Improvement was more sustained in area B during follow-up [13].

Rodríguez-Segura A and collaborators carried out an experimental and longitudinal study in which they included 23 patients between 30 and 70 years of age, 2 men and 21 women, who presented disagreement with the characteristics of the skin of the face and accepted the application of PRP. According to the results, they observed better hydration, coloration, texture and tone of the skin, from the clinical point of view; increase in the number and thickness of collagen and elastic fibers, in the histological study; 91% of patients satisfied and 9% very satisfied, in the satisfaction degree survey [14].

In order to evaluate the efficacy and safety of dermal injections of autologous PRP in facial skin rejuvenation, Cameli N et al conducted an investigation involving 12 patients, who underwent 3 sessions of PRP injection at 1-month intervals. The clinical and instrumental results were evaluated before and 1 month after the end of the treatment by corneometry, cutometer, Visioscan and Visioface. One month after completing the treatment, the clinical and patient evaluation showed an improvement in skin texture. Gross skin elasticity, skin smoothness parameters, skin barrier function, and capacitance were significantly improved ($p < 0.05$) [15].

Aust M et al. Published 20 patients treated three times at monthly intervals with 2 ml of PRP for each infraorbital region, administered laterally using 27G 38mm cannulas. The patients were evaluated on the days of treatment and one month after the third injection using photographic images and measurements of the firmness and elasticity of the skin using a cutometer to objectify the subjective evaluations of the questionnaires of the patient and the doctor. A progressive improvement of the aesthetic result and a high level of patient satisfaction were determined. Cutometer measurements showed a statistically significant higher level of skin firmness ($p = 0.0005$) (due to increased collagen production) and a statistically significant increase in skin elasticity ($p = 0.0021$) (thanks to increased elastin production). In addition to the swelling visible immediately after injection, there were no other undesirable side effects or complications. The typical burning sensation during injection was not reported [16].

In our study, the group treated with APC showed significant clinical and statistical improvement ($p < 0.001$) in texture, tone, elasticity and hydration, pores, skin homogeneity, on the global aesthetic improvement scale (GAIS), the group treated with FAP did not show clinical or statistical improvement in skin texture, tone, elasticity and hydration ($p > 0.05$), nor in pores and skin homogeneity ($p > 0, 05$), on the global aesthetic improvement scale ($p = 0.453$). The adverse events found in our study coincide with those reported in the literature, all secondary to puncture [17, 18] and not to the product under study, except for edema which was significantly higher in the group treated with autologous platelet concentrate at seem related to the high concentration of platelets and their supposed growth factors.

Conclusions

The response to treatment was significantly higher in the group treated with autologous platelet concentrate in terms of improved texture, tone, elasticity, hydration, enlarged pores, and homogeneity of the skin and on the global aesthetic improvement scale (GAIS). Adverse events (pain and bruising) were similar in both groups, secondary to the puncture and not to the product under study. Edema was significantly higher in the group treated with the autologous platelet concentrate. All were of mild intensity, without permanent consequences on the individuals. The degree of satisfaction was significantly higher in the patients treated with the autologous platelet concentrate.

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