ORIGINAL ARTICLE

BIOFILLER VS PLATELET-RICH PLASMA MESOTHERAPY IN THE TREATMENT OF PERI-ORBITAL HYPERPIGMENTATION

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Background: Peri orbital hyperpigmentation (POH) is a common presentation in dermatological outpatient departments and has multiple causes. Finding an appropriate treatment for POH can be challenging and requires a case-based approach. The objective of this research was to study the effect of Biofiller vs. PLATELET-RICH plasma meso-therapy in the treatment of Peri-orbital hyperpigmentation. Our hypothesis was "Biofillers are better than platelet-rich plasma therapy in the treatment of peri-orbital hyperpigmentation". It was a double-blinded randomized Control Trial (IRCT20230816059168N1) carried out in the Dermatology OPD of a tertiary care hospital in Rawalpindi over 4 months, i.e., 10.07.23 to 10.10.23. **Methods:** Forty-two patients meeting the inclusion criteria were included in the study after taking informed consent. Sampling was done by non-probability randomized sampling using the lottery method. 21 patients were treated with Bio fillers and another 21 with platelet-rich plasma therapy (PRP). Sessions with a 2-week interval were done in each case and results were analyzed by peri-orbital photo-metric pigmentation scale and clinical grading improvement scale rated by a physician. Patient satisfaction and complications were also recorded. **Results:** Statistically significant difference in results of Group A as compared to Group B, regarding improvement in photo numeric scale, evaluation of efficacy by a blinded dermatologist and patient satisfaction, i.e., *p*= 0.001, 0.014 and 0.001 respectively. In group A, pain was reported by 3 (14.3%), bruising by 1 (4.76%) and lumps by 2 (9.5%). PRP treated group had more side effects, i.e., 9 (42.8%) reported pain, 6 (28.6%) bruising and 4 (19%) more than one complaint (*p*-0.001). **Conclusion:** Biofillers are better than PRP in the treatment of POH.

Keywords: Biofiller; Dark circles; Mesotherapy; Peri-orbital hyperpigmentation; Platelet-rich plasma

Citation: Sadiq S, Bashir U, Rizwan A, Anwar A, Rao S, Shahid S. Biofiller vs Platelet-rich plasma mesotherapy in the treatment of peri-orbital hyperpigmentation. J Ayub Med Coll Abbottabad 2024;36(1):56–63.

DOI: 10.55519/JAMC-01-12585

INTRODUCTION

Dermatologists and aestheticians come across lots of patients in daily outpatient department seeking aesthetic treatment for their "periorbital hyperpigmentation" (POH) or "The dark circles", also known as periocular hyperpigmentation, periorbital melanosis, infraorbital darkening, infraorbital discolouration, or idiopathic cutaneous hyper-chromia of the orbital region.[2]

Periorbital hyperpigmentation includes bilateral hyperpigmented (blackish, greyish, bluish or brownish) macules and patches involving the area around the eyes bilaterally (mainly involving lower eyelids but sometimes the upper eyelids, malar regions and temporal regions and are involved too). The influence on the quality of life caused by POH is immense. It is more common in certain races and can be a familial trait.1 Hormonal influence makes women more prone to it, than men.[3]

Periorbital hyperpigmentation has multiple causes including genetics, dermal melanin deposition, post-inflammatory hyperpigmentation, superficial location of the vasculature, shadowing due to skin laxity, and multiple secondary causes. Secondary causes may be associated with faulty lifestyle, i.e., reading, computer usage and TV watching for more than 8 hours a day, errors of refraction i.e. myopia, use of glasses, eye rubbing, less sleep, cosmetics, alcohol intake and smoking. Similarly, local diseases of the eyes and skin like atopic dermatitis, contact dermatitis, recurrent eyelid oedema, and conjunctivitis have been found associated with the disorder.[4,5]

Different types of POH mentioned in literature are constitutional, vascular, post-inflammatory and shadow effect or structural. The commonest type of POH in Indians is of constitutional type as mentioned in studies, i.e., 51.50% of the patients presenting with POH.[6,7]

The relative assessment of the colour of the POH compared to the surrounding facial skin is the backbone of diagnosing, grading and treating POH. In 2020 M.M. O'Mahony *et al* made this assessment

easier by making a validated photo numeric scale for infraorbital dark circles. This scale was successfully validated by an assessor-blinded split-face, clinical trial of a cosmetic for improving POH, having 38% subjects of Fitz Patrick skin type 4 and 5.[8]

Huang *et al* proposed the classification of dark circles based on the clinical appearance of pigmentation and vasculature. POH was classified into pigmented (brown colour), vascular (blue/pink/purple colour), structural (skin colour), and mixed type based on the clinical appearance assessed by the physician.[9]

In managing POH, topical hydroquinone, kojic acid, azelaic acid, and retinol have been tried. Other options utilized are chemical peeling with alpha and beta hydroxyl acids, microneedling and mesotherapy. Lasers used for treating dark circles include Q-switched ruby laser (694 nm) and alexandrite laser, Nd: Yag laser (1064 nm) and fractional carbon dioxide laser. Autologous fat injections and hyaluronic acid dermal fillers can be used for volumizing the tear troughs and correcting dark circles.[7]

Recently, platelet-rich plasma has been used in treating dark circles due to tear trough deformity and wrinkles. 10 PRP is considered a safer and organic treatment option by both dermatologists and patients, because being autologous, it enjoys the advantages of reduced immunological reactions and disease transmission. Platelet-rich plasma therapy releases cytokines, which bind to target cells i.e. fibroblasts, endothelial and epidermal cells, which trigger cell proliferation, angiogenesis, collagen synthesis and reduced apoptosis. Platelet-rich plasma therapy increases the expression of matrix metalloproteases, stimulating the removal of fragments of collagen fibrils, accumulating in aging skin. It stimulates fibroblasts to synthesize new collagen fibres and more hyaluronic acid, which increases skin thickness and turgor. TGF-β plays a role in treating hyperpigmentation by decreasing tyrosinase and related proteins.[11]

Biofiller is a platelet-poor plasma (PPP) gel rich in fibrin and proteins. It has been used as a dermal filler in peri-orbital rejuvenation because it is not so expensive, autologous, semi-solid easy-to-mold material.[11] Platelet poor plasma is a novel finding for aesthetics, having collagen remodelling and tissue regeneration activity. It usually has platelets less than 104/μL. 12 It is converted into a viscous gel before injection by heating and then cooling. It has a lot of growth factors and platelet factor 3, which can induce tissue regeneration and collagen remodelling in addition to the immediate volumetric filling .[13,14]

The study aims to establish the efficacy of Biofiller Vs Platelet-rich plasma mesotherapy in the treatment of peri-orbital hyperpigmentation.

MATERIAL AND METHODS

Approval and Registry as clinical trial was done with Trial Id of 72138 with Iranian Registry of Clinical Trials: IRCT20230816059168N1. Ethical approval was taken: A/28/EC/576/23. The study was conducted in the Dermatology outpatient department of a tertiary care hospital in Rawalpindi over 4 months, i.e., 10th July to 10th Oct 2023. The study design was a "Randomized control trial", with two parallel intervention groups, double-blinded. The sample size was calculated by using the epi info sample size calculator and using the prevalence of dark circles in a study showing the prevalence of 47.50 % in people from India, 81% were females.[6] Taking a 2 –2-sided significance level of 95% and power of 80%, we took a sample size of 21 in each group. Inclusion Criteria was: All patients with peri-orbital hyperpigmentation willing to participate in our study, Patients with peri-orbital hyperpigmentation, aged 18–65 years, Patients of Fitzpatrick skin type 1–V. We included only these skin phototypes in our study as the photo numeric scale we used was made ideally for these. Exclusion criteria was: Patients having Hepatitis B or C or HIV (as PRP and bio fillers are blood products and dealing with infected people can be hazardous for treating staff), patients on immunosuppressant medications due to other diseases, pregnant women, patients on anti-platelet or anticoagulants or fibrinolytic, patients using or have used other treatments for dark circles and patients of Fitzpatrick skin type V1.

Forty-two patients presenting to dermatology OPD of PEMH were recruited in the study after applying the inclusion and exclusion criteria. Informed consent was taken from the patients and explained the minimally invasive nature of the procedure. Simple, non-probability randomized sampling in patients divided into two random groups was done, by the use of the lottery method, i.e., by giving the patients sealed envelopes of 2 types to choose one blindly from them. And afterwards were divided into two groups.

Periorbital hyperpigmentation in all cases were classified into pigmented, vascular, structural, and mixed type based on the clinical appearance and Wood's lamp examination, assessed by the physician, as proposed by Huang *et al*. 7 Half of them were treated by bio fillers (Group A) and another half by PRP meso-therapy (Group B). They were not knowing, which treatment they were undergoing exactly, as both methods required

materials made from their blood and to be injected peri-orbitally. After 02 weeks of completion of treatment, another dermatologist from our department blindly assessed the results, as she was not knowing which treatment the patient underwent.

For intervention group A, a topical eutectic mixture of local anaesthetic cream (EMLA) was applied over the peri-orbital area for 45 min. Ten ml of the patient's blood was drawn in a syringe pre-filled with 1 mL acid citrate dextrose (anticoagulant). It was centrifuged first at 3500 rotations per minute (RPM) for 15 min and then at 1500 RPM for 5 min. The upper part, i.e., platelet-poor plasma (PPP) was withdrawn in a 5 mL syringe. PPP was incubated in hot water at 100 a °C for 5 min and then cooled in a refrigerator for 5 min. It yielded 3- 4 ml of gel. 0.5 ml local anaesthetic, i.e., 2% lignocaine was injected at the entry point of the cannula. Biofiller was injected slowly just above the bone with 27G cannula in a linear threading technique, followed by gentle massage (ensuring uniform distribution of the injected Biofiller).[15,16]

In Intervention Group B, topical anaesthesia was done again by the above-mentioned method using EMLA. Centrifugation of the same amount of blood was done by the same protocol as for group 1. The lower part which is Platelet rich plasma (PRP) was withdrawn in insulin syringes. Around 2ml was injected by meso-therapy around each eye avoiding blood vessels and, hence bruising. Patients were advised to avoid NSAIDS for 5–7 days post-procedure in both groups and apply polyfax ointment on the treated area and the points from where cannula was entered for biofillers, for 3 days.15,16 The Procedure was repeated after 2-week intervals in both groups and a total of 2 sessions were done. Photographs were taken at the start of treatment and then 2 weeks after the last treatment. A validated photo-numeric scale for infraorbital dark circles proposed by M.M. O'Mahony *et al*, was used in our study as an objective measurement of periorbital dark circles intensity before and after treatment.[8]

Moreover, a blinded dermatologist performed clinical assessments at the end using the following grading scale: 0, i.e., less than 25% improvement (poor); 1, 26–50% improvement (fair); 2, 51–75% improvement (good); 3, more than 75% improvement (Excellent). She also rated the dark circles on the above-mentioned photo-numeric scale. The patient also gave feedback at the end as 0-Not satisfied, 1-Fairly satisfied, 2-Moderately satisfied and 3-Satisfied. They also gave feedback about side effects i.e. nil, pain, bruising, lumps and more than one complication. We did not include swelling intentionally in the feedback about complications as it was universally seen more or less, in all cases.

Data collected was analyzed using IBM SPSS 25.0 (Software Package for Social Science). As most data was categorical, so non-parametric tests were used. The chi-square test was used to compare the outcomes in the two independent samples. A p-value of less than 0.05 was regarded as statistically significant.

RESULTS

Out of 21 patients in group A, 7 (33.3%) were males and 14 (66.6%) were females. Similarly, in Group B,7 (33.3%) were male and 14 (66.6%) were females. In group A mean age was 31.29 years with SD of 9.382. The minimum age was 18 and the maximum was 51 years with a range of 33. In Group B mean age was 33.19 years with SD of 8.588. The minimum age in this group was 21 and the maximum was 52 years with a range of 31. So, we can see that there is a statistically significant difference in the results of treatment of Group A as compared to Group B, regarding improvement in photo-numeric scale, evaluation of efficacy by blinded dermatologist and patient satisfaction, i.e., p= 0.001, 0.014 and 0.001 respectively.

In Group A 15(71.4%) patients reported no side effects, pain was reported by 3 (14.3%), bruising by 1 (4.76%) and lumps by 2(9.5%). Group B had more side effects, i.e., 9 (42.8%) reported pain, 6 (28.6%) bruising and 4 (19%) more than one complaint. Only 2 (9.5%) had no complications and no reported lumps post intervention (p-0.001).

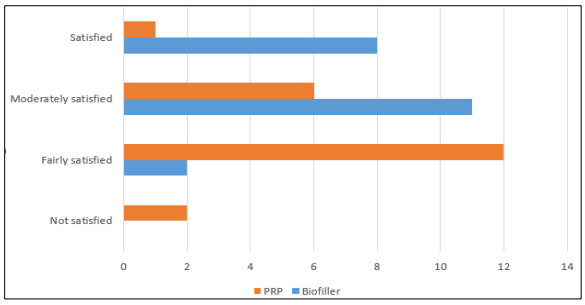


Figure-1: Patient Satisfaction Post Procedure (p-0.001)

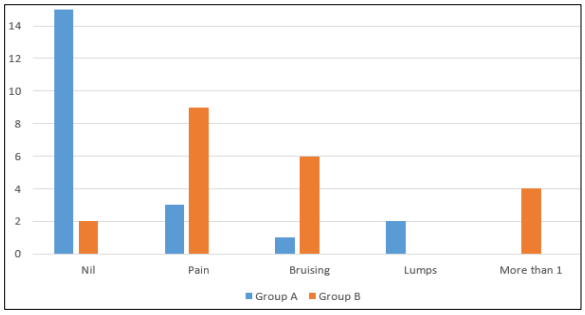
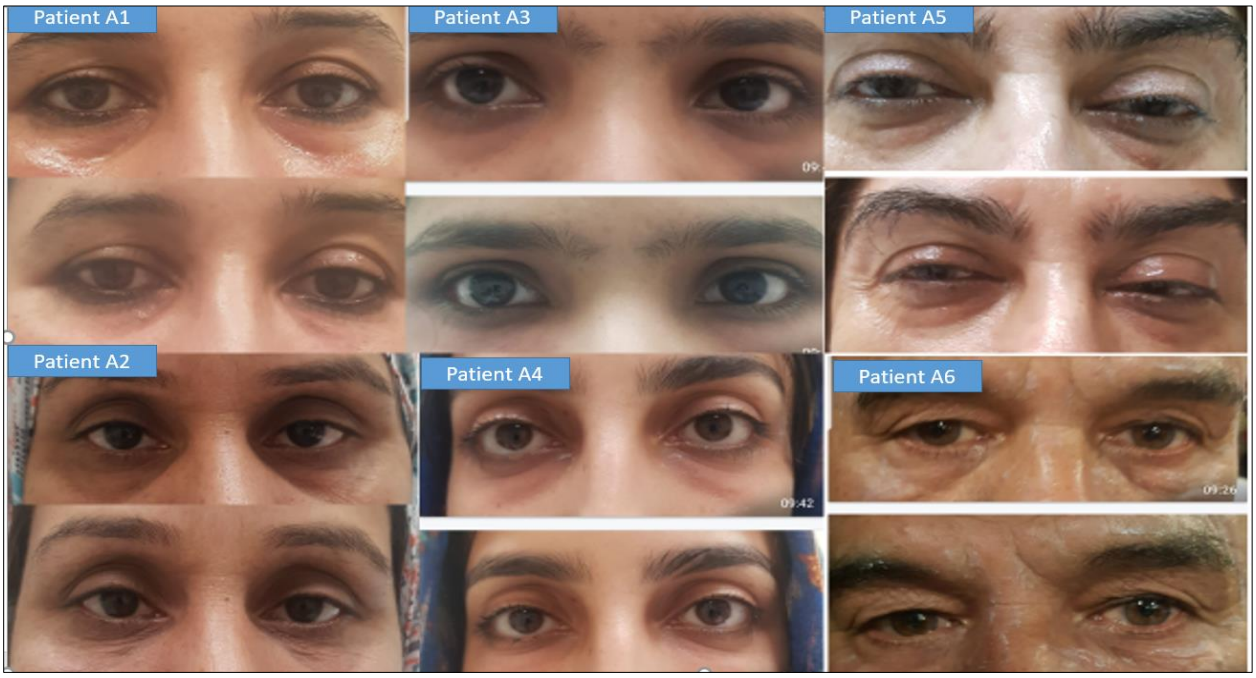


Figure-2: Frequency of Complications in Biofiller vs PRP treated Patients (p-0.001)

Table:1 Frequencies of Fitzpatrick skin type in Group A and B

Fitzpatrick Skin Type	Group A (n= 21)	Group B (n=21)	*p*-value
I	0	0	0.413
II 2 (4.75%)	0	2(9.5%)	
III 8 (19%)	4 (19%)	4 (19%)	
IV 21(50%)	10 (47.6%)	11 (52.3%)	
V 11 (26%)	7 (33%)	4 (19%)	
Type of POH			
Pigmented 19 (45.2%)	8 (38%)	11 (52.3%)	0.45
Vascular 3 (7%)	2 (9.5%)	1 (4.76%)	
Structural 14 (33.3%)	9 (42.8%)	5 (23.8%)	
Mixed 6 (14.2%)	2 (9.5%)	4 (19%)	
Dark circles graded as per photo numeric scale in Groups A and B before the intervention			
1-Barely perceptible	0	0	0.472
2-Slight	0	0	
3-Mild	2 (9.5%)	1 (4.76%)	
4- Mild to moderate	7 (33%)	3 (14.3%)	
5-Moderate	4 (19%)	8 (38%)	
6-Moderate to pronounced	5 (23.8%)	6 (28.6%)	
7- Pronounced, distinct	2 (9.5%)	3 (14.3%)	
8- Pronounced significant	1 (4.76%)	0	
9- Extensive, severe	0	0	
Dark circles graded as per photo numeric scale in Groups A and B after intervention			
1-Barely perceptible	3 (14.3%)	0	0.001
2-Slight	10 (47.6%)	1 (4.76%)	
3-Mild	7 (33%)	8 (38%)	
4- Mild to moderate	1 (4.76%)	10 (47.6%)	
5-Moderate	0	2 (9.5%)	
6-Moderate to pronounced	0	0	
7- Pronounced, distinct	0	0	
8- Pronounced significant	0	0	
9- Extensive, severe	0	0	
Evaluation of improvement by Blinded Dermatologist in Group A and B			
1-<25% (Poor)	0	2 (9.5%)	0.014
2-26-50% (Fair)	3 (14.3%)	7 (33.3%)	
3-51-75% (Good)	11 (52.38%)	12 (57%)	
4->75% (Very Good)	7 (33.3%)	0	



Pre and Post Pictures of Patients having Dark Circles Corrected with Biofillers (Gp:A)

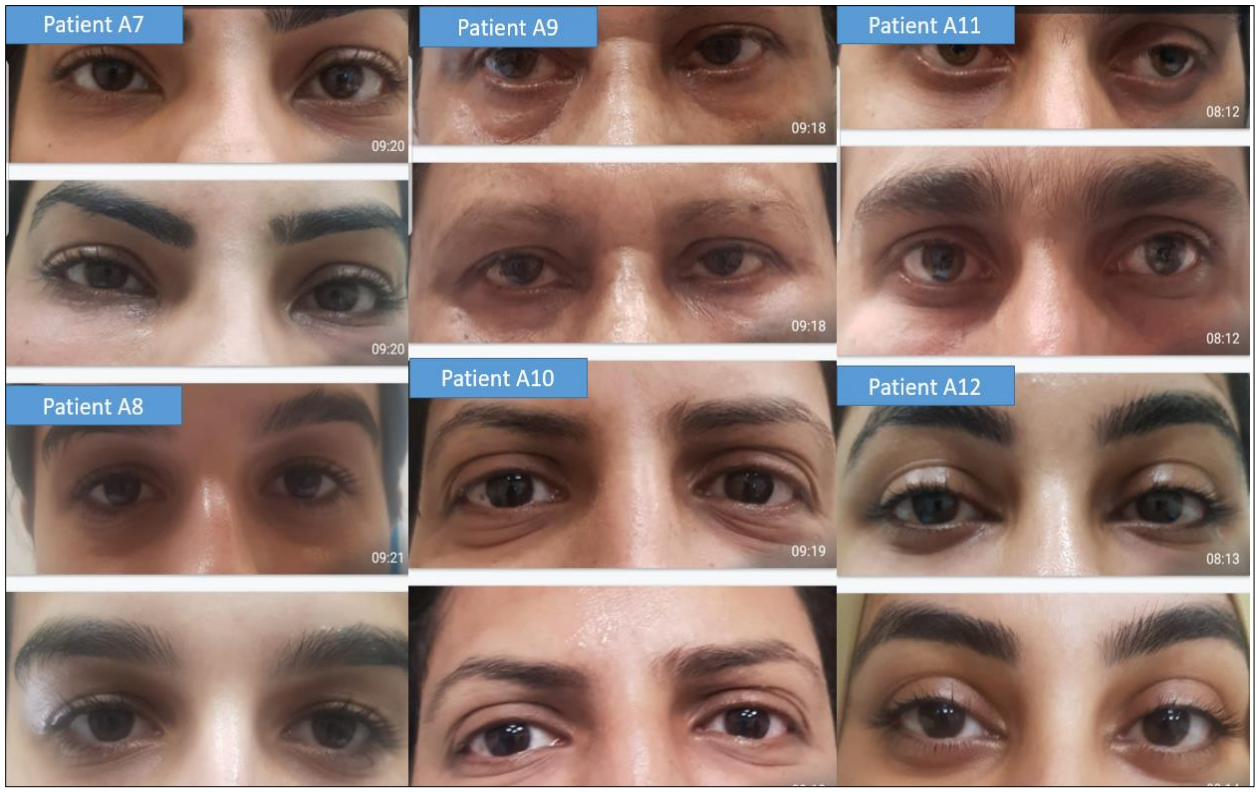
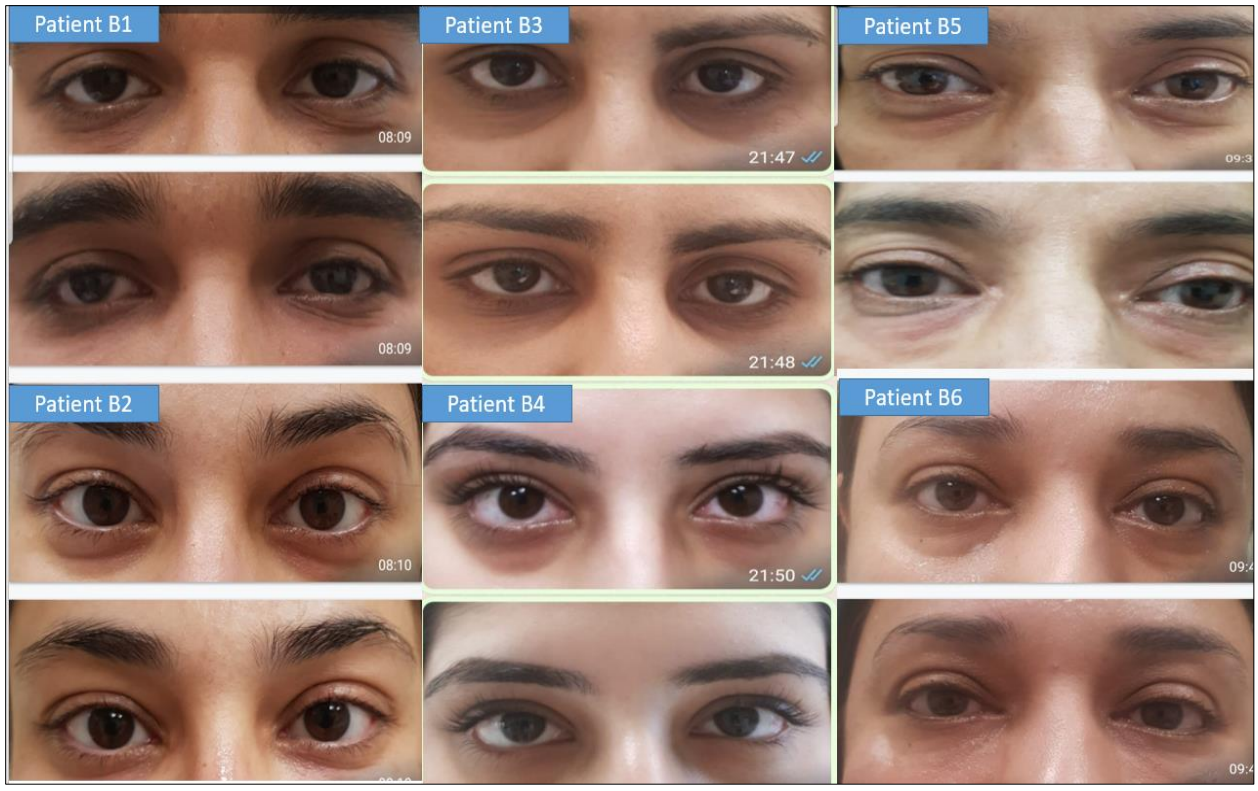


Figure-3: Pre and Post Pictures of Patients having Dark Circles Corrected with Biofillers (Gp:A)



Pre and Post Pictures of Patients having Dark Circles Corrected with PRP (Gp: B)

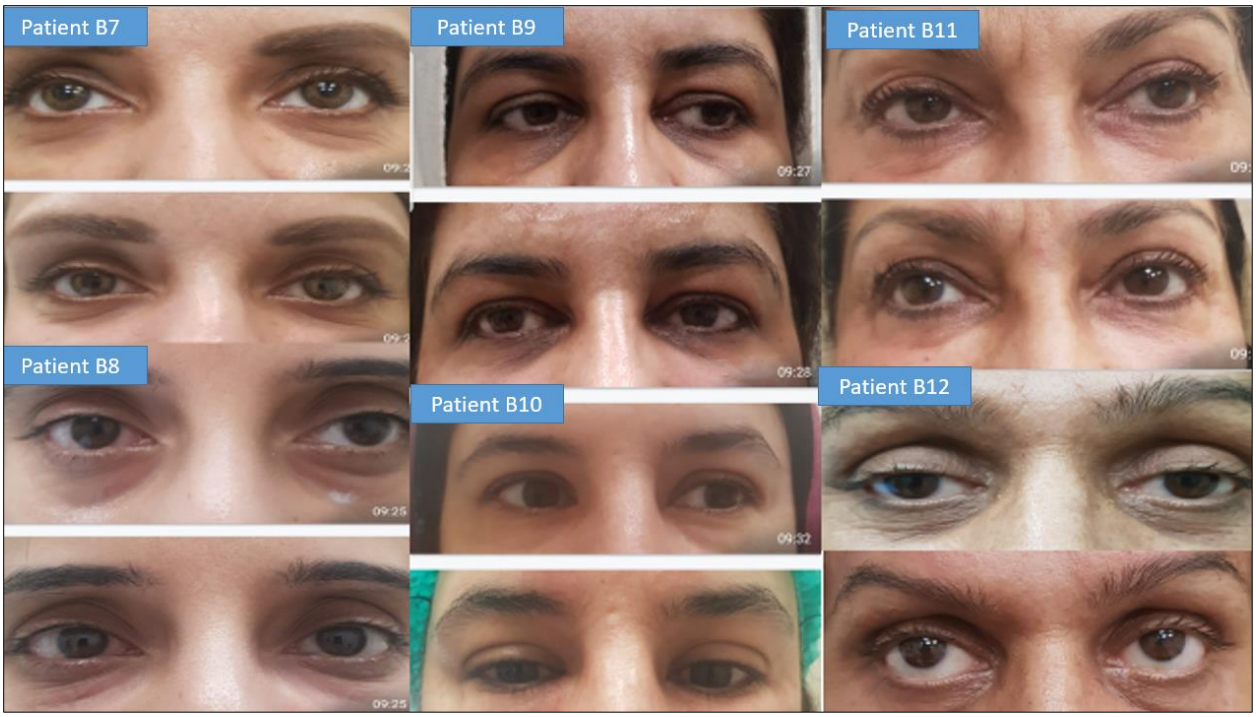


Figure-4: Pre and Post Pictures of Patients having Dark Circles Corrected with PRP (Gp: B)

DISCUSSION

In our study, there were 33% males and 66.6% females in each group. In an Indian study amongst 200 patients studied, it was more prevalent in women (162 [81%]) than men and the majority of the affected women were housewives.[7] In another study most patients were women (76%).[17] So our results support the previous studies as women are more affected than men and hence included in our study. The reasons could be hormonal or it might be that women are more concerned about their physical appearance than men, leading to increased reporting of POH in women.

The common age group was 16–25 years, i.e., 30%, followed by 26-35 years (23%), 36–45 years (20%) and finally >45 years (27%) in a study conducted in Andhra Pradesh India in 2018–19.[16] Two other studies carried out in India by Nayak *et al*.,17 and Mendiratta *et al*.[19] showed that the mean age of onset of POM was 30.44 years and 29.5 years, respectively, suggesting that POM is more common in the third and fourth decades. In another study carried out in Brazil and Germany, the age range of patients was 18−57 years (average: 36.1 years).19 In our study group A mean age was 31.29 SD±9.382. The minimum age was 18 and the maximum was 51 years. In Group B mean age was 33.19 SD±8.588. The minimum age in this group was 21 and the maximum was 52 years. So, most of the patients in our study were 31 to 42 years old, which is by the last 2 mentioned Indian studies. The reason for this could be that most patients in this age group are independent and earning and can afford interventions for their POH.

In the Indian study, Dermoscopy of POH revealed, three different patterns in patients studied, i.e., pigmentary (33%), vascular (15%), and mixed pigmentary vascular (52%).[16] The most common type of POH in our study was pigmented 45.2% followed by structural (33.3%). Vascular type was the least prevalent in our study (7%). We classified the POH clinically and by Wood's lamp based on the classification system by Huang *et al*.[9] Mixed-type, i.e., 78% and vascular-type, i.e., 14% were the most common types of POH as per Huang et al in Taiwan.[9] In a Korean study of 100 patients with POH, vascular-type (35%) and mixed-type (54%) were the prevalent most.[21] In a study done in Malaysia study vascular type was the most common (51%), while the pigmentary type was the least common with 6%. [22]

In a study carried out on patients presenting with facial pigmentary demarcation lines in Korea 173 volunteers, 18 (10.4%) were Fitzpatrick skin type II, 138 (79.8%) were type III and 17 (9.8%) were type IV.[23] We have quoted this study here as pigmentary demarcation lines are also a pigmentary disorder like POH. In our study, 47.6% of group A and 52.3% of group B had Fitzpatrick skin type IV. So, type IV was the most common skin type in our study. We excluded Fitzpatrick skin type VI from our study as our photo numeric scale was compromised for this group.[8]

Chi-square cross-tabulation of improvement in photo numeric scale post-intervention was better for Group A (*p*-value of 0.001). Fitzpatrick skin phototype III was the most common in both groups. However, regarding the type of POH, structural (42.8%) was more common in Group A and pigmented (52.3%) was more common in Group B. So, the difference in results could be attributable to the difference in POH type.

In Group A 14.3% had a fair response, 52.38% had a good and 33.3% had a very good response. In group B, 9.5% had a poor response, 33.3% had a fair and 57% had a good response. The *p*-value was 0.014 which was statistically significant. In a Korean study using autologous fat injections for POH, 40% showed 51–75% improvement and 60% showed 75–90% improvement. 24 In an Iranian study done using PRP injections for facial rejuvenation at 3 and 6 months, moderate to excellent improvement in POH (demonstrated by physician's evaluation) was observed respectively (47.8,60.9%).[24]

In our study in the Biofiller group, 9.5% were fairly satisfied, 52.38% of patients were moderately satisfied and 38% were completely satisfied while in the group treated with PRP 9.5% were not satisfied, 57% were fairly satisfied and 28.6% were moderately satisfied and only 4.76% were completely satisfied. The *p*-value was 0.001, so was significant. Patients in the Biofiller group were more satisfied than PRP group. In the Iranian study moderate to excellent improvement in periorbital dark circles (13%-moderate, 30%-good and 17% excellent) was noted by the patient with PRP injections given at 3 monthly intervals over 6 months.[23] This was comparatively more than our PRP-treated group but we only injected 2 times at 2 weeks' interval rather than 3 months' interval.

In our Biofiller-treated group, 15 (71.4%) patients reported no side effects, pain was reported by 3 (14.3%), bruising by 1 (4.76%) and lumps by 2 (9.5%). PRP treated group had more side effects, i.e., 9 (42.8%) reported pain, 6 (28.6%) bruising and 4 (19%) more than one complaint. Only 2 (9.5%) had no complications and no reported lumps post-intervention (*p*-0.001). So, lumps were only noted with Biofillers. These side effects could be attributed to the use of needles for PRP vs cannula for Biofillers. We used cannulas for Biofillers because Biofillers are thick gels and we wanted to avoid injecting fibrin clots in blood vessels, erroneously. In a study using Biofillers for atrophic acne scars, transient erythema was noted in 73.33%, oedema in 46.6% and transient pain in 53.3% of the treated patients.[14] In a study using autologous fat amongst 23 participants, 16 (69.6%) developed oedema or oedema and bruise at the site of injection. One patient fainted at the time of injection.[24] Analysis of complications during therapy with Biofiller for periorbital rejuvenation in Bhopal, India showed no side effects in 22 (88%) study participants while bruising was observed in 2 (8%) study participants, although they used a 30gauge needle for injections. The swelling was observed in 1 (4%) study participants.[15]

So, Group A, i.e., the one with Biofiller intervention showed more clinical improvement, patient satisfaction and fewer complications than Group B, i.e., with PRP intervention.

There is a case report of a woman developing sudden loss of vision in her left eye due to central retinal artery occlusion after receiving a PRP injection in the glabellae region.26 Three important factors that can lead to spread into the ophthalmic circulation are; retrograde movement of material, forceful injection with high pressure and adequate amount of injectable material. So, we should either use a cannula or if using a needle never push a large bolus of PRP forcefully in areas of the face with rich vascular anastomosis.[27]

Even after thorough massage immediately post injection, lumps were observed with Biofillers in our study, appearing 2nd to 3rd day and resolving within 2 weeks after 5 days of oral antibiotics, serratiopeptidase and massage. They need to be further investigated by biopsy of such lumps. There is no evidence from the literature for such complications with bio fillers, probably because it is a new treatment modality. With dermal fillers, nodules, induration, delayed hypersensitivity reactions, biofilms, sterile abscesses and granulomas can form termed as delayed onset nodules. These are more common in hypersensitive patients and those suffering from autoimmune diseases. Studies have shown that increased viscosity, roughness, hydrophobicity, charge, particle size, particle shape, and surface porosity effect nodule formation with hyaluronic and non-hyaluronic acid dermal fillers.[28]

CONCLUSION

Biofiller and platelet rich plasma therapy, both are effective in improving periorbital dark circles. Biofillers are better than PRP in treating POH as depicted by improvement in photo numeric scale, improvement as evaluated by a blinded dermatologist and patient satisfaction score. Complications i.e. pain and bruising are less with Biofiller technique as it is done by cannula, as opposed to PRP, which was done with insulin syringes. However, post intervention subcutaneous lump formation, which disappears within 2 weeks is observed only with bio fillers. So,

Bio fillers injected by cannula technique could be used as a novel treatment modality for POH.

Conflict of interest: The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

SS: Principal author and researcher. UB: Conceptualization of the study design, and data collection. AR: Literature search, the conceptualization of the study design. AA: Data collection and interpretation. SR: Data interpretation, proofreading. SS: Literature search.

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Submitted: October 23, 2023	*Revised: December 8, 2023*	*Accepted: December 21, 2023*

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