Platelet-Rich Plasma in Aesthetics

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Abstract

Platelet-rich plasma (PRP) is being used as a treatment modality for skin rejuvenation since the last decade. There has been a lot of ambiguity regarding the ideal protocol to be followed and the specific indications where its use should be promoted. The use of PRP as monotherapy for skin rejuvenation, acne scars, periorbital rejuvenation, lipofilling and in combination with fractional CO_2 and other resurfacing modalities is increasing rapidly. In this article, we have reviewed the current scientific evidence available and the IADVL national task force for PRP has come up with standard recommendations for use of PRP in esthetics along with the grade of evidence and strength of recommendation for each indication. The aim of this review is to provide a standard protocol for use of PRP in esthetics, for clinicians and academicians, leading to excellent results with this promising treatment modality.

Keywords: *Biofiller, esthetics, lipofilling, periorbital rejuvenation, platelet-rich plasma, recommendations, skin rejuvenation*

Introduction

The use of platelet-rich plasma (PRP) as a treatment modality for skin rejuvenation has been increasing rapidly over the past decade. Platelets become the logical choice for replacement and renewal of cells, tissues, or organs due to low invasiveness/high healing, easy availability, and abundance in growth factors. PRP is considered to be a growth factor cocktail, which promotes wound healing, angiogenesis, and tissue remodeling.

Studies have shown that PRP has around 578 different types of proteins like platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and transforming growth factor beta (TGFβ).[1] These proteins and growth factors can stimulate stem cells and improve cellular proliferation, differentiation, and regeneration, hence, leading to skin rejuvenation and hyaluronic acid production [Table 1].

PRP can activate fibroblasts and synthesize collagen and other elements of the extracellular matrix and hence becomes an attractive option for skin rejuvenation and scar attenuation.[1–4] The use of PRP as monotherapy for skin rejuvenation, acne scars, periorbital rejuvenation, lipofilling, and in combination with fractional CO_2 and other resurfacing modalities is increasing rapidly.

Scope of recommendations

Though the use of PRP as a modality for skin rejuvenation is increasing over the past decade, there is still no clarity about the licensed skin indications. A vast number of studies for various indications are available but good quality randomized controlled trials with consistent reporting of treatment parameters, use of adequate controls, and objective outcomes are lacking. Some classification systems have been proposed to improve comparison across studies but they have yet to be widely adopted.[5–7] In this article, we present a detailed review of literature and recommendations for approved skin indications with level of evidence.

Methodology of preparation of recommendations

A comprehensive literature search was done in the English language on the skin indications for PRP across multiple databases (PubMed, Embase, Medline, Google Scholar, and Cochrane). The search keywords used, alone or in combination,

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Table 1: Role of growth factors

Growth factor	Role
PDGF	Mitogen for fibroblasts and smooth muscle cells, promotes angiogenesis and collagen production
TGF-β	Increases collagen content
VEGF	Promotes angiogenesis
EGF	Promotes cell growth, differentiation, Angiogenesis, and collagen production
Pro and antiinflammatory cytokines (IL-4, IL-8, IL-13, IL-17)	Stimulate fibroblasts and collagen synthesis

were "PRP" AND "Skin rejuvenation," "Periorbital pigmentation," "acne scarring," "lipofilling," "Fractional CO2 laser," and "Dermaroller." All studies having more than 10 patients were included in the current study. The key studies and their outcomes are mentioned in Tables 2-4.

The grade of evidence and strength of recommendation were evaluated on the GRADE framework (Grading of Recommendation, Assessment, Development, and Evaluation).[19] The quality of evidence was graded on a four-point scale as follows.[20] This framework was used as this was found to be easy to comprehend.

1. High quality: Well performed randomized control trials or clear evidence from multiple well conducted observational studies showing very large effect.
2. Moderate quality: Randomized control trials with essential limitations.
3. Low quality: Observational studies or controlled trial with severe limitations
4. Very low quality: Nonsystematic observations, biologic reasoning, or observational studies with severe limitations

Strength of recommendation was determined based on the quality of evidence and other factors and was assigned as follows.[20]

1. Strong: A strong recommendation was given when benefits distinctly outweighed the risks for nearly all patients. As practitioners, most patients must receive this course of action.
2. Weak: A weak recommendation was given when risks and benefits were more closely balanced or were uncertain. As practitioners, patients must be explained about all the different options, and an option suitable for patients needs must be chosen.

Facial rejuvenation (I B quality of evidence and 1/2A strength of recommendation)

In today's world, the need for a firm, youthful skin is huge and is increasing by the day. The clinical signs of facial aging include wrinkles, open pores, pigmentation, and sagging. These are caused by changes in all layers of skin, loss of subcutaneous fat, downward migration of the fat pads, increased sebum and melanin production, and change in the bony structure. Skin aging is affected by a number of intrinsic and extrinsic factors. There are striking similarities between the events involved in wound healing and those that could effectively address the effects of intrinsic and extrinsic skin aging. It has been assumed that skin aging is analogous to a wound that is sufficiently extensive to overwhelm the skin's repair mechanisms, which becomes attenuated with age.[21]

PRP being an autologous mixture of growth factors scores highly among the treatment modalities offered to the patients. As skin ages, genetic and environmental factors lead to alterations in dermal extracellular matrix proteins (ECMP), degeneration of connective tissue, and decrease in the hyaluronic acid polymers. At a microscopic level, there is flattening of dermal-epidermal junction, dermal atrophy, and decrease in number of fibroblasts.[22] Activation of dermal fibroblasts and remodeling of the extracellular matrix are essential for rejuvenation of aged skin. Matrix metalloproteinase proteins are involved in the aging process by degradation of collagen and ECM proteins.[23]

Cytologically, PRP can regulate the secretion of biological factors and the proliferation and differentiation of many kinds of cells. PRP promotes collagen regeneration and angiogenesis, reduces pigment secretion, and further promotes facial rejuvenation.[24]

The antiaging effect of PRP has been found in animal studies as well. Cho *et al.*[25] observed 30 UV radiation exposed, nude mice and concluded that there were significantly fewer wrinkles in the nude mice injected with PRP than in the control groups. Also, significantly higher dermal thickness, fibroblast proliferation, and collagen synthesis were seen in the PRP group.

The utility of leucocytes in PRP for skin rejuvenation is debatable. The antiseptic role of leucocytes has been found to be useful in cases of wound healing. Leukocytes also help in angiogenesis and promote matrix production. The leukocyte population being proinflammatory, less amount of leucocytes in PRP reduces the incidence of inflammatory processes, hence gives better results in facial rejuvenation. Lin *et al.*[26] found that PRP poor in leukocytes provides objective improvements in skin bio stimulation. Also, RBC contamination is invariable in L-PRP which is not desirable in facial rejuvenation as this leads to the release of ROS and can affect platelet function by altering pH and promoting inflammation. Further studies on the specific cells and growth factors in PRP that contribute to facial rejuvenation would be required to assess the utility of leukocytes. On the basis of the current evidence, authors recommend P-PRP as the preferred type of PRP for facial rejuvenation.

Table 2: PRP method of preparation of included studies

Author	Study design	Sample size	Volume of blood drawn	PRP volume	Activator	Anticoagulant	Method of PRP preparation (any special features)
PRP monotherapy for facial rejuvenation							
Sevilla *et al*.[8]	Single blind, split-face prospective, comparative cohort	80 (1:20) (2:60)	34 ml	2.5 ml	nil	Acid citrate dextrose	Double spin 1): 150 g×15 min 2): 2700 rpm×10 min
Alam *et al*.[9]	Double-blind, split-face RCT	19	20 ml	3 ml	Nil	Acid citrate dextrose	Smart PREP2 APC (Harvest technologies)
Zenker[10]	Case series	418 from Germany, Japan, UK, Israel	10 ml	4 ml	Nil	NA	Single centrifugation
PRP in combination with laser resurfacing							
Hui *et al*.[11]	Single- blind split-face RCT	13	30 ml	2.2 ml	CaG	Heparin calcium	Double spin 1) 1200 rpm for 10 min 2) 3500 rpm for 5 min
Shin *et al*.[12]	Randomized controlled study, single-blind	22	12 ml	3 ml	CaCI2	CPD- A	Double spin 3000 rpm/5 min
PRP in combination with lipofilling							
Willemsen *et al*.[13]	Double-blind, RCT	25 (1:13) (2:12)	30 ml	3 ml	Nil	Acid citrate dextrose	3000 rpm/15 min
PRP in treatment of acne scarring							
Chawla[14]	Case series	30	10 ml	NA	Calcium gluconate	Acid citrate dextrose (ACD)	Double spin 1) 1500 rpm for 10 min 2) 3700 rpm for 10 min
Nofal *et al*.[15]	Randomized controlled trial	45	10 ml	2 ml	CaCI2	NA	Double spin 1) 175 g for 10 min 2) 1750 g for 15 min
Babu *et al*.[16]	Case series	20	10 ml	NA	NA	Acid citrate dextrose (ACD)	Two stage 1) 1500 rpm for 10 min 2) 3000 rpm for 20 min
PRP for infraorbital rejuvenation							
Kang *et al*.[17]	Single blind Split-face RCT	16	12 ml	1 ml	CaCI2	Acid citrate dextrose	My cells kit (Estar technology Ltd)
Mehryan *et al*.[18]	Case series	10	10 ml	1.5 ml	CaCI2	Acid citrate dextrose	PRP kit (Kimia teb rahavard co)

PRP is been increasingly used for skin and neck rejuvenation.[27,28] Most of the studies have shown improvement in skin color and texture and better tissue tension which helps in decreasing wrinkle depth. Activated PRP has been shown to stimulate dermal fibroblast proliferation, and activated PPP has been reported to increase type I collagen. PRP has been reported to increase the dermal elasticity, hyaluronic acid synthesis, and collagen production leading to a smooth and tighter skin. By improving the skin moisturization, hyaluronic acid improves volume and skin turgor. Both, direct intradermal injections and topical PRP under occlusion have been tried. Much evidence for topical PRP under occlusion does not exist in literature.

The application of PRP monotherapy for rejuvenation of aging facial skin was evaluated in 518 patients across three studies.[8,9] Two studies performed single session,[8,9] whereas one study performed two to four sessions depending on the age of the patient.[10] The infraorbital area, nasolabial folds, and crow's feet areas were the most commonly injected; other areas of treatment included the forehead/malar region, the preauricular region, and the jaw region. All studies

Table 3: Treatment details of the included studies

Author	Area treated	Type of intervention	Technique of PRP given	Number of PRP sessions
PRP monotheraphy for facial rejuvenation				
Sevilla *et al*.[8]	Naso labial fold	PRP monotherapy	First group was given growth factor concentrate intradermally on both sides. Second group was given growth factor concentrate intradermally on one side and intradermally PRP on the other side.	One
Alam *et al*.[9]	Cheeks	PRP monotherapy	One side of the face was given intradermal PRP. Other side of the face was given intradermal saline.	One
Zenker[10]	Full face and neck	PRP monotherapy	Linear threading fan like placements or cross hatching technique of intradermal PRP	2 to 4 PRP injections depending on the age of patients
PRP in combination with laser resurfacing				
Hui *et al*.[11]	Full face	PRP combined with ultra-pulsed fractional CO_2 laser therapy for facial rejuvenation	One side of face was given fractional CO_2 laser with intradermal PRP. Other side was given fractional CO_2 with saline	3 sessions at 12 weeks interval
Shin *et al*.[12]	Full face	Platelet rich plasma get combined with fractional laser therapy or fractional laser treatment alone	PRP gel	3 sessions of PRP after fractional laser 4 weeks apart
PRP in combination with lipofilling				
Willemsen *et al*.[13]	Full face	Intradermal PRP with lipofilling and saline	PRP was injected in lipofilling planes in middle of face and temporal regions	One
PRP in treatment of acne scarring				
Chawla[14]	Atrophic acne scars	Split-face comparative study of micro needling with PRP versus micro needling with vitamin C in treating atrophic post acne scars	In one half of the face, micro needling was followed by topical application of PRP	4 sessions at 4 weeks interval
Nofal *et al*.[15]	Atrophic acne scars	PRP versus combined skin needling and PRP in the treatment of atrophic acne scars	One group was given intradermal injection of PRP. Other group was given combination of skin needling and PRP	3 sessions at 2 weeks interval
Babu *et al*.[16]	Post acne scars	PRP verses fractional CO_2 laser in the treatment of post acne scars	One group of patients were given intradermal PRP into each scar	3 sessions at the interval of 1 month.
PRP for infraorbital rejuvenation				
Kang *et al*.[17]	Infraorbital rejuvenation	Infraorbital rejuvenation using PRP-A prospective study	One group was given intradermal PRP on one side and PPP on the other side of face. Second group was given intradermal PRP on one side and saline on the other side of face	3 sessions at the interval of 4 weeks
Mehryan *et al*.[18]	Infraorbital and crow's feet	Assessment of efficacy of PRP on infraorbital dark circles and crow's feet wrinkles	Intradermal PRP was given (1 ml was injected into infraorbital region and 0.5 ml was injected into crow's feet	Single session

performed intradermal injections; in addition, Yuksel *et al*.[23] used a Dermaroller (Cynergy, Carson City, Nev.) and draped each patient's face in gauze soaked in platelet-poor plasma for 30 minutes. Follow-up periods ranged from 1 week to 1 year. Studies within this review confirmed PRP to be beneficial for rejuvenating aging facial skin. Results showed improvements in the volume, texture, and tone of facial skin and decrease both fine and deep wrinkles.

To evaluate the effect of multiple needle punctures during PRP, serial puncture PRP injections were compared to saline injections in 127 patients. PRP injections resulted in significantly greater improvements in skin texture, tone, wrinkles, and dermal collagen compared to saline though plain saline injections also lead to increase in dermal collagen and improvement in skin sallowness to some extent.

Table 4: Outcome assessment of the included studies

Author	Duration of follow-up	Assessment method	Results with PRP	Quantitative and Qualitative improvement	Adverse events
PRP monotheraphy for facial rejuvenation					
Sevilla *et al*.[8]	52 weeks	Patients subjective satisfaction, GAIS assessment by two blinded dermatologists	Better improvement in global esthetic improvement scale in growth factor concentrate group compared to PRP group	Mean PRP vs Growth factor concentrate: GAIS 0.8 vs1.5	NR
Alam *et al*.[9]	24 weeks	Patient subjective satisfaction, patient evaluation of texture and wrinkles by 2 blinded dermatologists	Patient reported better improvement in texture and wrinkles with PRP when compared to control at 6 months	Patient assessment showed mean difference between PRP and control: texture: 0.79, wrinkles: 0.73	Peeling and dryness, redness, edema, itching
Zenker[10]	3,6,9,12, and 24 months following 1st injection	Comparing photographs before and after treatment	Patient's subjective satisfaction was good with natural looking skin	PRP produced immediate, long lasting and volumetric result	No side effects reported
PRP in combination with laser resurfacing					
Hui *et al*.[11]	12 weeks	Patient subjective assessment, photographic evaluation by 2 blinded dermatologists. Wrinkles, texture and pore size by VISIA	Patient subjective assessment showed greater improvement in wrinkles, texture and elasticity by VISIA in PRP + Laser group	Patient's self-evaluation in PRP + laser group, Mean (SD) Wrinkles 2.3 (0.9) Texture 2.4 (0.8)	Redness, swelling
Shin *et al*.[12]	One month after completion of treatment	photographs taken by blinded investigators, patients subjective satisfaction, skin biopsies	Good patient satisfaction and increased skin elasticity in the group subjected to PRP gel with fractional laser	erythema index was decreased in group subjected to PRP gel with fractional laser	Pain, redness, edema
PRP in combination with lipofilling					
Willemsen *et al*.[13]	52 weeks	Photographic assessment by 2 blinded dermatologist, Elasticity by cutometer	Recovering time was significantly reduced in PRP with lipofilling group	NR	NR
PRP in treatment of acne scarring					
Chawla *et al*.[14]	4,8,12,16 weeks	Physician assessment, patient subjective assessment	Good patient satisfaction and improved acne scars	Excellent response was seen in 18.5% of patients who received PRP according to physician assessment	Post inflam matory hyper pig mentation
Nofal *et al*.[15]	2,4,6, weeks	Patient subjective assessment acne scarring grading system	Acne scars improved and good patient satisfaction in both injection and micro needling groups	Both groups showed significant statistical improvement in degree of acne scars post treatment (P<0.001)	No major adverse events
Babu *et al*.[16]	4,8 weeks	Digital photographs, qualitative acne scaring grading system	Majority of the patients (70%) showed excellent response on subjective evaluation	Statistically significant difference (P=0.0312) was seen between the baseline and final score among the group who received PRP	No major Adverse events

Contd...

Table 4: Contd...

Author	Duration of follow-up	Assessment method	Results with PRP	Quantitative and Qualitative improvement	Adverse events
PRP for infraorbital rejuvenation					
Kang *et al*.[17]	12 weeks	Patient subjective assessment. Erythema index and melanin index by spectro photometer	Patient satisfaction was greater in PRP group when compared to PPP and saline control group EI and MI improved	19% of patients showed good improvement in wrinkles, 25% of patients showed moderate improvement in skin tone with PRP	Pain, swelling, redness
Mehryan *et al*.[18]	12 weeks	Degree of improvement by blinded dermatologists using photograph. Melanin index by mexameters. Hydration by corneometer	Improvement in infraorbital color homogeneity after treatment when compared to the baseline	Degree of improvement was fair to good in 80% of patients	Swelling, burning sensation.

Standardized tools for standard recording of results have been developed. The FACE-Q is a validated tool for facial esthetic assessment, assessing patient reported outcomes and patient satisfaction. The five-point photo numeric Allergan Skin Roughness Scale was developed in accordance with U.S. Food and Drug Administration requirements to measure facial skin texture and is similar to the Wrinkle Severity Rating Scale.[29,30]

PRP appears to be safe, with a low-risk profile. The commonly reported side effects include pain during injections, erythema, edema, and bruising. A single case of blindness followed by PRP injection in glabellar region has been reported in literature.[31]

Studies have shown that as the age of the patient increases, the ability for tissue regeneration gradually declines, the expression of growth factor receptors decreases, and the ability of fibroblasts to produce collagen is reduced.[32] Vavken *et al.*[33] confirmed that young fibroblasts respond well to PRP treatment. Furthermore, as age increases, the tissue regeneration ability is poor and the expression of the cell growth factor receptor is reduced, resulting in poor PRP action.[34] At present, there are few reports of age-related changes in the response to PRP in facial rejuvenation. However, young fibroblasts respond well to PRP treatment, which may imply that the regenerative ability of PRP will decline with age. Hence, PRP might be a better modality in young patients.

PRP is an excellent treatment modality with high safety profile for improving texture, tone, and early signs of aging in young patients [Figure 1a and b]. The absolute contraindications for PRP include platelet dysfunction syndrome, critical thrombocytopenia, hemodynamic instability, septicemia, and patients with unrealistic expectations. Relative contraindications include heavy smokers, drug or alcohol users, patients with chronic liver

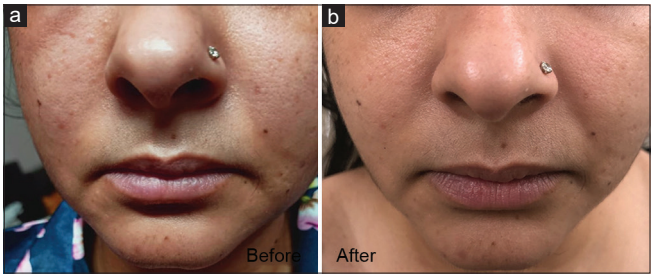

Figure 1: (a) Open pores, uneven texture, tone. (b) Improvement in 4 weeks after 1 session

pathology, severe metabolic or systemic disorders, patients with cancer especially hematopoietic, patients having low hemoglobin (<10 g/ml) or platelet count (<1 lakh/microL), and patients having a history of recent fever or other illnesses. Also patients on regular use of NSAIDS, omnacortil more than 20 mg per day, and anticoagulant therapy should be avoided. A baseline hemoglobin, platelet count, HIV, HbsAg, and HCV should be done for all cases. In the current Covid era, a rapid antigen test for Covid-19 can be undertaken before the procedure. Patients having a history of herpes simplex can be started on antiviral prophylaxis; acyclovir 400 mg twice a day or valacyclovir 500 mg once a day for 5-7 days started a day before the procedure.

The entire procedure should be carried out in a minor OT maintaining strict asepsis. PRP is filled in insulin syringes with 31 G needle (PRP preparation is beyond the purview of this article). The local area can be anesthetized using topical anesthetic creams before, during, and after the procedure or nerve blocks. Intradermal or subdermal injections of PRP are given. Very superficial injections should be avoided as these can lead to cobblestone appearance on the skin. Around 3–4 ml is required for full face injections, 1 ml per cheek, 1 ml for forehead, nose,

and chin, and 1 ml for neck. Around 0.01 ml–0.02 ml of PRP is delivered per prick. Slow injections are advocated to decrease the pain. PPP can be used with machines like electroporation which marginally increase the penetration of the fluid. Slight pain and redness are expected post procedure in all cases. Use of NSAIDS 2 weeks post procedure should be avoided. Patients are advised strict sun protection and liberal use of moisturizers for 2 weeks after the procedure. 3–6 sessions at a gap of 4–6 weeks are recommended. Results are usually visible after 4–6 weeks.

The effect of PRP in combination with CO_2 laser in skin rejuvenation has been evaluated in a number of studies with beneficial effect. Shin *et al.*[12] conducted a study on 22 Korean women, of which half of the cases were treated with the laser alone and the rest with laser combined with PRP. The results showed that women treated with PRP and laser were more satisfied with the treatment effect, their skin elasticity was better, and the skin erythema index was lower than that of the women treated with the laser alone. PRP increased the length of the junction between the epidermis and the dermis, the content of collagen, and the number of fibroblasts. Hui *et al.*[11] found that patient reported better improvement in wrinkles, texture, and elasticity when CO2 laser was combined with PRP compared to PRP alone. Study done by Willemsen *et al.*[13] concluded that recovery time was significantly reduced in PRP assisted with lipofilling.

The effectiveness of PRP in improving facial skin has a I B quality of evidence and 1/2A strength of recommendation and is recommended by ID PRP for temporary, modest improvement of overall appearance, texture, and wrinkles in aged facial skin. Effectiveness of PRP in improving appearance of perioral skin has a II A quality of evidence, 2B strength of recommendation. PRP basically has a low-quality evidence for modest, temporary improvement of NLF wrinkle severity.[35,36] Effectiveness of PRP in improving appearance of forehead skin has level III quality of evidence and 2 B strength of recommendation. Hence, more good quality randomized trials are needed.

Acne scarring

A number of treatment modalities of proven efficacy including peels, derma rollers, MNRF, fractional CO_2 laser, and fillers are being used extensively for treatment of acne scars. The use of PRP for acne scars was first observed by Redaelli *et al.*,[37] who had also used intradermal injections of PRP for facial skin rejuvenation. Leukocytes have a favorable role in scar healing; hence, L-PRP is the preferred type of PRP for acne scars.

PRP can be used alone or in combination with the conventional treatment modalities like subcision, dermaroller, or laser resurfacing procedures, to increase the efficacy of these treatments.[38] PRP improves and accelerates post-treatment recovery when combined with fractional CO2 laser.[39,40]

PRP monotherapy

PRP reconstitutes an atrophic acne scar through various growth factors which promote connective tissue regeneration by up regulating collagen and protein production. Histologic studies following PRP administration have revealed that there is an increased collagen bundles formation and a thicker epidermal layer compared to control.[41]

A randomized study was conducted by Pooja *et al.*[42] wherein authors compared the efficacy of fractional CO2 monotherapy, micro needling monotherapy, and PRP intradermal injection monotherapy in post acne scarring. It was concluded that CO2 and micro needling monotherapy was significantly more efficacious than PRP monotherapy. The utility of PRP as a monotherapy for acne scars is still debatable.

PRP in combination with micro needling

Both topical and intradermal PRP have been safely combined with micro needling producing variable results.[43]
1) Topical PRP in combination with micro needling

The beneficial effect of topical PRP in combination with micro needling is still debatable. A decreased healing time has been observed in majority of the studies but statically significant difference in results due to addition of topical PRP has not been consistently seen. A split-face trial of 35 patients compared micro needling with and without topical PRP.[44] Both side of the face showed a significant improvement of acne scars, as rated by Goodman's Qualitative scoring system. Although the PRP-treated side showed greater improvement, this difference was not determined to be statistically significant. The addition of PRP did, however, appear to reduce erythema and edema.[44]

A randomized split-face trial evaluated micro needling alone or in combination with either topical PRP or trichloroacetic acid (TCA) 15% peels.[45] Both combination treatments showed significant cosmetic improvement in acne scars compared to micro needling alone. Assessment was done by blinded dermatologists and independent observers. No significant difference was observed between the combination treatments. On histology, both combination treatments produced a thicker epidermis than micro needling alone. All groups showed more organized and dense collagen bundles following treatment, but this was more pronounced in the topical PRP group.[45]

2) Intradermal PRP in combination micro needling

Micro needling along with PRP has a synergistic action. This combination would intensify the natural wound

healing cascade because of high concentration of patients own growth factors induced by skin needling and PRP. This enhanced wound healing response thereby improves the acne scars.

A recent randomized trial for the treatment of scars included 90 patients separated into three treatment groups.[46] One group received micro needling, another group received intradermal PRP, and the third group was treated with alternating micro needling and intradermal PRP treatments. Though improvement was seen in all groups, combination treatment was associated with the greatest mean improvement score, followed by micro needling, then PRP. Patient satisfaction was significantly greater in the combination group. On histology, the combination treatment yielded a thickened epidermis with more developed rete ridges compared to the single treatment modalities.[46]

Chawla[14] and Nofal *et al.*[15] confirmed the improvement in atrophic acne scars when PRP was applied by means of either micro needling or intradermal injection.

A recent split-face study concluded that the combination of both intradermal injections and micro needling with PRP improved the clinical outcomes when compared to micro needling with distilled water.[47] A 50-patient split-face study evaluated micro needling for acne scars with and without the addition of PRP: Post micro needling, intradermal PRP was injected within acne scars and topical PRP was subsequently spread over the same half and distilled water was used on the other half. Though improvement was seen on both sides, the PRP-treated side scored a higher response using Goodman's Qualitative and Quantitative scoring systems and independent physician assessment scores. Patient satisfaction was also greater, and majority of the patients reported that PRP led to a reduction in the visibility of acne scars and an improvement in skin roughness.[47]

A comparative study was done by Porwal *et al.*,[48] wherein derma roller alone was used on one side and intradermal injections of PRP with derma roller on other side of the face with acne scars. Authors observed significantly better results on PRP side (58% vs 43%).

The above studies clearly highlight that topical PRP has limited efficacy; hence, intradermal PRP should be the preferred mode of PRP delivery. Interstitial fluid and fibrin fill up the open channels post micro needling or AFR very fast, hence, limiting the uptake of PRP; therefore, topical PRP has very limited efficacy.

PRP in combination with other treatment modalities for acne scars

PRP has been used with a number of routinely done procedures like fractional CO_2 laser and autologous fat grafting. Studies have shown encouraging results with decrease in healing time and improved patient satisfaction rate.

1. PRP combined with Fractional CO_2 Laser (PRP in combination with laser resurfacing for minimization of laser associated downtime has a 1B quality of evidence and ½ A strength of recommendation.)

The beneficial effect of combination with PRP with ablative lasers like fractional CO_2 has been established in a number of studies. Both topical PRP and intradermal PRP have been studied.

Combination topical PRP with laser has been associated with decreased erythema, swelling, and pain though significant improvement in the final results has not been seen. It is suggested that topical PRP could be used to improve both post-procedural downtime and patient satisfaction when used with ablative fractional laser (AFL).[40]

Intradermal PRP has also been tested with ablative laser procedures in a number of studies. Lee *et al.*[40] conducted a study on fourteen patients to examine the effects of PRP after treating acne scars with an ablative fractional resurfacing laser (AFR). Split-face trial with two treatments of AFR combined with PRP injections on one side and saline injections on the other was carried out. Compared to saline, PRP treatment was associated with less erythema by Day 4 and decreased duration of erythema. Likewise, after the second treatment, less edema for decreased duration was noted. The authors concluded that PRP hastened recovery of laser-induced injury.

A split-face study by Faghihi *et al.*[49] evaluated AFR combined with either intradermal PRP or saline in 16 patients found conflicting results. Although atrophic acne scars improved with intradermal PRP compared to control, this difference was not statistically significant at 1 month after the first treatment or 4 months after the second treatment. Unlike other studies, participants experienced more edema and prolonged erythema on the side treated with PRP. The authors concluded that the addition of PRP resulted in worse side effects with longer downtime.[49]

Gawdat *et al.*[50] conducted a 30-patient split-face study to compare intradermal and topical PRP modalities. One group was subjected to AFR with either intradermal PRP or saline to each side, while the other group received AFR with either intradermal or topical PRP to each side. Combined treatment with AFR and PRP showed better response, shorter downtime, and fewer side effects than laser therapy alone. There were no statistical differences between intradermal and topical PRP with regards to the degree of response and downtime. Topical PRP was associated with lower pain scores compared to intradermal administration. Interestingly, the efficacy of PRP was not compromised by using the less painful topical administration.[50]

In our study on 20 patients, we observed that both PRP and CO2 laser produced statistically significant improvement in the qualitative scoring of acne scars.[16] PRP combined

with subcision gives good results [Figure 2a and b]. Both the modalities are effective in treating acne scars with good safety profile. The principle points of interest of PRP are that it prohibits the treatment dismissal. It also avoids transmissible contamination as it is an autologous product and it is a cost-effective treatment.[51,52]

It is recommended as a adjuvant treatment to fractional laser to decrease duration and intensity of laser associated side effects especially edema and erythema.

2 PRP combined with autologous fat grafting

During fat injection, the period of ischemia is produced, which makes the adipose cells susceptible to necrosis. The proangiogenic activity of PRP may play a critical role in improving the fat graft retention at this stage. The addition of PRP to fat grafting procedures maintained facial volume.[53]

Azzam *et al.*[54] conducted a comparative study in 28 patients to evaluate the PRP enhanced fat grafting versus fat grafting alone in the treatment of post acne scars. It was concluded that overall improvement in the individual scars was better in PRP enriched fat graft. Autologous fat grafting had advantage of single-session therapy, with minimal downtime and long-lasting results during follow-up period.

Periorbital Rejuvenation (The current quality of evidence is I b and the strength of recommendation is 2 A)

Although periorbital aging is a condition of cosmetic concern, it is usually the first sign of aging and can cause immense psychological distress. All available minimally invasive treatment options have limitations. PRP can be used to treat esthetic problems in the periorbital regions like wrinkles, pigmentation, erythema, xerosis, loss of skin elasticity, and volume. Inspite of the number of treatment options available ranging from topicals to resurfacing lasers, PRP is emerging as a promising treatment for this difficult to treat condition.[55]

Skin fibroblasts in PRP have been found to secrete endogenous hyaluronic acid in high concentration leading to a significant improvement in skin quality and decrease in the signs of skin aging.[54,55] Hyaluronic acid, being hygroscopic leads to improvement in skin turgor and volume. The decrease in production of melanin is attributed to the presence of TGF β. PRP leads to increased collagen production by inducing mild inflammation leading to an improvement in the tear trough deformity. Theoretically PRP has an effect similar to injection of hyaluronic acid fillers with the added effect on pigmentation as well.

A statistically significant reduction in the severity of wrinkles, assessed using Wrinkle severity rating scale, was found in a study conducted in 20 patients. The response was found to be better in patients younger than 40 years of age.[36] Kang *et al.*[17] reported improvement in both infraorbital wrinkles and skin tone in subjective and objective satisfaction scales in 20 Korean females. Three sessions were done at 1-month interval each. A decrease in the erythema index and melanin index was seen in the PRP-treated side. A significant improvement in dark circles has been reported after the third session of monthly PRP sessions in a trial conducted in Jordan on 50 patients. The improvement lasted through a follow-up of 6 months.[56] After a single injection of PRP statistically significant improvement has been reported in infraorbital color homogeneity, but statistically significant changes in melanin content, stratum corneum hydration, wrinkle volume, and visibility index were not seen.[18] Skin elasticity and skin firmness of lower eyelid showed a statistically significant improvement after three monthly injections of PRP.[57] 2 sessions of PRP at 3 months interval have been found to have improvements in periorbital wrinkles and dyschromia in a case series of 30 patients.[58]

PRP does improve the skin texture, decrease the pigmentation, and reduce the appearance of tear trough after 3 sessions done at monthly intervals [Figure 3a and b]. This area is especially prone to bruising; hence, the patient should be aligned before the procedure for the same. Topical PRP is a modality worth investigating for use in

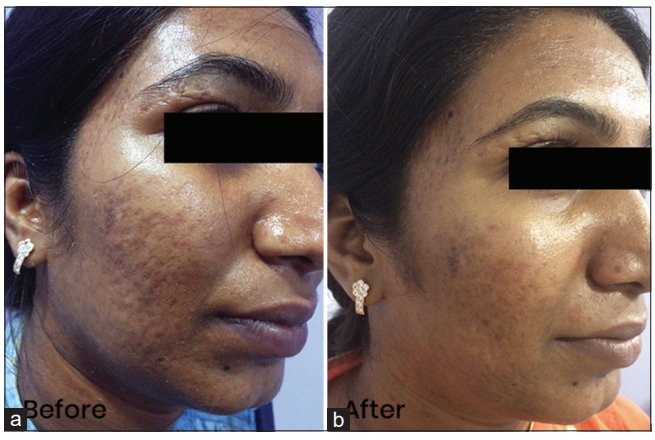

Figure 2: (a) Acne scars grade 2. (b) Improvement after 1 month of 2 sessions

Figure 3: (a) Loss of volume, tone of periorbital area. (b) Improvement seen, 1 month after 3 monthly sessions

this area. Also, better results are seen in younger patients. The above studies indicate some efficacy of PRP in periorbital rejuvenation, but more data is needed to assess the longevity of the effect. As repeatedly shown, PRP decreases the healing time and enhances the healing overall when combined with other resurfacing modalities. PRP as a monotherapy and in combination with other treatments hold promise for periorbital rejuvenation.

The best response was observed after three monthly injections and that is being recommended. The evidence discussed in this article indicates the increasing importance of minimally invasive modalities in periorbital rejuvenation and a promising role for PRP as solo therapy or in multimodality regimens.

Melasma

The role of intradermal PRP in treatment of melasma is under evaluation currently. Intradermal PRP is being tried as an alternative or adjuvant therapy for melasma. Very few studies have been conducted.

Hofny *et al.*[59] conducted a split-face study on 23 adult Egyptian melasma patients. PRP was delivered through micro needling with derma pen on one side of face and intradermal microinjections of PRP using mesoneedles on other side of face. A statistically significant decrease in the hemi-MASI score was observed on each side of face following PRP treatment.

A split-face, randomized, single-blinded pilot study was done by Sirithanabadeekul *et al.*[60] on ten female mixed-type of melasma patients. Intradermal PRP was injected on one side of face and normal saline on other side every 2 weeks for 4 sessions. It was observed that mMASI score and Antera 3 D assessed melanin level showed significant improvement in PRP treated side compared to control side.

Platelet poor plasma biofiller in esthetics

Tissue loss following inflammation and volume loss in the face due to aging are common, yet difficult to treat conditions. Punched out scars like post varicella scars respond poorly to subcision also.[61] Dermal fillers are quite effective in restoring volume loss in these conditions; however, the cost of fillers have always been prohibitive. An innovative new solution to this problem is the use of platelet-poor plasma (PPP) biofiller. PPP, which is normally discarded during the preparation of PRP, is a good source of plasma proteins. These plasma proteins can be coagulated using heat to form a gel-like substance which can be injected in the skin to provide a lift. Dental syringe is used to prepare this biofiller. PPP is filled in glass vial of dental syringe. Glass vial is kept in water bath at 80ºC–90ºC. Transparent plasma turns opaque. Glass vial is inserted in the dental syringe and 27 G needle is attached[61] [Figure 4a-f].

Woo *et al.*[62] performed an animal study using rats. They injected biofiller in the dorsal surface of the skin of the rats and measured the swelling over 6 months. They found that swelling slowly reduced and disappeared 6 months following the procedure. They also performed a histopathological examination of the biofiller. They did not report any chronic inflammatory infiltrate or foreign body like reaction around the amorphous eosinophilic substance during the period of study duration.

Dashore and Dashore[63] performed biofiller injections in chickenpox scars and found that the biofiller started to disappear and filler volume reduction started to appear by the end of 1 month and the treatment had to be repeated every 3 to 4 months although the filler took nearly 6 months to completely disappear.

Neinaa *et al.*[64] performed a comparative study between PPP biofiller injection vs PRP injection for infraorbital rejuvenation. This was a split-face study where three injections 2 weeks apart of PRP were given while only single injection of biofiller was performed. Both groups showed significant improvement in tear trough reduction and hyperpigmentation reduction; however, biofiller injection was found to be significantly more effective than PRP on both the parameters. They found the results of biofiller injections to persist up to the end of the study, which was of 3 months duration.

Doghaim *et al.*[65] performed biofiller injections in various facial wrinkles and tear trough deformities in 52 women in an pre-post study. They found significant improvement in all the facial wrinkles and found the results to be maintained up to 3 months. Main adverse effects seen were transient erythema and edema, which disappeared after few hours. Bruising was also seen predominantly following tear trough injections, which disappeared within a few days. No major long-term adverse effects were seen.

At present, PPP biofiller injection for facial rejuvenation is in its nascent stages and needs further evidence to understand the long-term properties of this product. It is a cost-effective option which can be easily repeated over a few months and is found to be especially effective for superficial volume defects like chicken pox scars [Figure 5a and b].

Limitations

No doubt, PRP is showing promising results in a number of skin conditions but there is an urgent need for large, randomized, controlled trials. Majority studies have small numbers, lack of uniform criteria for preparation protocols and comparison of outcomes, and small follow-up periods. Inspite of the number of studies, the importance of different parameters on the clinical efficacy of PRP in esthetic medicine is not known. Lack of PRP standardization is the main problem with assessing its efficacy between studies. Another major limitation is inadequacy and variability in outcomes assessment. Further studies are needed to determine optimal

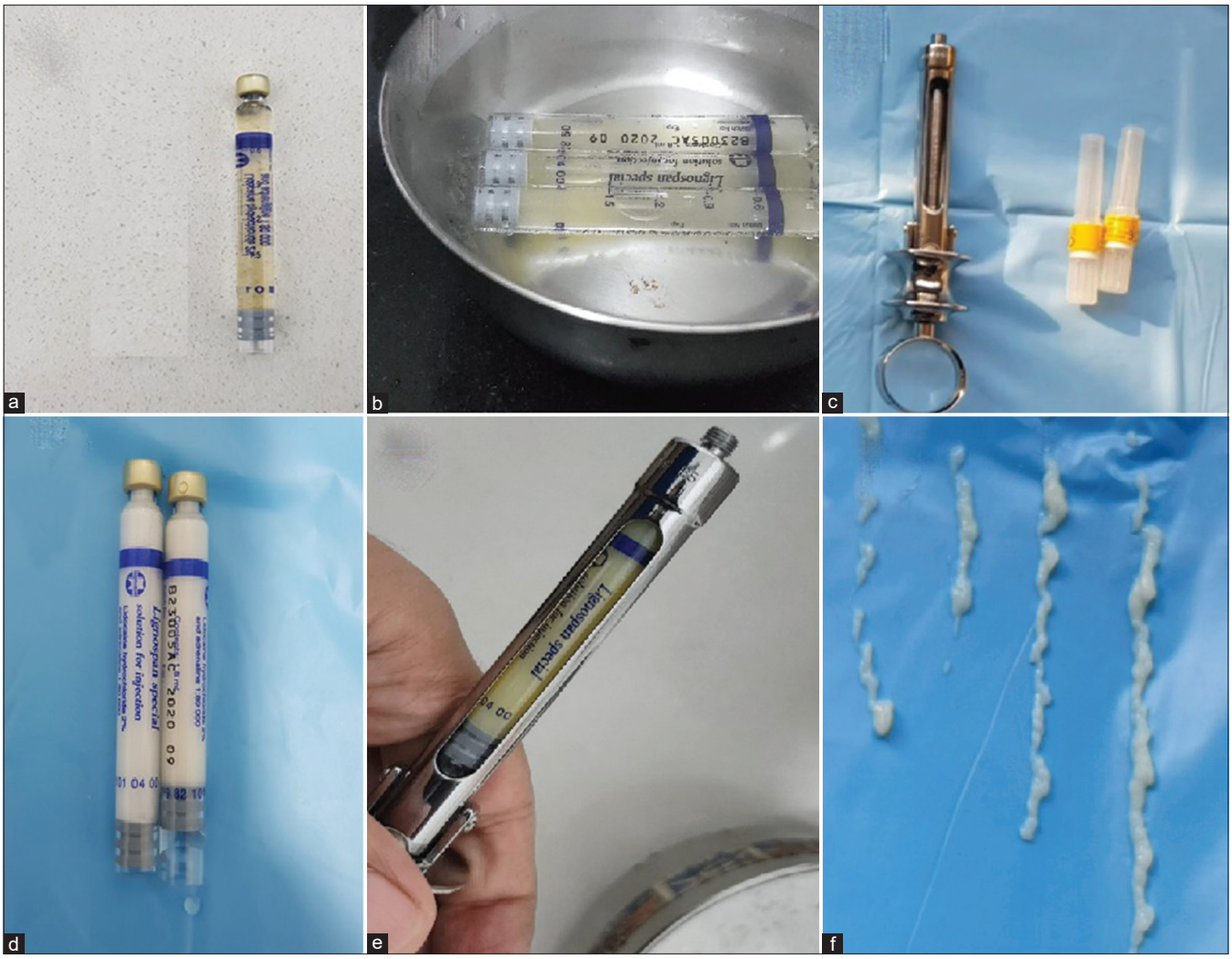

Figure 4: (a) Vial for dental syringe is filled with PPP. (b) Vial kept in water bowl at 70°C –80°C. (c) Dental syringe, 27G needles. (d) Biofiller in vials. (e) Vial loaded in the dental syringe. (f) Gel-like consistency

methods and procedures for collection, treatment, and administration of PRP.

Future research

Future studies are required to determine which aging-specific features (e.g., texture versus color) are most responsive to treatment with PRP and which patient characteristics (e.g., age, gender, ethnicity, history of sun exposure, smoking) best predict a favorable response to treatment. The optimal number of treatments and intervals between them also need to be elucidated. Quantification of fundamental PRP parameters and growth factor concentrations, long-term (≥ 6 months) outcomes, blinded rater assessments, and other specific agreed-upon (i.e., core) standardized outcomes are needed. Uniform outcome reporting across studies would enable pooling of data and more detailed analysis.

IADVL Consensus Statement

1. P-PRP is the preferred type of PRP for facial rejuvenation while L-PRP is preferred for acne scars.
2. Moderate level of evidence is available in literature for PRP as a treatment modality for skin rejuvenation, acne scars, periorbital rejuvenation, lipofilling and as a combination therapy with ablative services like Fractional CO2 laser and dermarollers.
3. Young patients with early signs of aging and those seeking an improvement in texture and tone by a natural, autologous treatment are the ideal patients.
4. PRP showed an improvement in all types of acne scars in terms of reduction in acne scar size. On visual analogue scale, rolling scars responded better to PRP as compared to boxcar and ice-pick scars.
5. PRP when combined with needling and subcision can be an effective treatment for even severe atrophic acne scars.
6. PRP in authors experience is an excellent modality for temporary, modest improvement of periorbital area in terms of texture, pigmentation, and superficial wrinkles.
7. Addition of PRP to AFR significantly decreases the healing time, hence decreasing the chances of post

Figure 5: (a) Varioliform Scar pretreatment. (b) Scar filled

inflammatory hyperpigmentation and increasing the patient satisfaction.

8. Bio-filler could prove to be a very cost-effective modality for treating superficial volume defects; further research is needed to establish the longevity and safety of this modality.
9. Intradermal PRP is the preferred mode to deliver PRP in all cases, as of today.
10. 3–6 sessions at monthly interval are recommended. Results are expected only after 4–6 weeks of treatment.
11. Topical anesthesia, nerve blocks, icing, and vibrators can be used to make the procedure comfortable for the patient.
12. The safety of the procedure has been established but the longevity of results is still questionable.

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Conflicts of interest

There are no conflicts of interest.

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