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ORIGINAL PAPER

Efficacy and safety of plasma gel versus platelet-rich plasma in periorbital rejuvenation: a comparative split-face clinical and Antera 3D camera study

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Abstract

Background Periorbital skin is the thinnest. That is why, it is the easiest to wrinkle and the most challenging to rejuvenate. Platelet-rich plasma (PRP) as well as plasma gel have been used for skin rejuvenation and considered relatively safe and effective.

Methods This split-face study was conducted on forty female patients seeking periorbital rejuvenation where PRP was injected in the right (Rt) side and plasma gel in the left (Lt) side, two treatment sessions 4 weeks apart (week 0 and week 4). Patients were followed up 2 weeks after each treatment session (week 2 and week 6) as well as 12 weeks after the last session (week 16) using both subjective [physician assessment through Global Aesthetic Improvement score (GAIS) and patient's satisfaction (Likert scale)] and objective [Antera 3D camera] assessment methods.

Results Both modalities yielded a significant improvement of periorbital wrinkles after the 2nd session, with significantly better results on the plasma gel injected side; however, the improvement achieved through both modalities could not be maintained for the following 3 months. Besides, objective assessment could not prove any improvement in periorbital hyperpigmentation.

Conclusion Two sessions of both PRP and plasma gel are effective for periorbital rejuvenation, with plasma gel showing significantly better results. However, improvement was not maintained for 3 months.

Keywords Platelet-rich plasma · Periorbital · Wrinkles · Pigmentation · Plasma gel

Background

Being the thinnest skin of the body, mainly because of its diminished dermis, the eyelid skin is almost transparent and easily wrinkles [1, 2] The periorbital facial subunit consists of the eyebrows, upper and lower eyelids, glabellar region, and pericanthal area. It is one of the first regions to reveal signs of aging and plays an important role in overall facial appearance. The aging process is ruled by genetic as well as environmental factors. Aging skin manifests by the appearance of coarse and fine rhytides (wrinkles), uneven texture, dryness, and mottled pigmentation [3, 4]

Hyperpigmentation of the periorbital area can be divided into primary (idiopathic) that occurs in individuals with otherwise healthy skin, and secondary types [5]. Secondary type may be caused by many etiologic factors such as familial or ethnic tendency, periorbital edema, and post-inflammatory hyperpigmentation, caused by atopic or allergic contact dermatitis, medications, and systemic diseases. Other factors that can be included are fatigue, smoking, excessive sun exposure, superficial location of vasculature of the eyelids, tear trough depression, and shadowing due to laxity of the skin [6, 7]

Platelet-Rich Plasma (PRP), an autologous source of platelet-derived growth factors, could play a role in skin rejuvenation. Several hypotheses were suggested for mechanisms of rejuvenation by PRP such as increased proliferation of human dermal fibroblasts, increased expression of Matrix Metalloproteinase (MMP-1 and MMP-3), increased

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production of procollagen type 1 peptide, and expression of collagen type1-alpha 1 leading to the synthesis of new collagen [8]. A newer approach based on autologous plasma gel has been introduced for periorbital rejuvenation and correction of aging with variable results and outcomes [9].

A high viscosity plasma gel was first introduced by Krajcik and co-workers in 1999 who reported the efficacy and safety of plasma gel injection in the correction of nasolabial folds [10]. Plasma gel has been commonly made by added activators, such as thrombin or calcium chloride, or by slow activation from contact with the glass storage tube and has more concentrated fibrin matrix than PRP [11, 12]. It is thought to induce immediate volumization upon injection, and contain more growth factors [13].

Given the variability of the findings seen with the previous studies, we designed this split-face comparative study aiming at evaluating the efficacy, durability, and possible side effects, of platelet-rich plasma injection versus plasma gel injection in periorbital rejuvenation.

Patients and methods

Recruitment of participants

This comparative split-face study included 40 females with periorbital wrinkles and/or dark circles recruited from the Dermatology outpatient clinic Demerdash hospitals, between February and October 2019. The study was approved by the Research Ethical Committee, Faculty of Medicine, Ain Shams University (FMASU 296/2019), and fulfilled all the ethical aspects required in human research. All patients received full information about the description of the procedure of treatment, possible side effects, and photo-documentation, and they all provided informed consent. All patients were housewives with a lifestyle that includes little sun exposure to avoid the confounding effect of photoaging. Selection was limited to skin types II and III to minimize the variables. We excluded patients who received any cosmetic treatment within the last 6 months prior to enrollment including botulinum toxin injection, laser, fillers, or any other procedure, patients with autoimmune or hematologic disorders, patients receiving anticoagulant therapy, and patients with periorbital infection or eczema.

Full history was obtained from all candidates before a thorough dermatological examination. Periorbital skin was examined and given a grading of dark circles and a grading for wrinkles according to Glogau wrinkles scale [14] and photographed using Canon IXUS145 digital camera and Antera 3D® Camera (Miravex) Dublin, Ireland. Evaluation of treatment response was done subjectively (by both the physician and patients) and objectively using Antera 3D camera, 2 weeks after each treatment session as well as 12 weeks after the last session. Physician assessment was done through Global Aesthetic Improvement Score (GAIS), which is a 5-point scale: 1—very much improved; 2—moderately improved; 3—somewhat improved; 4—no change; 5—worse [15]. A patient's satisfaction questionnaire was obtained from the patients using a four-point (0–3) Likert scale: 0—unsatisfied; 1—partially satisfied; 2—moderately satisfied; 3—completely satisfied [16]. Antera 3D® camera is a camera which allows capturing high-resolution images. It uses an innovative optical method and complex mathematical algorithms to obtain three-dimensional images which allowed us to quantify the efficacy of treatments and monitor the changes over time [17] We used three modes in our study that are indentation index for wrinkle's depth, roughness index for skin texture and average melanin concentration for skin pigmentation. Furthermore, potential side effects were documented including post-procedural pain, erythema, and edema using a 4—point scale: 0—absent, 1—mild, 2—moderate, and 3—severe [18].

Platelet-rich plasma and plasma gel preparation

Under complete aseptic conditions, 10 mL of venous blood were withdrawn from each participant and collected in two sterile vacuum tubes (5.0 mL) each equipped with premeasured amounts of anticoagulant citrate dextrose solution. Each blood sample was centrifuged at $320 \times g$, for 15 min at 4 °C, resulting in blood separation into: the lower layer formed of red blood cells, the middle layer formed of white blood cells (the buffy coat), and the upper layer formed of plasma. Then centrifuged again for another 5 min at 1000 g to collect plasma sample: the upper part consisting of platelet-poor plasma (PPP) and the lower part composed of PRP for injection. The PPP was then gently aspirated and placed in a sterile injection syringe, carefully not to mix it with PRP, prepared for activation by calcium gluconate (0.01 mL per 1 mL of PPP). The activated PPP was distributed into five 1.0-mL syringes and heated in a hot water bath at a temperature between 60 and 100 °C for 1 min, and then in a cold bath at a temperature between 8 and 0 °C for 1 min. Finally, PPP was transformed into a viscous gel (plasma gel) ready for use [19].

Technique

After 45 min of topical anesthetic application, eyelids were disinfected. PRP was injected intradermally using 26 G needles in the Rt-sided periorbital area, while plasma gel was injected subdermally in the Left (Lt) side using 22 G needles. Each patient received two treatment sessions 4 weeks apart.

Statistical analysis

Data were collected, revised, coded, and entered into the Statistical Package for Social Science (Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). The quantitative data were presented as mean, standard deviations (SD) , and ranges when their distribution was found parametric, while non-parametric were presented as median with inter-quartile range (IQR). Also, qualitative variables were presented as number and percentages (%).

The comparison between groups regarding qualitative data was done using Chi-square test. The comparison between two independent groups with quantitative data and parametric distribution was done using Independent *t* test, while the comparison between more than two paired groups with quantitative data and parametric distribution was done by using Repeated-Measures ANOVA. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group. The confidence interval was set to 95% and the margin of error accepted was set to 5%. Therefore, the p value was considered significant if $P < 0.05$.

Results

Demographic and clinical data of all patients are shown in Table 1.

Table 1 Demographic data and clinical characteristics of studied subjects

	No. = 40%
Age	
Mean ± SD	32.48 ± 5.27
Range	21–40
Glogau scale (types of wrinkles)	
II	18 (45.0%)
III	22 (55.0%)
Duration (years)	
Median (IQR)	5 (3–10)
Range	1–16

Evaluation of treatment response

I. Subjective assessments (GAIS scale and patient's satisfaction) (Table 2; Figs. 1 and 2)

Two weeks following the first session, there was no significant difference in treatment response between both sides on the first visit according to GAIS ($P = 0.280$). However, two weeks following the second session (6 weeks following the first visit), both sides showed significant improvement. The plasma gel injected side showed significantly better improvement than the PRP injected side ($P = 0.009$). During the last follow-up visit at the 16th week (12 weeks following the last session), an improvement on both sides showed declining; however, there was still a significant difference between the two sides with better improvement on the plasma gel injected side.

Table 2 Comparison between treatment response of periorbital wrinkles and/or dark hallows on right and left sides according to GAIS

GAIS	Right side No. = 40	Left side No. = 40	Test value	*P* value	Sig
1st visit week 2					
Very much improved	1 (2.5%)	0 (0.0%)	5.075	0.280	NS
Moderate improved	2 (5.0%)	5 (12.5%)			
Somewhat improved	12 (30.0%)	18 (45.0%)			
No change	23 (57.5%)	16 (40.0%)			
Worse	2 (5.0%)	1 (2.5%)			
2nd visit week 6					
Very much improved	2 (5.0%)	6 (15.0%)	13.422	0.009	HS
Moderate improved	9 (22.5%)	20 (50.0%)			
Somewhat improved	14 (35.0%)	10 (25.0%)			
No change	13 (32.5%)	3 (7.5%)			
Worse	2 (5.0%)	1 (2.5%)			
3rd Visit week 16					
Very much improved	0 (0.0%)	0 (0.0%)	8.284	0.040	S
Moderate improved	0 (0.0%)	1 (2.5%)			
Somewhat improved	8 (20.0%)	19 (47.5%)			
No change	30 (75.0%)	19 (47.5%)			
Worse	2 (5.0%)	1 (2.5%)			

P value > 0.05: Non-significant; *P* value ≤ 0.05: Significant; *P* value ≤ 0.01: Highly significant

*:Chi-square test

Fig. 1 Digital clinical photography of a 34-year-old female with periorbital wrinkles, of 6 years duration. Glogau scale 4. Before treatment (**A**, **C**). 2 weeks after last treatment session, (**B**, **D**). Before treatment (week 0): **A** Right-sided periorbital area. **C** Left-sided periorbital area. Two weeks after last session (week 6): **B** Right-sided periorbital areas, GAIS score improved, patient satisfaction rated good. **D** Left-sided periorbital areas, GAIS score improved, patient satisfaction rated good

According to patient's satisfaction score at week 2, no significant difference was noted between right and left sides regarding wrinkles or dark hallows ($P = 0.882$). None of the 40 recruited subjects showed complete satisfaction to plasma gel or PRP injection, and 50% of patients showed partial satisfaction to plasma gel compared to 47.5% of patients to PRP, while 27.5% of patients were unsatisfied following plasma gel injection, compared to 32.5% of patients who were unsatisfied after PRP injection. While during the second visit (2 weeks after the second session), a significant difference was noted between the left and right sides of periorbital wrinkles and/or dark hallows ($P = 0.005$). No patients were unsatisfied after plasma gel injection in comparison with 20% of patients who were unsatisfied after PRP injection. Forty percent of patients were completely satisfied after plasma gel injection compared to 20% of patients after PRP injection, 30% of patients expressed moderate satisfaction to plasma gel compared to 17.5% of patients with PRP, and 30% of patients were partially satisfied after plasma gel, while 42.5% of patients to PRP.

II. Objective assessment (Antera 3D camera) (Figs. 3 and 4)

Data regarding indentation index are shown in Table 3, roughness index in Table 4, and average melanin concentration in Table 5. On comparing right and left sides, indentation index was highly significant in the 1st and 2nd visits being higher on right side, while non-significant difference was seen before treatment and at the 3rd visit. Roughness index also showed significant difference at 1st visit, while non-significant difference was noted before treatment and at 2nd and 3rd visits. Also, average melanin concentration showed non-significant difference at 1st, 2nd, or 3rd visits.

Evaluation of encountered side effects

At the first visit, there was a significant difference between right and left sides ($P = 0.015$). Side effects reported were pain, erythema, ecchymoses, swelling, and a feeling of pressure. They were documented according to the surface area. All side effects were documented and classified into 0 = absent, 1 = mild pain and/or erythema + ecchymosis

Fig. 2 Digital clinical photography of a 28-year-old female with periorbital wrinkles, of 2 years duration. Glogau scale II. Week 0: Before treatment (**A**, **C**). Week 6: two weeks after last session, (**B**, **D**). Before treatment (week 0): A Right-sided periorbital area. **C** Left-sided periorbital area. Two weeks after last treatment session (week 6): **B** Right-sided periorbital area, GAIS improved patient satisfaction rated good. **D** Left-sided periorbital area, GAIS much improved patient satisfaction rated excellent

and/or edema over up to one-third of the eyelid surface area, 2 = moderate pain and/or erythema + ecchymosis and/or edema covering two-thirds of the eyelid surface area, 3 = severe pain and/or erythema + ecchymosis and/or edema covering more than 2/3 of the eyelid area. No patients experienced severe complications following PRP injection compared to 10% of patients after plasma gel injection, and only 2.5% of the patients showed moderate complications following PRP injection, while 17.5% of patients showed moderate complications following plasma gel injection, 45% of patients showed mild complications after PRP and 40% of patients after plasma gel. While, no complications were witnessed in 52.5% of patients after PRP injection compared to 32.5% of patients after plasma gel. All complications were temporary and resolved completely before the next follow-up sessions 2 weeks later, stopping treatment was not recommended and none of the patients asked to quit the study. However, during the second visit, no significant difference was noted between right and left sides ($P = 0.173$). No patients experienced any severe complications on the right side, while 2.5% of patients showed severe complications on the left side. Moderate complications were experienced in 17.5% of patients on the left side and 10% of patients on the right side. Mild complications were witnessed in 37.5% of patients on the right side compared to 50% of patients on the left side. No complications were found in 52.5% of the patients on the left side compared to 30% of patients on the right side.

Our results showed no significant association between the type or course of wrinkles and all the Antera 3D indices (indentation index, roughness index, and average melanin concentration) before and 2 weeks after 2nd session on both sides. Yet, a significant association was noted between age of patients and indentation index before treatment on left side only ($P = 0.043$). A significant association was also found between age of patients and roughness index on right side ($P = 0.002$) and left side ($P = 0.042$) before treatment, as well as, at 2nd visit on the left side only ($P = 0.005$), while there was no significant association between age of patients and melanin concentration before and after treatment on

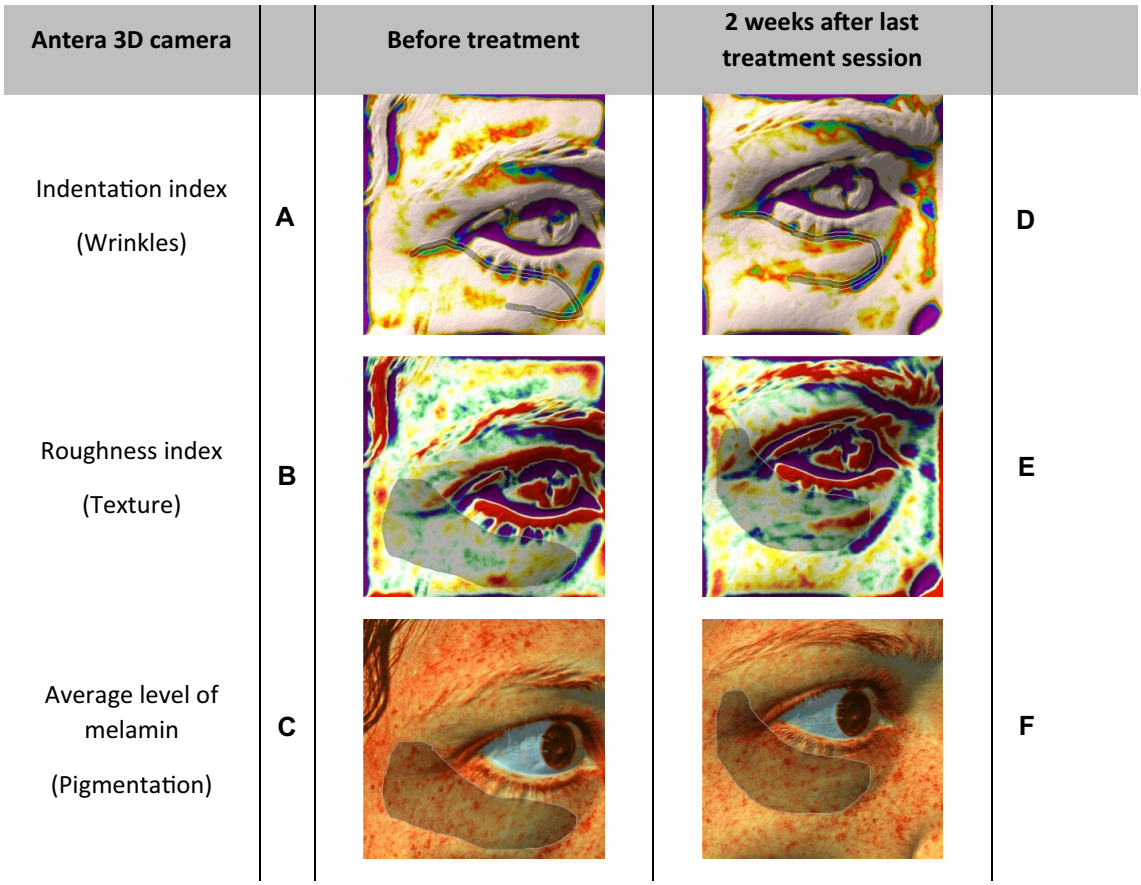

Fig. 3 Antera 3D camera photography of right periorbital area of the same patient before treatment and 2 weeks after last session. Before treatment: **a** Indentation index was 83.9. **b** Roughness index was 36.657. **c** Average melanin level was 0.649. Two weeks after last session. **d** Indentation index decreased to 67.5. **e** Roughness index decreased to 32.465. **f** Average melanin level slightly increased to 0.658

both sides. Furthermore, there was no significant correlation found between the duration of wrinkles and Antera 3D results of both periorbital areas except for the roughness index before treatment on Rt side ($P=0.006$) and indentation index on Lt side before treatment ($P=0.046$).

Discussion

The characteristic signs of skin aging are surface irregularity, atrophy, fine-coarse wrinkles, and dyschromia resulting in leathery and pale skin [18]. Treatments for periorbital wrinkles and pigmentation include several non-surgical modalities, such as hyaluronic acid injections, chemical peeling, microneedling, laser ablative and nonablative resurfacing, botulinum toxin, and carboxytherapy injection [20]. As an autologous source of platelet-derived growth factors, PRP has been used to improve signs of skin aging [9].

To our knowledge, widely variable results were obtained comparing PRP to plasma gel in managing signs of skin aging, and a very wide gap of evidence comparing their role in periorbital rejuvenation. Thus, the aim of our study was to evaluate the efficacy, tolerability, and durability of platelet-rich plasma injection versus plasma gel injection in the treatment of periorbital wrinkles and/or dark hallows.

Our study included 40 patients, whose age ranged from 21 to 40 years seeking periorbital rejuvenation. Each patient received two sessions, 1 month apart, of PRP injection on the right side and plasma gel on the left side of periorbital areas. Evaluation of treatment response was done 2 weeks after each session as well as 12 weeks after last session to assess durability of obtained clinical improvement through patient's satisfaction (Likert scale), GAIS score, and Antera 3D results (indentation index, roughness index, and average melanin concentration).

On comparing treatment response seen with PRP injection on the right-sided versus plasma gel injection on the left-sided periorbital areas regarding GAIS scale; there was non-significant difference following the 1st session; However, plasma gel showed significantly better improvement

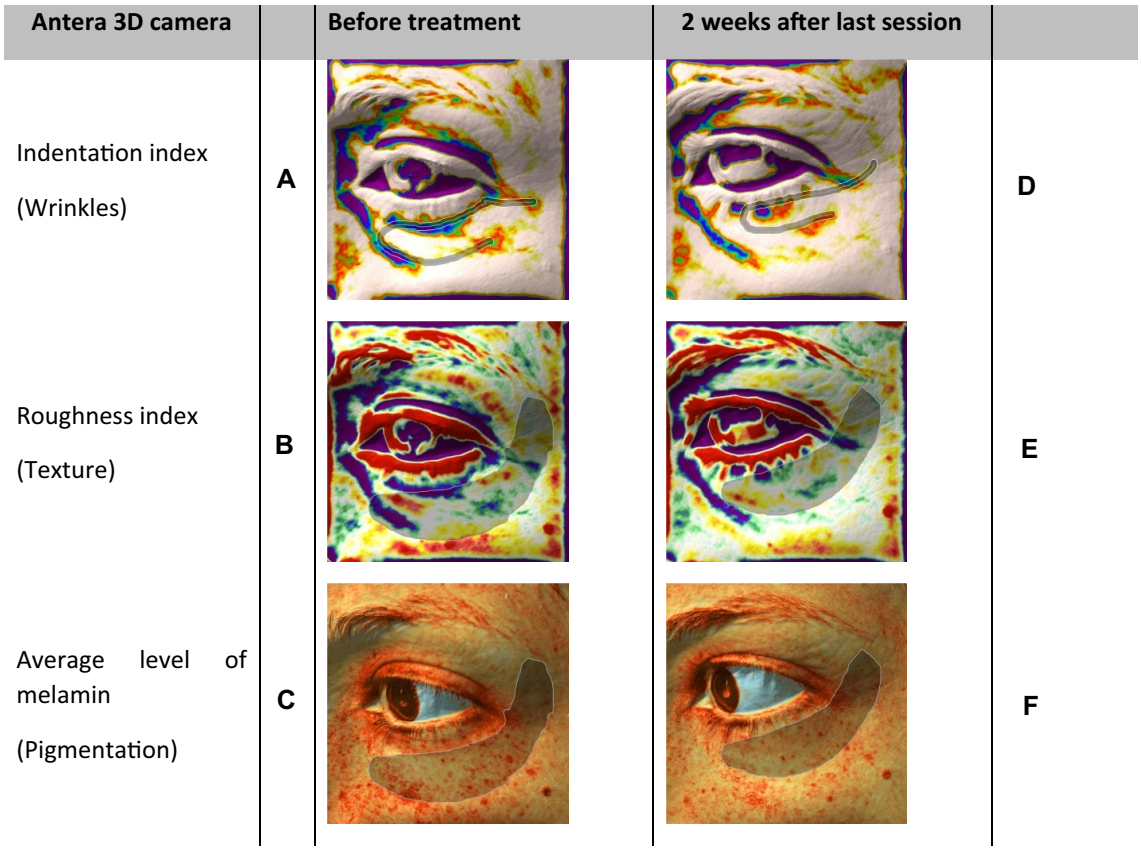

Fig. 4 Antera 3D camera photography of left periorbital area of the same patient before treatment and 2 weeks after last treatment session. Before treatment: **a** Indentation index was 91.1. **b** Roughness index was 53.216. **c** Average melanin level was 0.652. 2 weeks after last session: **d** Indentation index decreased to 39.3. **e** Roughness index decreased to 39.707. **f** Average melanin level decreased to 0.639

following the 2nd session as well as on the 16th week follow-up. On the other hand, according to patient's satisfaction, there was significant difference between right and left side at the 2nd visit being higher with plasma gel, while there was non-significant difference at the first and final visits. Thus, plasma gel was better than PRP in periorbital rejuvenation but both had a short efficacy.

In a recent systematic review and metanalysis of PRP and plasma gel treatment of periorbital skin, the results of 19 types of research that took place between 2010 and 2019 using Likert scale for assessment, periorbital wrinkles showed significant improvement that persisted for variable periods of time. However, unlike ours, most of these studies lacked objective assessment. Authors recommended more comparative studies with objective assessments [20].

On contrary to our short-term efficacy results, plasma gel injection in nasolabial fold in a study on 20 patients, in the whole face in another study on 52 patients as well as a third pilot study on ten women for malar area and marionette lines; the improvement in all lasted for more than 3 months [21–23]; this can be attributed to the uniqueness of the eyelid skin being the thinnest with the least supporting structures. We suggest that periorbital rejuvenation needs more sessions to obtain the same long lasting results as the rest of facial skin. this difference can also be attributed to different preparation methods where Jiménez Gómez [23] used PRP gel, while our plasma gel was prepared from PPP.

With objective assessment using the Antera camera, the right side injected with PRP showed significant decreased indentation index following the 2nd session only and nearly returned to baseline when assessed 12 weeks after the 2nd session. While at left side injected with plasma gel, the wrinkles depth assessed by indentation index improved significantly following the 1st session, still significantly improved following the 2nd session. However, at the follow-up visit (12 weeks after the 2nd session), indentation index also returned nearly as baseline.

Meanwhile, there was significant difference in indentation index between right- and left-sided periorbital areas (being higher on right side following both 1st and 2nd sessions).

Regarding the texture of the skin (roughness index) measured by Antera 3D camera, both modalities showed

Table 3 Comparison between right- and left-sided periorbital areas regarding Indentation index before and after treatment

Indentation Index	Right side No. = 40	Left side No. = 40	Test value●	*P* value	Sig
Baseline					
Mean ± SD	93.56 ± 23.99	90.84 ± 18.61	− 0.568	0.572	NS
Range	37.1–143.3	58.7–141			
Week 2					
Mean ± SD	95.12 ± 24.69	76.70 ± 20.02	− 3.665	0.000	HS
Range	44.3–157	36.1–126.5			
week 6					
Mean ± SD	84.69 ± 21.83	69.40 ± 19.95	− 3.268	0.002	HS
Range	38.2–156.1	39.3–117.6			
week 16					
Mean ± SD	93.41 ± 18.96	88.04 ± 23.86	− 1.113	0.269	NS
Ranges	46–142.1	46.7–141			
P value●●	0.016 (S)	< 0.001 (HS)			
Before Vs 1st visit	1.000 (NS)	0.001 (HS)			
Before Vs 2nd visit	0.073 (NS)	< 0.001 (HS)			
Before Vs 3rd visit	1.000 (NS)	1.000 (NS)			
1st visit Vs 2nd visit	0.037 (S)	0.226 (NS)			
1st visit Vs 3rd visit	1.000 (NS)	0.013 (S)			
2nd visit Vs 3rd visit	0.133 (NS)	0.001 (HS)			

P value > 0.05: Non-significant (NS); *P* value ≤ 0.05: Significant (S); *P* value ≤ 0.01: highly significant (HS)

●: Independent *t* test; ●●: Repeated-Measures ANOVA test

Table 4 Comparison between right and left-sided periorbital areas regarding roughness index before and after treatment

Roughness Index	Right side No. = 40	Left side No. = 40	Test value●	*P* value	Sig
Baseline					
Mean ± SD	52.63 ± 11.38	49.34 ± 12.19	− 1.246	0.217	NS
Range	27.9–75.52	26.43–84.05			
Week 2					
Mean ± SD	53.45 ± 13.23	47.83 ± 11.55	− 2.026	0.046	S
Range	27.24–89.12	30.15–77.27			
Week 6					
Mean ± SD	50.12 ± 12.74	48.27 ± 13.32	− 0.635	0.527	NS
Range	28.52–96.74	20.16–82.12			
Week 16					
Mean ± SD	50.37 ± 15.16	48.93 ± 15.47	− 0.420	0.675	NS
Ranges	14.46–101.08	16.33–85.06			
p value●●	0.439 (NS)	0.866 (NS)			

P value > 0.05: Non-significant (NS); *P* value ≤ 0.05: Significant (S); *P* value ≤ 0.01: highly significant (HS)

●: Independent *t* test; ●●: Repeated-Measures ANOVA test

relatively similar results with no significant difference between the two sides, both showed significant improvement only following the 2nd session with the index returned back to baseline by the 16th week.

Objective assessment of wrinkles following PRP and plasma gel injection was reported by several studies using different assessment methods [23–26]. All their results were similar to ours with significant improvement of wrinkles.

Table 5 Comparison between right-and-left-sided periorbital areas regarding average melanin concentration before and after treatment.

Melanin Conc	Right Side No. = 40	Left Side No. = 40	Test value•	*P* value	Sig
Baseline					
Mean ± SD	0.72 ± 0.10	0.72 ± 0.10	− 0.307	0.759	NS
Range	0.5–0.98	0.51–1.02			
Week 2					
Mean ± SD	0.71 ± 0.10	0.72 ± 0.09	0.144	0.885	NS
Range	0.45–0.92	0.51–0.92			
Week 6					
Mean ± SD	0.72 ± 0.10	0.71 ± 0.11	− 0.318	0.751	NS
Range	0.48–0.95	0.5–1			
Week 16					
Mean ± SD	0.73 ± 0.10	0.72 ± 0.10	− 0.317	0.752	NS
Range	0.54–0.97	0.55–1.04			
P value••	0.258 (NS)	0.323 (NS)			

P value > 0.05: Non-significant (NS); *P* value ≤ 0.05: Significant (S); *P* value ≤ 0.01: highly significant (HS)

•: Independent *t* test; ••: Repeated-Measures ANOVA test,

Elnehrawy and co-workers [25] reported that 8 week persistent improvement of wrinkles was evident in the nasolabial folds but not in crow's feet, this is in accordance with our results regarding the persistence of improvement in the periorbital area.

Regarding average melanin concentration of the dark hallows measured by Antera 3D camera in both right and left sides, there was no significant improvement seen at the right side or left side at any follow-up visits with no difference between both sides either. This was in accordance with Mehryan et al. [27] who showed no improvement of average melanin concentration in infraorbital dark circles measured using the Mexameter probe. However, unlike our results, they found no improvement in periorbital wrinkles depth either. We attribute this to the fact that their assessment of wrinkles was subjective, unlike the objective assessment of the melanin concentration. Although their objective assessment of the melanin concentration showed no significant change, the subjective assessment of the very same cases in this study showed improvement of periorbital darkening [27].

Thus, although PRP may be considered as a good method for treatment of periorbital wrinkles, our results showed that plasma gel seems to be superior causing significant decrease of wrinkles depth than PRP. The improvement seen by plasma gel may be attributed to the three-dimensional fibrin matrix that allows adherence of platelets at the fibrin scaffold, and causes a sustained release of growth factors [28].

On the other hand, a significant positive correlation was found between the age of the patients and the indentation index of the wrinkles on the left side only before treatment and the roughness Index on both sides before treatment as well as left side only 2 weeks after 2nd session but not with the average melanin level.

The improvement seen by plasma gel may be attributed to the three-dimensional fibrin matrix that allows adherence of platelets at the fibrin scaffold, and causes a sustained release of growth factors [28].

This is logically expected, the depth of periorbital wrinkles and texture of the skin is increasing with progressive aging, while dark hallows are not affected by aging. This was in concordance with another study that used the skin imaging analysis instruments to reveal the differences and associations in measuring wrinkles and skin texture, they did their study on 28 patients with wider age range (20–62) using Antera 3D camera, and they found that the indentation index of the wrinkles and the roughness index of the texture were positively correlated with age. However, contradicting our results, average melanin level showed also positive correlation with progressive aging. Racial difference can be an explanation as their study was conducted on Chinese candidates [17].

According to patient's safety (possible side effects) evaluated during the first and second visits including pain, erythema, and edema using a 4-point scale. Although there was no significant statistical difference between the two maneuvers, higher side effects were encountered with plasma gel injection. In a recent systematic review, all of the 19 studies included showed the same safety regarding PRP and plasma gel injection. Both procedures can be considered as relatively safe.

Our study had several methodological and scientific strengths, we used a split-face study that markedly limited the variation between individual groups. We also used variable subjective and objective methods of assessment to eliminate the bias in obtaining results. Candidates' selection aimed at limiting the confounders and the variables by choosing minimal sun-exposure lifestyles and limit the selection to skin types II and III.

However, it is still important to consider our results with certain limitations in mind, our study lacked assessment of effect of photoaging and only assessed chronological aging, this aimed at minimizing the variables. Also the mean age of our study population was relatively young, as the results showed significant association between patents' age and improvement, further studies are needed to assess PRP and plasma gel results in older age.

Conclusion

Subjective and objective assessment shows that PRP and plasma gel can both be effective in periorbital rejuvenation with better improvement by plasma gel. However, both

modalities do not decrease melanin concentration. Both modalities were well tolerated, and further research and innovations may be needed to determine methods for prolongation of these modalities' beneficial effects.

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Declarations

Conflict of interest None of the authors has any potential conflict of interest.

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