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ORIGINAL CONTRIBUTION

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Autologous platelet-rich plasma versus readymade growth factors in skin rejuvenation: A split face study

Heba I Gawdat MD[1] | Amira M Tawdy MD[1] | Rehab A Hegazy MD[1] | Mohga M Zakaria MSc[1] | Ryham S Allam MD[2]

[1]Dermatology Department, Faculty of Medicine, Cairo University, Cairo, Egypt

[2]Ophthalmology Department, Faculty of Medicine, Cairo University, Cairo, Egypt

Correspondence
Dr Heba I Gawdat, Dermatology Department, Faculty of Medicine, Cairo University, Cairo, Egypt.
Email: heba.gawdat@yahoo.com

Summary

Background: The escalating urge for a youthful-looking skin instigates continuous innovations with minimally invasive procedures. Readymade growth factors and autologous platelet-rich plasma (PRP) represent such therapeutic interventions.

Objective: Compare the efficacy and safety of PRP to readymade growth factors in skin rejuvenation.

Patients and Methods: Twenty adult females with Fitzpatrick skin types III-IV and Glogau photoaging types II and III were enrolled in this study. They underwent a split face therapy where each side was randomly assigned to treatment by either readymade growth factors (area A) or autologous PRP (area B). All patients received six sessions at 2-weeks interval. Evaluation was carried out using Global Aesthetic Improvement Scale (GAIS) and optical coherence tomography (OCT). Patients were followed up for 6 months.

Results: Both procedures yielded significant improvement regarding both GAIS (skin turgor and overall vitality) and OCT (epidermal and dermal thickness) assessment. Significant negative correlation was detected between patients' 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 on follow-up.

Conclusion: Platelet-rich plasma is effective and safe for skin rejuvenation, comparable to readymade growth factors with noticeable higher longevity.

KEYWORDS
efficacy, OCT, PRP, readymade growth factors, skin rejuvenation

1 | INTRODUCTION

Aging of the skin consists of a combination of genetically predisposed factors (intrinsic aging) and environmental factors (photoaging). The resulting clinical manifestations include mottled pigmentation, wrinkles, and change of the superficial texture leading to coarseness of the skin.[1] In the cosmetic field, prevention and treatment of skin aging represent a driving force for technological innovations aiming at the improvement of such condition with minimal downtime. Among such interventions are mesotherapy and platelet-rich plasma (PRP).

Mesotherapy (from Greek mesos, "middle," and therapia, "to treat medically") is a nonsurgical cosmetic treatment.[2] It consists of intradermal injection of biocompatible and totally absorbable pharmacologic substances, such as nutrients, hormones, vitamins, enzymes, and other reagents that are administered directly into the region to be treated. The aim behind its use in skin rejuvenation is maintenance and restoration of healthy and youthful texture of the skin.[3]

PRP is an autologous concentration of human platelets in a small volume of plasma.[4] The concentrated platelets found in PRP contain large reservoirs of bioactive proteins, including growth factors that are vital to initiate and accelerate tissue repair and regeneration. It

contains autologous growth factors, especially epidermal growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factor β (TGF β), and vascular endothelial growth factor (VEGF), that act synergistically with other growth factors.[5] PRP has been shown to promote tissue remodeling in aged skin and thereby a potential tool for skin rejuvenation.[6]

To the best of our knowledge, no studies comparing both techniques in the field of skin rejuvenation have been conducted. This was the impetus behind the current study, in which we aimed to assess and compare the efficacy and safety of the use of readymade growth factors solution (mesotherapy) to autologous PRP in skin rejuvenation. Clinical evaluation and objective measures in the form of optical coherence tomography (OCT) were utilized.

2 | PATIENTS AND METHODS

The current prospective randomized comparative clinical trial was approved by the dermatology research ethical committee, and a written informed consent was obtained from each patient before participation. The study included 20 adult female patients aged between 35 and 55 years, with Glogau Photoaging Classification[7] type II "wrinkles in motion" and type III "wrinkles at rest."

2.1 | Patient selection

Pregnancy, lactation, smoking, as well as evidence of any dermatological and/or systemic disease were considered as exclusion criteria. In addition, patients who received any facial cosmetic procedure or anti-aging treatments (creams, tablets) during the preceding 6 months prior to the study were considered ineligible. Patients with medical or psychiatric problems that could interfere with their compliance, cooperation, or expectations were disqualified.

On the first visit, eligibility was determined through thorough history taking, to document the personal data, history of any dermatological and/or systemic disease, as well as any anti-aging procedures or treatment. In addition, frequency of unprotected sun exposure was noted according to a grading score (3: daily for an average of more than 2 hours, 2: daily for an average of less than 2 hours, 1: not daily).

2.2 | Baseline evaluation

Dermatological examination was carried out to detect the skin phototypes (SPT) according to the Fitzpatrick classification.[8] The type of photoaging using Glogau Photoaging Classification[7] was carried out. Signs of skin aging including wrinkles, pigmentary changes, laxity, dryness, and atrophy of the skin were further documented.

All participants were photographed in the frontal and profile views using a digital camera (Sony DSC-W530, 14 mega pixel resolution) with standardized settings.

In addition, images of both sides of the face using OCT (RTVue premier, Optovue Medical Industries, Fremont, CA, USA) were taken to provide scan range with a depth of 2-2.3 mm, scan beam of wave length λ=840±10 nm, external image of 13 mm×9 mm, depth resolution in tissue of 5.0 μm, transverse resolution of 8 μm and with working distance of 22 mm. OCT was used to measure the thickness of both the epidermis and dermis. All patients were scanned by a single investigator at fixed site of examination (crossing point of the tangential line from lateral canthus of the eye to the zygomatic process of the temporal bone on both sides).

2.3 | Treatment protocol

All included participants were subjected to a split face treatment. Each side of the face was randomly assigned to one of two treatment protocols, readymade growth factors solution (mesotherapy) (area A) or PRP (area B) using envelope concealment method. Patients were blinded to the assigned treatment for each side of the face.

The injection of the therapeutic solution was preceded by application of topical anesthetic cream (lidocaine and prilocaine 5%) for 45 minutes under occlusion followed by disinfection using alcohol.

2.3.1 | Area A (Mesotherapy)

Mesotherapy (MRS FACE, mesologica®, MRS Lift solution, Jakarta Barat, Indonesia) is a mixture of epidermal growth factor (EGF), insulin-like growth factor (IGF)-1, basic fibroblast growth factor (bFGF), thioredoxin (TRX), copper tripeptide-1, multivitamins, amino acids, and minerals. Each vial contains 5, 3 mL of which was intradermally injected (at points 1 cm apart) on one side of the face (area A).

2.3.2 | Area B (Autologous PRP)

Ten milliliters of venous blood was drawn from each patient under sterile conditions in a syringe prefilled with 1.5 mL of anticoagulant solution (acid citrate dextrose) and then centrifuged at 150×*g* for 15 minutes.

After the first spin, the lower red blood cell portion was discarded, and the supernatant was centrifuged at 400×*g* for 10 minutes. The resulting pellet of platelets was mixed with 1.5 mL of supernatant, which made 2 mL of PRP. One milliliter of 3% calcium chloride was added to the PRP to induce platelet activation. 3 mL of activated PRP was intradermally injected (at points 1 cm apart) on one side of the face (area B).

All patients were instructed to apply moisturizing cream (after the session), sun screen together with the avoidance of direct sun exposure. In addition, they were strictly asked to refrain from the usage of any topical anti-aging products during the study period (9 months).

The treatment protocol was repeated every 2 weeks for a period of 3 months.

2.4 | Evaluation

2.4.1 | Physician assessment

With the aid of digital photographs, three investigators—blinded to the assigned treatment—evaluated the degree of clinical

improvement of skin aging signs in all patients. The average of their scores was recorded.

Evaluation was carried out for each side of the face using the Global Aesthetic Improvement Scale (GAIS),[9] regarding the skin turgor, smoothness, hydration, and overall vitality of the face. It was carried out 1 and 6 months after the last session.

2.4.2 | Optical coherence tomography (OCT)

OCT imaging of a fixed site (crossing point of the tangential line from lateral canthus of the eye to the zygomatic process of the temporal bone) was carried out for both treated areas (A and B). The epidermal and dermal thicknesses were measured and compared. OCT was performed 1 month and 6 months after the last session.

2.4.3 | Side effects

The occurrence of side effects such as erythema, burning sensation, allergic reaction or postinflammatory hyperpigmentation (PIH) was meticulously reported for both treated areas at all sessions.

2.4.4 | Patient satisfaction level (PSL)

All patients were asked to record their opinion regarding the benefits and side effects of both therapeutic procedures and to score their level of satisfaction from (0-3)[9] 1 month and 6 months after the last session.

2.5 | Statistical analysis

Data were statistically described in terms of mean, standard deviation (SD), median and range, or frequencies (number of cases), and percentages when appropriate. Comparison of numerical variables between the study groups was carried out using Mann-Whitney *U* test for independent samples. Within group, comparison of numerical variables was carried out using Wilcoxon signed rank test for paired (matched) samples. For comparing categorical data, McNemar test was performed. *P* values less than .05 was considered statistically significant. All statistical calculations were carried out using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

3 | RESULTS

This split face randomized comparative clinical study included 20 female patients with age ranging between 35 and 55 years (mean 41±5.156), years) with a primary complaint of facial aging signs. These signs included wrinkles (100%, n=20), pigmentary changes (45%, n=9), and laxity (25%, n=5). Regarding the Glogau Photoaging Classification, the severity of aging signs was classified as type II (55%, n=11) and type III (45%, n=9). The demographic and clinical data of the patients are summarized in Table 1.

TABLE 1 Demographic and clinical data of the 20 included female patients; n: number of patients, %: percentage of patients

Variable	Patients (n=20)
Age (y)	
Range,	35-45
Mean±SD	41±5.156
Skin Phototype (n, %)	
III	6 (30)
IV	14 (70)
Frequency of sun exposure (n, %)	
3	8 (40)
2	8 (40)
1	4 (20)
Glogau Photoaging Classification (n, %)	
II	11 (55)
III	9 (45)
Aging signs (n, %)	
Wrinkles	20 (100)
Pigmentation	9 (45)
Laxity	5 (25)

3.1 | Four-month evaluation (1 month after final session)

3.1.1 | Physician assessment

Based on the average GAIS score of the three blinded investigators, none of the patients showed worsening of the aging signs (GAIS=−1). The GAIS for both treated areas is illustrated in Table 2. There was no statistically significant difference with respect to GAIS between both areas, regarding skin turgor, smoothness, hydration, and overall vitality of the face ($P>.05$) (Figure 1).

Significant negative correlations were documented between the GAIS on the one hand, and both the age ($r=-.475$, $P=.034$ in area A, $r=-.468$, $P=.037$ in area B), and the frequency of sun exposure ($r=-.478$, $P=.033$ in area A, $r=-.469$, $P=.026$ in area B) on the other hand.

Neither the SPT nor the Glogau Photoaging Classification showed a significant correlation with the GAIS.

TABLE 2 Global aesthetic improvement scale (GAIS) in both treated areas (1 mo after last session)

GAIS (n, %)	Area A (Mesotherapy; %)	Area B (Autologous PRP; %)
0 (No change)	0 (0)	0 (0)
1 (Improved)	7 (35)	4 (20)
2 (Much Improved)	11 (55)	10 (50)
3 (Very much improved)	2 (10)	6 (30)

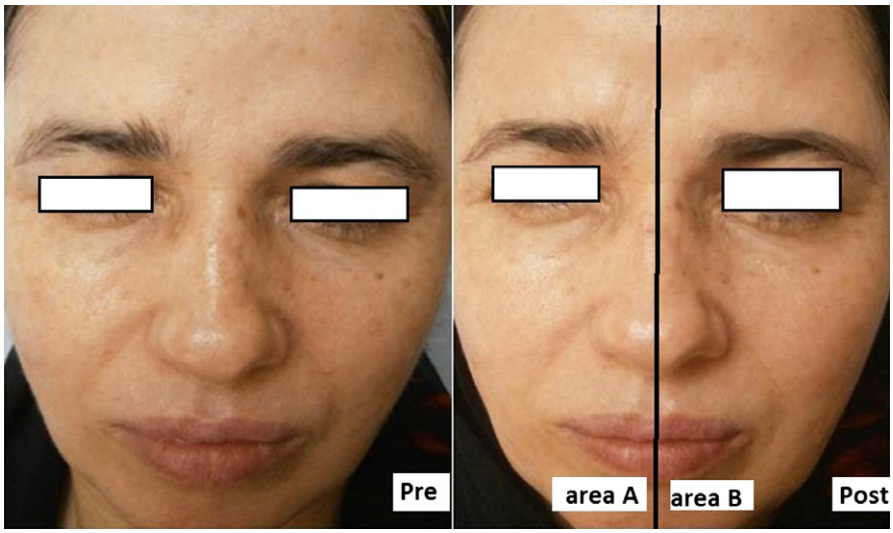

FIGURE 1 Front view of a 49-y-old woman; Pre: at baseline and post: 6 mo after the last treatment session showing a significant improvement of aging signs (global aesthetic improvement scale [GAIS] =3; very much improved) at both treated areas A (readymade growth factors) and B (autologous platelet-rich plasma [PRP])

3.1.2 | OCT

In comparison with the baseline, area A (mesotherapy) demonstrated a significant increase in both the epidermal thickness (mean: 182 - 222.55 μm; *P*=.003), and dermal thickness (mean: 220.75-282.85 μm, *P*=.005) (Figure 2A and B). Similarly, area B (PRP) showed a significant increase in both the epidermal thickness (mean: 173.35-222.60 μm; *P*=.002) and dermal thickness (226.10-286.70 μm; *P*=.001; Figure 3A and B). A further observation was the notification of improvement of the surface irregularities in both areas.

No significant difference was recorded between both areas regarding the final epidermal and dermal thicknesses, or the percent of improvement (*P*>.05). Statistically significant positive correlation was documented between the GAIS and the percentage of improvement of both epidermal (*r*=.5, *P*=.025 in area A, *r*=.53, *P*=.034 in area

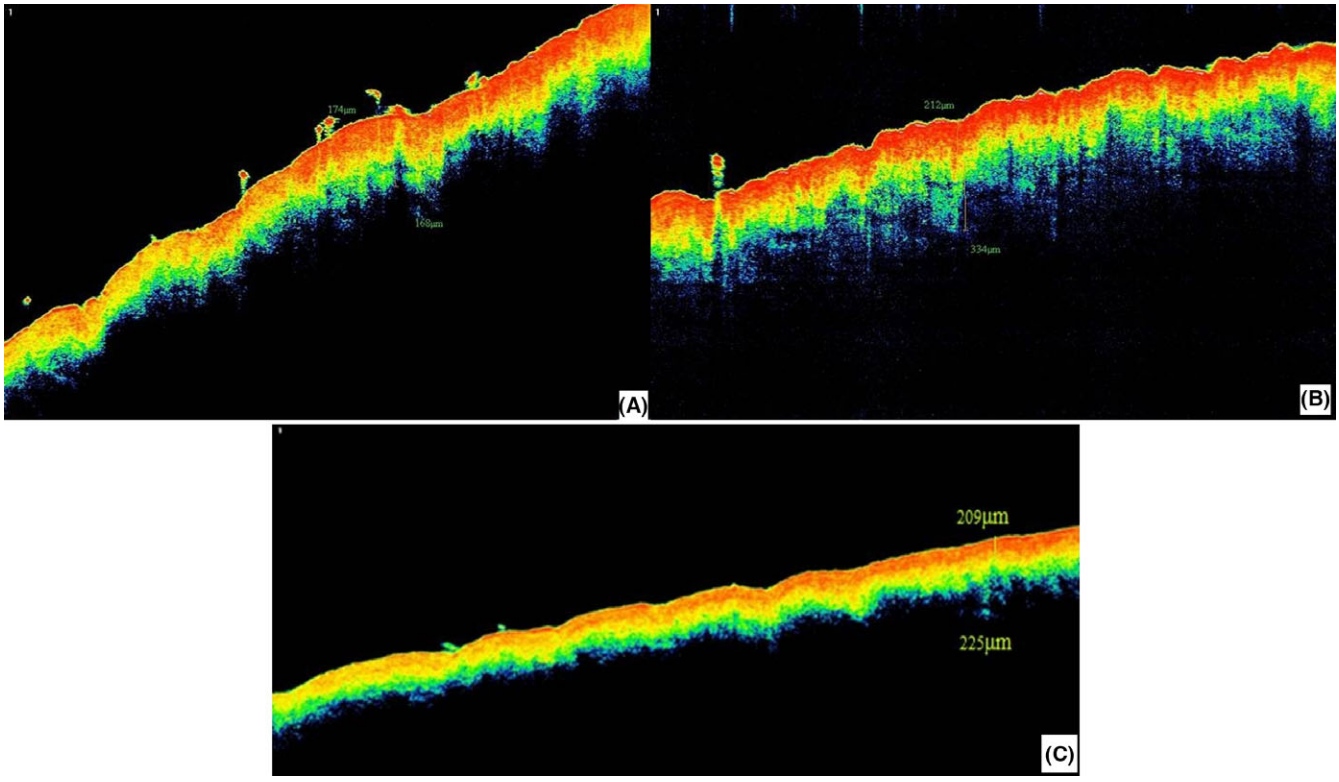

FIGURE 2 Optical coherence tomography (OCT) images of the same female patient at treated area A (readymade growth factors); A: at baseline showing epidermal thickness of 174 μm and dermal thickness of 168 μm, B: 1 mo after the last treatment session showing significant increase in both epidermal (212 μm) and dermal (334 μm) thickness, C: 6 mo after the last treatment session showing a decrease in both epidermal (209 μm) and dermal (225 μm) thickness. An improvement in surface irregularities (wrinkles) was observed

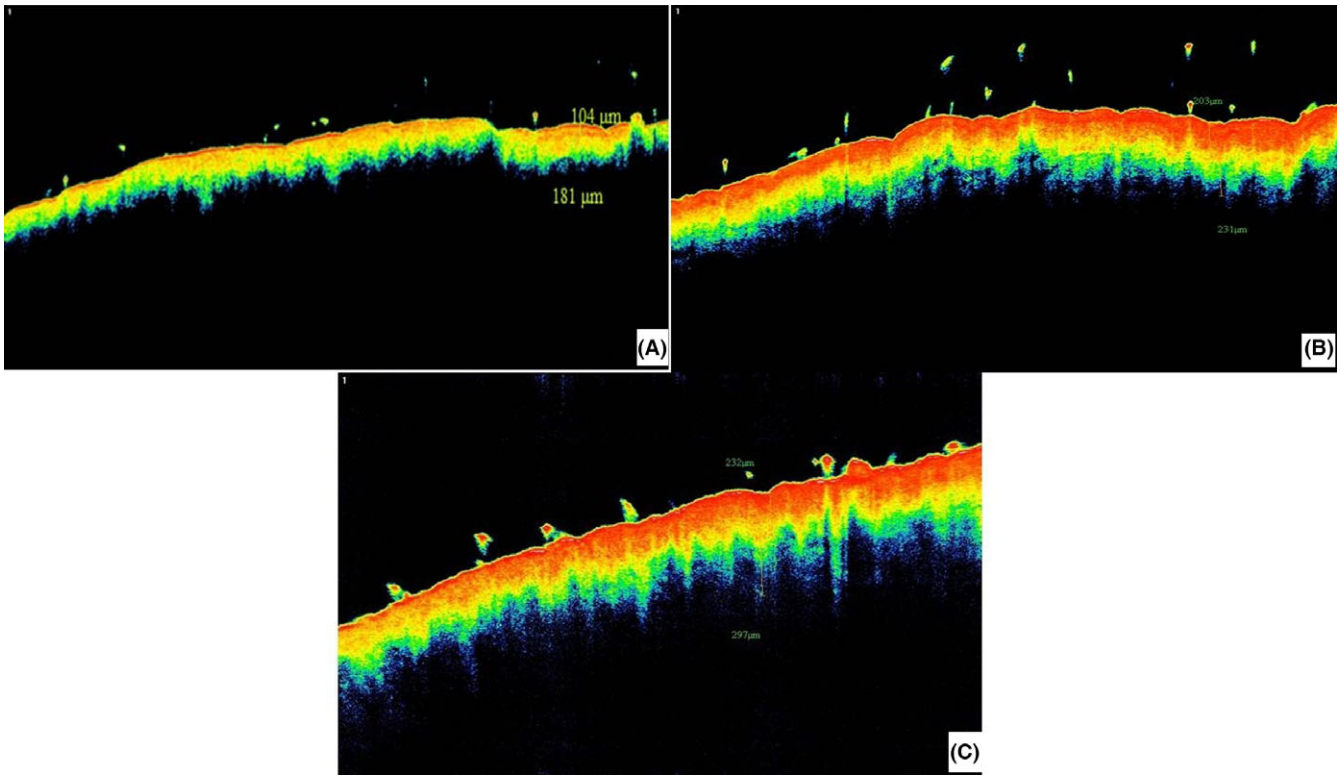

FIGURE 3 Optical coherence tomography (OCT) images of the same female patient at treated area B (autologous platelet-rich plasma [PRP]); A: at baseline showing epidermal thickness of 104 μm and dermal thickness of 181 μm, B: 1 mo after the last treatment session showing sign

B) and dermal thickness (r=.5, P=.025 in area A, r=.53, P=.034 in area B).

3.1.3 | Side effects

Among all assessed side effects, only the degree of burning sensation showed a statistically significant difference between both treated areas, being more in area A (P=.001). Transient erythema was witnessed similarly on both areas that resolved maximally in 2 days. No cases showed allergic reactions or PIH.

3.1.4 | PSL

Patients recorded a significantly higher level of satisfaction with area B receiving autologous PRP, when compared to area A receiving mesotherapy (P=.04; Table 3).

TABLE 3 Patient satisfaction level (PSL) in both treated areas (1 mo after last session)

PSL (n, %)	Area A (Mesotherapy; %)	Area B (Autologous PRP; %)
0 (Dissatisfied)	0 (0)	0 (0)
1 (Slightly satisfied)	4 (20)	2 (10)
2 (Moderately satisfied)	10 (50)	8 (40)
3 (Highly satisfied)	6 (30)	10 (50)

3.2 | Nine-months evaluation (6 months after final session)

Of the 20 patients, 14 patients (70%) returned for this long-term follow-up. No long-term side effects were detected in any of the patients on both treated areas. Area B (autologous PRP) (Figures 3C and 4) showed a more sustained improvement when compared to area A (mesotherapy) (Figures 2C and 4) as documented by clinical and OCT images.

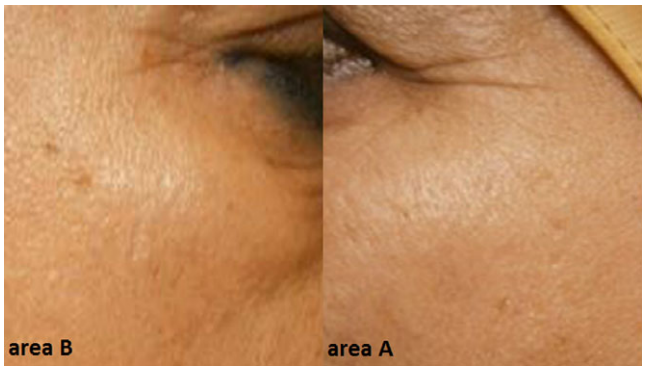

FIGURE 4 Profile view of a 52-y-old woman; area B(autologous platelet-rich plasma [PRP]) showing sustained efficacy as evident by maintained improvement of periorbital wrinkles, area A(readymade growth factors) showing reduced efficacy as evident by more noticeable periorbital wrinkles

4 | DISCUSSION

The growing interest to maintain a youthful appearance prompted the development of new dermatological procedures for treatment of skin aging. In recent years, there has been an increasing emphasis on minimally invasive treatments and techniques designed to treat volume loss, wrinkles, and skin photodamage.[10] Such procedures include mesotherapy[11] and autologous PRP.[12] Among the relevant literature, this is the first clinical study to compare both techniques as regards their efficacy as well as safety.

The efficacy of both techniques was clearly highlighted via the significant improvement in all assessed parameters (GAIS and OCT) at 4 months (1 month after last session) in both treated areas (A and B), with no significant differences between them. Furthermore, no serious side effects were noted on both sides, with only the burning sensation being more evident on the mesotherapy side. However, the autologous PRP showed an upper hand regarding the long-term beneficial effects at 6 months after last session.

Many studies have been conducted to investigate the efficacy of mesotherapy injection alone in skin rejuvenation.[3,13–18] However, these studies used a combination of hyaluronic acid with multivitamins, in contrast to the current study in which growth factors rich solution (mesotherapy) was used to be comparable to the composition of autologous PRP. Thereby, it is hard to compare the results reported by the current study to those of previous studies.

Furthermore, few studies were carried out using growth factors rich mesotherapy in a topical gel form for skin rejuvenation,[19–21] in contrast to our intradermal injection. They all revealed a significant clinical improvement in the form of reduction in fine and coarse wrinkles together with improvement of skin texture, tone, and radiance, in accordance with the results achieved by the present work.

Regarding the PRP, most of the previous studies[22–24] reported clinical efficacy and safety of PRP in skin rejuvenation (reduction of skin wrinkles, as well as improvement of texture, and elasticity with no serious or persistent side effects) as demonstrated by our results, despite the differences as regards study design.

On the other hand, in contrast to the results achieved by the current study and the previously mentioned ones,[22–24] both[25,26] reported no statistically significant changes regarding melanin content, stratum corneum hydration, wrinkles volume, upon usage of PRP. However, they did only one single session (1.5 and 1 mL respectively) for 10 and 2005 patients, respectively, and assessed their patients using GAIS 3 months after the injection. This raises the orientation that such procedures are most probably a result of cumulative effect rather than a single session.

The improvement shown by both techniques could be attributed mainly to the influence of the growth factors either supplied directly by mesotherapy, or induced by PRP. Growth factors classically promote several important functions in the regenerative medium; they are able to stimulate reparative cell proliferation, migration, differentiation, and angiogenesis.[27,28] Definitely, the other mesotherapy constituents as the multivitamins, amino acids, and minerals, and the PRP-induced cytokines have additive anti-aging effects. Vitamins C, A, and E are well known for their antioxidant effects, as well as their importance in collagen and intercellular matrix synthesis.[11] In addition to the energy related and metabolic functions of vitamin B,[29] the amino acids represent the relevant substrates required to build dermal extra cellular matrix proteins, mainly collagen. Moreover, calcium, phosphorus, and magnesium are all required for numerous biological and enzymatic reactions.[29]

An intriguing point here is the sustained effect of the PRP compared to the mesotherapy. This suggests the longevity of the effects of the growth factors and cytokines naturally induced by the PRP, and the shorter life of the readymade products, a point that prompts further investigation with longer follow-up periods.

A significant negative correlation was reported between the age of the patients as well as the frequency of sun exposure and the GAIS. Accordingly, the privilege of early intervention and avoidance of unnecessary sun exposure is further highlighted in the present study. The absence of the influence of SPT and the Glogau Photoaging Classification on the clinical improvement can be simply attributed to the lack of diversity in the current study, because all patients have SPT III and IV and Glogau type II and III.

Another point of interest is that despite the absence of a significant difference between both treated areas regarding their improvement of GAIS and OCT, the PSL was significantly higher with area B. This can be explained by the more frequent burning sensation reported in area A, pointing to the importance of comfort in addition to efficacy when dealing with cosmetic procedures.

In conclusion PRP shows superiority over readymade growth factors rich solution (mesotherapy)—although both are not FDA approved—as an effective and safe tool for combating aging signs, owing to the significantly higher patient satisfaction, fewer side effects, and more sustainable results. Accordingly, PRP use is recommended for skin rejuvenation. Larger-scale studies with longer follow-up periods are needed to reach standardized protocols.

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