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Treatment of cutaneous photoaging lesions with autologous platelet concentrate

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Abstract

Background: Facial aging causes a devastating physical and mental impact on quality of life.
Objective: To evaluate the efficacy and safety of autologous platelet concentrate (APC) in the treatment of cutaneous photoaging (SCF).
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 ECF. A group treated with CPA was compared to another treated with fresh autologous plasma (AFP). 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 CPA compared to those treated with PFA in terms of the improvement in the degree of photodamage and the 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 to reduce the signs of skin aging, associated with a high degree of patient satisfaction.

Introduction

Cutaneous photoaging (CEF) is characterized, from a clinical point of view, by the presence of fine and deep wrinkles, dryness, sagging and roughness of the skin, as well as telangiectasias and pigmentary changes (hypopigmentation or hyperpigmentation) such as circumscribed hypomelanosis or puntata leukoderma, reticular leukoderma, stellate scars, solar lentigos and ephelides, respectively. The pores are larger, filled with horny material [1,2].

The massive promotion directed at consumers through the Internet and social networks has attracted the attention of the aesthetic industry towards the use of platelet-rich plasma in different diseases, including dermatological ones [3,4]; however, little research (clinical trials) supports its application and benefits in skin photoaging. That is why the following scientific question arises: Will the microinjection of autologous platelet concentrate be effective and safe in the treatment of skin photoaging?

Objectives

The primary objective was to evaluate the efficacy and safety of autologous platelet concentrate in the treatment of cutaneous photoaging 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 (AFP). 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 was sent to it (final evaluation), 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 the adverse reactions they received, including hematology and clinical biochemistry.

Inclusion criteria

Patients between 20 and 60 years old, of any sex and skin phototype, skin photoaging grade II to IV according to Glogau's classification [5], normal complementary tests (hemogram

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with differential, coagulogram, blood chemistry and serology for HIV, hepatitis B and C), with signed informed consent.

Exclusion criteria (table 1).

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 CPA or PFA were obtained with the Rotixa centrifuge (221 mm radius) according to international standards [6]. To obtain the CPA, a first light centrifugation of the whole blood was carried out in the plastic bag for 3 minutes at 2800 rpm at 22oC, with a centrifugation force of 2000 g, in this way 250 ml of red blood cells and 250 ml were obtained of PRP; then a second weighted centrifugation was performed on the PRP in the plastic bag for 5 minutes at 4500 rpm at 22oC, 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 resuspended bottom of the bag as results of the centrifugation procedure. To obtain the PFA, a single heavy centrifugation was performed on the plastic blood bag containing 500 ml of whole blood for 7 minutes at 4500 rpm at 4oC, 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 CPA or PFA was performed, distributed throughout the facial area. Asepsis and antisepsis of the facial area was 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, backtrace and nap).

Variables related to the response to treatment

The response to treatment was classified by category of specialists in dermatology, with teaching and research between assistant and holder, scientific degree between master and doctor of medical sciences, and between 20 and 40 years of age, who did not know the therapeutic modality used.

The final result of cutaneous photoaging lesions was evaluated by the evolution of the Glogau photoaging classification scale (Table 2) [5] and by means of the dermatological physical examination which evaluated the presence or absence of cutaneous photoaging lesions (actinic lentigos, telangiectasias and keratoses The amount of solar erythema and ultraviolet radiation were evaluated by photographic examination with FotoFinder® (Adonia) for skin analysis.

Adverse events

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

Classification of adverse events (Table 3)[7]

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) [8].

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

Table 2. *Classification of photoaging according to Glogau.[5]*

Type	Characterization
Type I "No wrinkles"	Early photoaging: slight pigmentary changes, no keratosis, minimal wrinkles, no scars, young patient, generally 28-35 years of age, no or minimal makeup.
Type II "Movement wrinkles"	Early to moderate photoaging: visible early senile lentigo, early actinic keratosis, slight signs of scars, wrinkles and parallel smile lines begin to appear, patient age: late 30s or 40s, usually she wears some makeup.
Type III "Wrinkles at rest"	Advanced photoaging: obvious dyschromia and telangiectasias, visible keratoses, neoplasms (+), wrinkles even when not moving, patient age: fifty years or older, always wears a lot of makeup.
Type IV "Wrinkles only"	Intense photoaging: grayish-yellow skin, cutaneous neoplasms (+++), all wrinkled skin, no normal skin, age of patient: sixties or seventies, cannot wear makeup, "hard and cracked".

Table 3. *Intensity scale of adverse events.[7]*

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 [8].*

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 to 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. In addition, this protocol was submitted to scientific and methodological review and approval by the Institutional Scientific Council of the Hospital Clínico Quirúrgico "Hermanos Ameijeiras".

Statistical methods used

The medical records of the patients included in the study were stored in the Department. With the information collected, a Microsoft Office version XP database in Excel format was made, 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, the standard deviation and the 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 for independent samples was used for the age variable 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 photodamage) before and after treatment, the signs test was used in variables with two categories and the Friedman test with more than two categories. To search for an association between the qualitative variables (degree of photodamage and degree of satisfaction) after treatment between the groups, the Pearson's Chi-square test was used. To find an association between the quantitative variables (ultraviolet B radiation, solar erythema) before and after the treatment, the student t was used for paired samples. To find an association between the quantitative variables (ultraviolet B radiation, solar erythema) after treatment with respect to the groups, Student's t was used for independent samples. To evaluate the agreement between observers in the dermatological evaluation, the Kappa coefficient was used. In all the hypothesis tests carried out, a significance level $\alpha = 0.05$ was performed.

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 [9]; 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 study group. 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 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. The age of the patients showed a global mean of 45, 2 years with values between 25 and 58 years, and 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.

At the beginning of the study, regarding the Glogau photodamage scale, in the group that received CPA, 9 patients were classified as grade IV, 43 as grade III, 27 as grade II, and 3 as grade I. In the group that received AFP 10 patients were classified as grade IV, 45 as grade III, 25 as grade II, and 2 as grade I.

After treatment, in the group that received CPA of the 9 patients who were classified as grade IV, 6 were reclassified as grade III (66.6%) and 1 as grade II (11.1%). Of the 43 patients who were classified as grade III, 32 were reclassified as grade II (74.4%) and 3 as grade I (6.9%). Of the 27 patients who were classified as grade II, 21 were reclassified as grade I (77.7%) and 4 as grade 0 (14.8%). The 3 patients who were classified as grade I were reclassified as grade 0 (100%) (p = 0.001). The rest of the patients remained in the same assigned grade before treatment.

In the group that received AFP, of the 10 patients who were classified as grade IV, 1 was reclassified as grade III (10%). Of the 45 patients who were classified as grade III, 6 were reclassified as grade II (13.3%). Of the 25 patients who were classified as grade II, 6 were reclassified as grade I (24%). Of the 2 patients who were classified as grade I, 1 was reclassified as grade 0 (50%), (p = 0.324). The rest of the patients remained in the same assigned grade before treatment.

The difference in the modification in the degrees of photoaging of the group treated with CPA compared to the group treated with PFA was significant (p = 0.002) (Table 5).

At the end of treatment, in relation to photoaging lesions (lentigos, telangiectasias and actinic keratoses) there was a significant reduction in the group treated with CPA (p <0.05) (figure 1A and 2A); whereas this was not the case in the group treated with PFA. The difference between both groups after treatment was significant (p <0.001) (Table 6).

The analysis of the skin using the Adonia software with the FotoFinder® showed significant improvement both from the photographic and statistical point of view in relation to the scanning of type B ultraviolet radiation (UVB) (figure 1B and 2B) and solar erythema (figure 1C and 2C) in the group treated with CPA (p <0.001),. There was no photographic or statistical improvement in relation to the scanning of type B ultraviolet radiation (UVB) (p = 0.942) and solar erythema (p = 0.857) in the group treated with AFP. The difference between both groups after treatment was significant (p <0.001) (Table 7).

All patients in both groups reported some adverse event (pain, edema or ecchymosis), which were of intensity level, 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 only lasted 2 to 3 days, it was higher in frequency in the group that received CPA (100%) compared to the group that received AFP (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 in duration) (Table 8).

Of the 82 patients treated with CPA, 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 PFA, 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).

Discussion

Although it is impossible to stop the passage of time, skin aging goes beyond aesthetics since it can greatly affect the quality of life of patients, so it is very important to know the different mechanisms that originate it and become familiar with the various anti-aging strategies that exist today. In addition, it is essential that the doctor understand the wishes and expectations of the patient in order to guide him towards a therapeutic modality that leads to the best results [10].

In recent years, platelet-rich plasma, collagen peptides,

Table 5. *Degree of photoaging according to Glogau.*

APC (n = 82)							AFP (n = 82)						
Before			After				Before			After			
Degree	n	%	Degree	n	%	p*	Degree	n	%	Degree	n	%	p*
I	3	3,7	0	3	100	0,001	I	2	2,4	0	1	50	0,324
			I	0	0					I	1	50	
II	27	32,9	0	4	14,8		II	25	30,5	0	0	0	
			I	21	77,7					I	6	24,0	
			II	2	7,4					II	19	76,0	
III	43	52,4	I	3	6,9		III	45	54,8	I	0	0	
			II	32	74,4					II	6	13,3	
			III	8	18,6					III	39	86,6	
IV	9	11,0	II	1	11,1		IV	10	2,4	II	0	0	
			III	6	66,6					III	1	10,0	
			IV	2	22,2					IV	9	90,0	

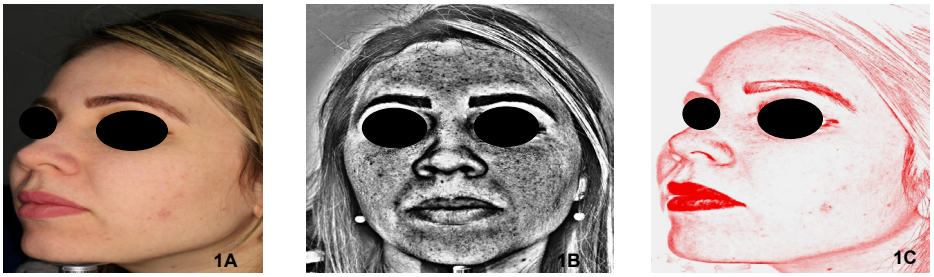

Figure 1: *Before treatment. 1A photograph (presence of lentigines), 1B ultraviolet radiation scan (abundant), 1C scan of solar erythema (intense).*

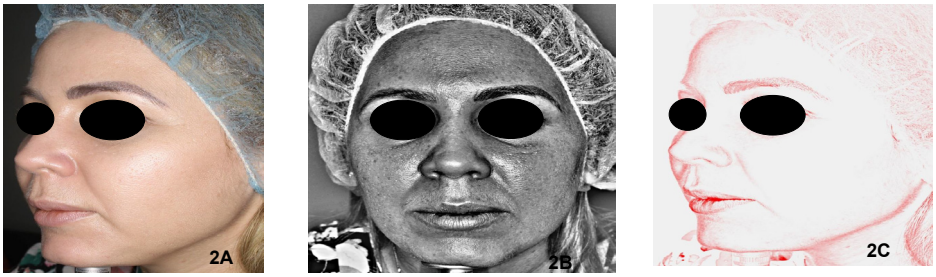

Figure 2: *After treatment. 2A photograph (absence of lentigines), 2B ultraviolet radiation scan (scarce), 2C scan of solar erythema (mild).*

	APC (n = 82)					AFP (n = 82)				
	Before		After			Before		After		
	n	%	n	%	p*	n	%	n	%	p*
Actinic lentigos	79	96,3	8	10,1	0,004	72	87,8	70	97,2	0,742
Telangiectasias	70	85,3	10	14,3	0,002	70	85,3	70	100	0,835
Actinic Keratosis	52	63,4	4	7,7	0,003	55	67,1	51	92,7	0,768

* Signs test

Table 7. *Photographic analysis of RUVB and solar erythema on the skin using FotoFinder Adonia®.*

Parameters	**APC (n = 82)**			**AFP (n = 82)**		
	Before	**After**	**p***	**Before**	**After**	**p***
	Arithmetic Average	**Arithmetic Average**		**Arithmetic Average**	**Arithmetic Average**	
RUVB	68,3	15,8	0,000	69,2	66,4	0,942
Solar Erythema	64,2	20,2%	0,000	65,6	62,1	0,857

*t de Student

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 8. *Adverse events.*

	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

and stem cells have become popular treatments for skin rejuvenation. Massive consumer promotion through the Internet and social media has drawn the attention of the beauty industry to these treatments. The reviewed studies affirm the effectiveness of this new therapeutic trend in the world of aesthetic medicine [11].

Du R et al conducted a study with the aim of clarifying the possible molecular mechanisms of PRP in the rejuvenation of wrinkled and aged skin. They recruited 30 healthy women between the ages of 30 and 50. They administered a total of 3 injections of autologous PRP in the right side and of SS in the left side to each patient with 15-day intervals between injections. The effects of PRP injections were evaluated using the VISIA® analysis system and computed tomography of the skin (TCP). A human organotypic skin model was established and treated with PRP or SS before irradiation with ultraviolet (UV) -B light (10 mJ / cm2). The distribution of the epidermal structure and dermal fibers were evaluated by hematoxylin and eosin staining and Masson's stain. The expression of matrix metalloproteinase-1 (MMP-1), tyrosinase, fibrillin and tropoelastin was detected by quantitative PCR with reverse transcription, Western blotting and immunofluorescence. The results show that PRP treatment improved skin quality in the participants. Furthermore, the VISIA® analysis reveals that wrinkles and pores decreased in the PRP group compared to the SS treatment. Examination of TCP around the injection sites showed decreased pigmentation and increased number and thickness of collagen fibers. The in vitro study demonstrated that treatment with PRP improved photoaging by inhibiting the UV-B-induced upregulation of tyrosinase and MMP-1, and by inducing the expression of fibrillin and tropoelastin that was negatively regulated by UV-B [12].

Cabrera-Ramírez JO et al applied 3 subcutaneous PRP sessions with a cannula on the back of the hands. At the end of the treatment, the subjects had clinical improvement in the Fitzpatrick wrinkle and elastosis classification scale ($p < 0.001$) and in the Glogau photodamage scale ($p = 0.01$) and a histological increase in the number of fibroblasts ($p = 0.000$), number of vessels ($p = 0.000$) and amount of collagen ($p = 0.27$) [13].

Redaelli A et al conducted a study in 23 patients with the objective of evaluating real results, benefits and side effects of PRP in revitalizing aging skin. The patients were treated with a monthly session of injections with 4 ml of PRP (a total of three sessions). The study was imaged before and after each session using a dermatoscope, a digital camera, a state-of-the-art comprehensive imaging system, and imaging software. The results were evaluated one month after the last session by the photographic score, the patient satisfaction score and the doctor satisfaction score. Finally, a final graded score was calculated for each patient. In general, the results were satisfactory. No serious and persistent side effects were detected [14].

Kim DH et al conducted a study where they investigated the effects of activated platelet-rich plasma (aPRP) and activated platelet-poor plasma (aPPP) on the remodeling of the extracellular matrix, a process that requires the activation of dermal fibroblasts, essential for the rejuvenation of aged skin. Platelet rich plasma (PRP) and platelet poor plasma (PPP) were prepared using a double spin method and then activated with thrombin and calcium chloride. The proliferative effects of aPRP and aPPP were measured by the [3H] thymidine incorporation assay, and their effects on matrix protein synthesis were evaluated by quantifying the levels of carboxy-terminal peptide (PIP) of type I procollagen by an immunosorbent assay enzyme-linked (ELISA). The production of collagen and matrix metalloproteinases (MMP) was studied by Western blotting and reverse transcriptase polymerase chain reaction. The results show that the number of platelets in the PRP increased to 9.4 times the initial values. Both aPRP and aPPP stimulated cell proliferation, and maximum proliferation occurred in cells grown in 5% aPRP. PIP levels were higher in cells grown in the presence of 5% aPRP. Furthermore, aPRP and aPPP increased the expression of type I collagen, MMP-1 protein, and mRNA in human dermal fibroblasts [15].

Frautschi RS et al conducted a systematic review to evaluate the clinical evidence of the efficacy of PRP in cosmetic surgery. They found 38 studies. Eleven articles were related to skin rejuvenation. Although all the studies showed more than 95% efficacy, limitations in the heterogeneity of the preparation and administration of the PRP, associated with the lack of standardization in the evaluation of the results. They recommended further high-quality trials with sufficient follow-up to optimize treatment regimens [16].

In our study, the group treated with CPA showed significant clinical and statistical improvement in the Glogau photodamage scale, in the reduction of skin photoaging lesions, in the scan of type B ultraviolet radiation and solar erythema ($p < 0.001$). The group treated with AFP did not show clinical or statistical improvement in the Glogau photodamage scale ($p = 0.324$), in the reduction of cutaneous photoaging lesions ($p > 0.05$), in the ultraviolet radiation type scan B ($p = 0.942$) and solar erythema ($p = 0.857$).

From the point of view of safety, it should be noted that all the authors, including Schoenberg BAE et al. [17] and Al-Shami et al. [18], have documented that all adverse events (pain, edema, and ecchymosis) They have been mild and of spontaneous resolution, secondary treatment to the technique of applying the product with needles and not related to the product under study. Cepeda Páez et al reported a significant decrease in adverse events as the number of sessions increased

[19]. The adverse events found in our study coincide with those reported in the literature, all secondary to the puncture and not to the product under study, except for edema, which was significantly higher in the group treated with autologous platelet concentrate, apparently related to elevated concentration of platelets and their putative growth factors.

Conclusions

The response to treatment was superior in the group with the autologous platelet concentrate in terms of the improvement in the degree of photodamage, the RUVB scan and the solar erythema. Adverse events (pain and ecchymosis) 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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