Systematic Review: Platelet-Rich Plasma Use in Facial Rejuvenation

Pietro Gentile, MD, PhD[1,2]
Simone Garcovich, MD, PhD[3]

Rome, Italy; and Geneva, Switzerland

Background: An increasing interest in maintaining a youthful appearance has led to the development of innovative and noninvasive aesthetic procedures for the treatment of facial aging, such as the recent use of autologous platelet-rich plasma (PRP). This article aims to review the literature and critically appraise the available evidence regarding the efficacy of autologous activated PRP and/or nonactivated PRP injection used for facial rejuvenation.

Methods: A systematic review regarding the clinical use of autologous activated PRP and autologous nonactivated PRP injection in facial rejuvenation against signs of aging was performed using the PubMed, MEDLINE, Embase, PreMEDLINE, Ebase, CINAHL, PsycINFO, Clinicaltrials.gov, Scopus, and Cochrane databases. The protocol was developed following the Preferred Reporting for Items for Systematic Reviews-Protocols guidelines. The included studies had to match predetermined criteria according to the patients, intervention, comparator, outcomes, and study design approach.

Results: Eleven of the 12 studies identified, including three randomized split-face trials, showed improved results despite differences in study design and outcome measures, many of which were subjective.

Conclusion: Further randomized controlled trials and related systematic reviews need to be performed, as evidence-based medicine studies of level I are required to confirm PRP injection efficacy in facial rejuvenation, to consolidate the promising results of the studies identified in this systematic review. *(Plast. Reconstr. Surg.* 152: 72e, 2023.)

Aging is the consequence of cellular function reduction and soft-tissue subsidence.[1] The long-term and/or repetitive exposure to the sunlight and related ultraviolet radiation may change the face skin structure, promoting premature skin aging, termed "photoaging." Human skin undergoes both chronologic aging (genetic factors) and photoaging (ultraviolet radiation), resulting in decreased vascularization, degradation of dermal extracellular matrix proteins, skin appendage disorders, fat atrophy, and loss of muscle tone.[2,3] Also, cessation of collagen and elastin synthesis, with degradation of proteoglycans, results in loss of skin elasticity.[4] These changes become clinically evident as mottled pigmentation, wrinkles, and deterioration in skin texture with subsequent deterioration in youthful appearance, which can be classified into four types.[5]

An increasing interest in maintaining a youthful appearance, also incentivized by social media, has led to the development of noninvasive aesthetic procedures for the treatment of skin aging.[6] It is believed that activation of dermal fibroblasts, remodeling of extracellular matrix, and collagen synthesis are required for the maintenance of youthful skin appearance.[7] The request for nonsurgical and surgical noninvasive procedures aiming to treat soft-tissue volume loss, wrinkles, and photodamage continues to rise, which includes topical retinoic acid, botulinum toxin type A, fillers, chemical peels, lasers, lipofilling or miniface lifting,[8] and more recently platelet-rich plasma (PRP).[9] As is known, it is possible to distinguish autologous activated (AA-PRP) and autologous

From the [1]Department of Surgical Science, Medical School, "Tor Vergata" University; [2]Academy of International Regenerative Medicine and Surgery Societies; and [3]Institute of Dermatology, F. Policlinico Gemelli IRCSS, Università Cattolica del Sacro Cuore.

Received for publication July 17, 2021; accepted May 26, 2022.

DOI: 10.1097/PRS.0000000000010150

Disclosure statements are at the end of this article, following the correspondence information.

nonactivated PRP (ANA-PRP), both containing many signaling proteins. After platelet activation, several major growth factors (GFs) are released, and every one is implicated in a specific biomolecular pathway during skin rejuvenation. This article aims to perform a systematic review of the literature and critically appraise the available evidence regarding the efficacy of AA-PRP and ANA-PRP used for facial rejuvenation.

MATERIALS AND METHODS

PRP Role, Protocols, and Effects

PRP role, protocols, and effects have been described by several authors: Marx et al.,[10] Bennett and Schultz,[11] Kim et al.,[12] Park et al.,[13] Yuksel et al.,[14] and Frautschi et al.[15] Marx et al.[10] described a PRP showing a three/six times average platelet concentration above baseline values (1×10^6 μL ± 20%). Platelets, in addition to their pivotal role in hemostasis, represent a rich source of proteins and GFs including platelet-derived growth factor, insulin-like growth factor, vascular endothelial growth factor, epidermal growth factor, fibroblast growth factor, and transforming growth factor-β, released during platelet degranulation when activated by thrombin or calcium chloride. The GFs were demonstrated to play a fundamental role in wound healing and tissue regeneration through chemotaxis, proliferation, differentiation, and angiogenesis.[11] In vivo studies have demonstrated that PRP acts by means of stimulation of fibroblast proliferation, producing an anti-inflammatory factor increase, and angiogenic factors and extracellular matrix remodeling proteins including procollagen I, hyaluronic acid, and tissue inhibitor of metallopeptidase.[12,13] This leads to an increase in collagen remodeling, epidermal thickening, increased vascularization, and reduced degradation of the dermal extracellular matrix required for skin rejuvenation.[14]

Several protocols of ANA-PRP and AA-PRP preparations have been described depending on the centrifugation's time, *g* force, platelet number, GFs, chemokine availability, blood collected, and anticoagulant use. Three layers following centrifugation were obtained: the lower layer of red blood cells, the middle layer of white blood cells and platelets ("buffy coat"), and the upper layer composed of plasma. The upper layer can be further subdivided into three fractions, according to platelet content, with the "platelet-rich layer" being near the buffy coat layer.[15] In the single-spin method, the lower portion of the plasma layer is collected as PRP. To increase the platelet concentration, the plasma and buffy coat can be further isolated, and a second centrifugation can be performed. The platelet-rich fraction can then be activated with different agents, depending on the method. The final product can then be administered by means of injection or topically.

Study Overview

A multistep search, without a language or publishing-time restriction, of the PubMed, MEDLINE, Embase, PreMEDLINE, Ebase, Clinicaltrials.gov, Scopus, and Cochrane databases was performed to identify studies on PRP in facial rejuvenation published before April 15, 2021. Fifty-four articles using the keywords "PRP facial rejuvenation," 42 articles using the keywords "PRP facial aging," 192 articles using the keywords "PRP face," and 47 articles using the keywords "PRP facial skin rejuvenation" were found, as reported in Figure 1.

Study Assessment

This systematic review assessed the selected articles comparing local injections/applications of autologous PRP compared with any control for facial rejuvenation. Articles included in this work had to match predetermined criteria according to the patients, intervention, comparator, outcomes, and study design approach. The study assessment was based on inclusion and exclusion criteria (Table 1).

Data Extraction

The two investigators independently screened titles and abstracts for duplicates and poor fit within the focus of the systematic review. If at least one investigator coded the title to continue to the next round, the other investigator independently reviewed the full-text article and classified the article based on the eligibility criteria. Both investigators independently assessed all articles deemed eligible for full-text review. Any disagreement on the extracted data has been settled by means of their consensus. The following data have been identified: first author, year of publication, study design, number of patients, type of procedure, and primary and secondary outcomes. The quality of the included investigations was independently assessed among the two investigators using the Cochrane Collaboration's Risk of Bias Assessment tool for randomized controlled trials (RCTs),[16] and the Newcastle-Ottawa Scale

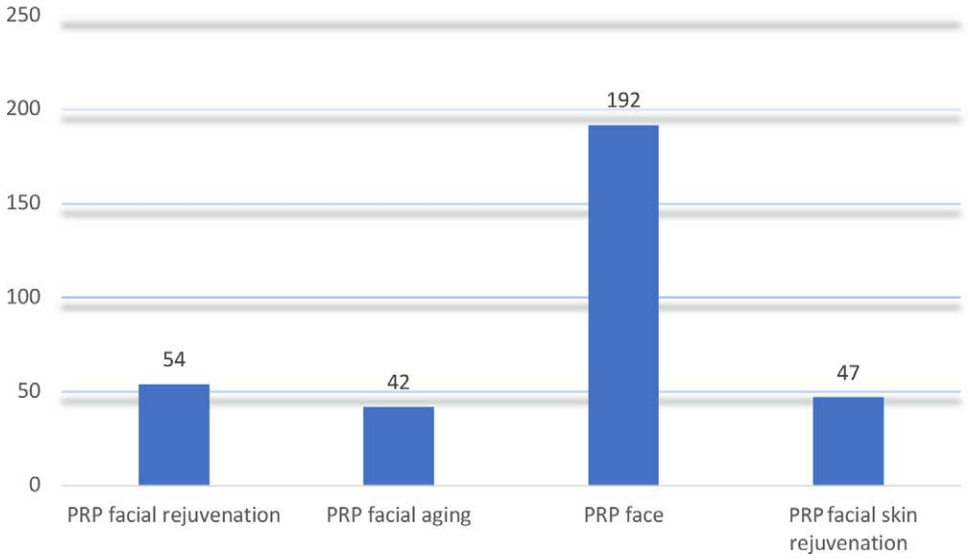

Fig. 1. Articles initially found on autologous PRP use in facial rejuvenation.

Table 1. Study Assessment Based on Inclusion and Exclusion Criteria According to the Patients, Intervention, Comparator, Outcomes, and Study Design Approach

	Criteria
	Inclusion
P: Patients	Age 18–80 yr, patients with facial soft-tissue defects, facial skin aging, signs of facial aging
I: Intervention	Local injection or topical application of AA-PRP or ANA-PRP
C: Comparator	Any type of control, internal, external, and different product
O: Outcomes	Aging signs reduction, skin quality, facial tissues improvement
S: Study design	Clinical trial, randomized clinical trial, case-series, case report, case-controlled studies
	Exclusion
P: Patients	Other types of defects and abnormalities, patients with platelets disorders, thrombocytopenia, antiaggregating therapy, use of pharmacologic therapeutics against facial skin aging as filler, hyaluronic acid, skin booster, botulinum toxin type A (all these treatments were tested as control in PRP studies, uncompensated diabetes, sepsis, cancer)
I: Intervention	Filler, hyaluronic acid, skin booster, botulinum toxin type A, steroid injections, surgical procedures
C: Comparator	Not applied
O: Outcomes	Not applied
S: Study design	Comments, letters to the editor, preclinical model (animal studies), in vitro studies, articles identified as bias; not correct match with the keywords used and with the treatment; follow-up shorter than 3 mo (review, and systematic review); no limitations were applied on ethnicity or method of PRP processing

was used to evaluate the individual nonrandomized studies.[17]

Statistical Analysis

Statistical analysis was carried out on GraphPad online program and outcomes significance was tested using the t test. A value of $P < 0.05$ was the cutoff for statistical significance. The principal summary measures were reported as P value, percentage, and ratio.

RESULTS

Literature Search

Three hundred thirty-five articles focused on PRP use in facial SR against signs of aging were initially identified and selected using Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flow (Fig. 2). Three hundred twenty-three articles have been excluded for several reasons, including duplicates ($n = 168$), bias attributable to not correctly matching with the treatment, and keywords ($n = 91$).

Seventy-six articles were initially assessed for eligibility; of these, 43 articles not correctly matched with the topic were excluded. Only 33 articles were related to the use of AA-PRP and/or ANA-PRP in facial rejuvenation. Nineteen articles were identified as preclinical, experimental, or in vitro studies, whereas two articles identified as comment and systematic reviews were excluded. For the above-mentioned reasons, only 12 articles were strictly correlated with AA-PRP and/or ANA-PRP use in facial rejuvenation.[3,18–28]

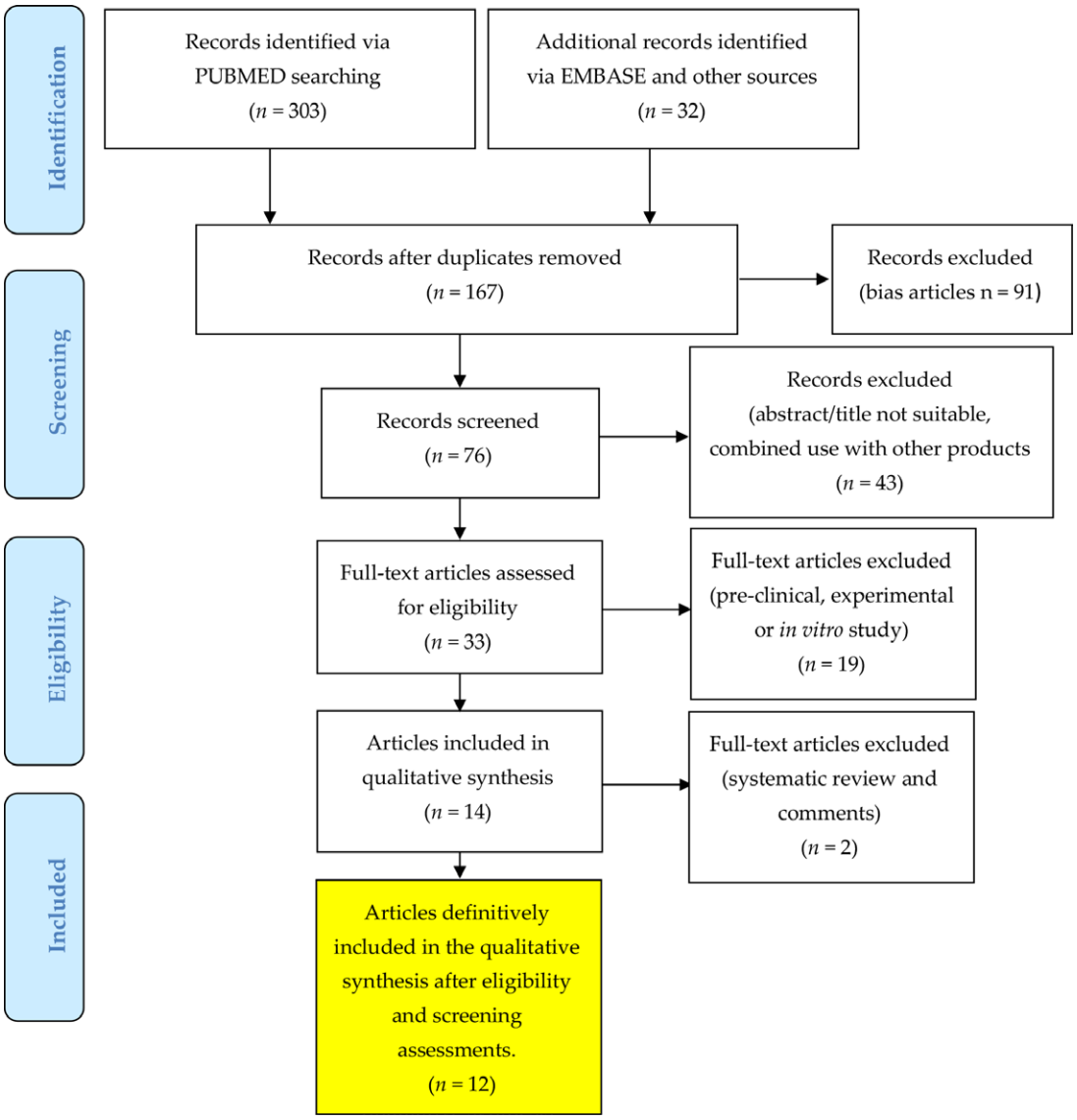

Fig. 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow.

Study Subjects

The protocol of PRP preparation demonstrated considerable heterogeneity among the identified studies as reported in Table 2. The final platelet concentration obtained during PRP preparation was documented in only three studies (25%). Centrifugation protocol details were reported in nine studies (75%), with five studies using single-spin and four studies using double-spin methods. Of the 12 studies identified, nine reported the use of anticoagulants (75%), five with sodium citrate and four with acid citrate dextrose. Three studies (25%) did not report whether anticoagulant was used in their protocol. The platelet activation agent was reported in nine studies with a calcium-based activator used in most studies (58%), plasma rich in GFs activator in one (8%), and no activator used in one study (8%). Three studies failed to report whether platelet activation was performed.

Selected Studies Analyzed

Twelve articles [eight case series[3,18–24] (67%), four split-face[25–28] (33%, three of which were RCTs[25,27,28] and one was not randomized[26])] were included in qualitative synthesis as reported in Table 2. In the prospective case series of 10 patients, Díaz-Ley et al.[18] performed three treatments of both intradermal and deep dermal injections of AA-PRP, reporting histologic analysis in addition to subjective clinical assessment. A statistically significant increase in epidermal

Table 2. PRP Studies Analyzed

Reference	PRP Injection Procedures	PRP Preparation Procedures	Study Type	No. of Patients	Platelet Yield	Activation	Anticoagulant	Outcomes
Elnehrawy et al., 2016[3]	Technique: AA-PRP single treatment Injection: N/A Volume: N/A	1. First centrifugation, 388 *g* × 7 min; 2. Second centrifugation, 1376 *g* × 5 min	Case series	20	N/A	10% calcium chloride	Sodium citrate	Statistically significant improvement in Wrinkle Severity Rating Scale, Skin Homogeneity and Texture Scale, Physician Assessment Scale, and Subject Satisfaction Scale
Díaz-Ley et al., 2015[18]	Technique: AA-PRP into whole face Injection: Deep dermis and intradermally Volume: N/A	1. Only one centrifugation, 580 *g* × 8 min	Case series	10	N/A	PRGF activator	Sodium citrate	Statistically significant increase in epidermis and papillary dermis thickness, effective for photodamage
Mehryan et al., 2014[19]	Technique: AA-PRP single treatment Injection: intradermal-periorbital Volume: N/A	1. First centrifugation, 1600–1800 *g* × 6 min 2. Second centrifugation, 2000 *g* × 5 min	Case series	10	3–4 × baseline	Calcium chloride	Acid citrate dextrose	Statistically significant improvement in infraorbital color homogeneity, no statistically significant change in melanin content, stratum corneum hydration, wrinkle volume, or visibility index
Sclafani, 2011[20]	Technique: AA-PRP for fine rhytides and deeper folds Injection: intradermal for fine rhytides and dermal/subdermal junction for deeper folds Volume: N/A	1. Only one centrifugation, 1100 rpm × 6 min	Case series	50	N/A	Calcium chloride	Sodium citrate	Most patients perceived improvement by 5–7 days, with majority (90%) noting continued improvement until 2–4 wk after injection
Sclafani, 2010[21]	Technique: AA-PRP for NLFs Injection: N/A Volume: N/A	Only one centrifugation, 1100 rpm × 6 min	Case series	15	N/A	Calcium chloride	N/A	All Wrinkle Severity Rating Scale scores were significantly improved, can provide long-term diminution of deep NLFs
Redaelli et al., 2010[22]	Technique: AA-PRP into forehead, periorbital, nasolabial fold and neck for 3 mo Injection: N/A Volume: N/A	1. Only one centrifugation, 3500 rpm × 5 min	Case series	23	N/A	Calcium chloride	N/A	Improvements in the following: nasolabial folds, 24%; horizontal neck bands, 28%; periocular wrinkles, 30%; skin homogeneity/texture, 33%
Everts et al., 2019[23]	Technique: AA-PRP monthly for 3 mo Injection: N/A Volume: N/A	N/A	Case series	11	N/A	Calcium chloride	Sodium citrate	Significant skin rejuvenation demonstrated by biometric parameters and confirmed by patient self-assessment score
Cameli et al., 2017[24]	Technique: ANA-PRP monthly for 3 mo Injection: N/A Volume: N/A	1. Only one centrifugation, 1100 rpm × 8 min	Case series	12	1680×10^6	Excluded	Sodium citrate	Clinical and patient evaluation showed improvement of skin texture; skin gross elasticity, skin smoothness parameters, skin barrier function, and capacitance were significantly improved

(*Continued*)

Table 2. *Continued*

Reference	PRP Injection Procedures	PRP Preparation Procedures	Study Type	No. of Patients	Platelet Yield	Activation	Anticoagulant	Outcomes
Kang et al., 2014[25]	Technique: ANA-PRP vs. saline into infraorbital area; three sessions at 4-wk intervals Injection: N/A Volume: N/A	N/A	Split-face randomized study	20	N/A	N/A	N/A	Infraorbital skin treated with PRP showed significant improvement of wrinkles and skin tone compared with saline-treated skin
Sevilla et al., 2015[26]	Technique: single injection of GFC on right side of face and ANA-PRP on left side of face Injection: N/A Volume: N/A	1. First centrifugation, 380 *g* × 15 min; 2. Second centrifugation, 2700 *g* × 10 minute	Split-face not randomized study	60	625×10^6 platelets/mL	N/A	Acid citrate dextrose	Improvement score analysis showed that GFC was superior to PRP in treating nasolabial folds
Gawdat et al., 2017[27]	Technique: AA-PRP vs ready-made growth factor split face study; six sessions at 2-wk intervals Injection: N/A Volume: N/A	1. First centrifugation, 150 *g* × 15 min 2. Second centrifugation, 400 *g* x 10 min	Split-face randomized study	20	N/A	3% calcium chloride	Acid citrate dextrose	Both procedures yielded significant improvement in skin turgor and overall vitality, and epidermal and dermal thickness assessment; patient satisfaction was significantly higher on the AA-PRP side; improvement was more sustained on the AA-PRP side
Alam et al., 2018[28]	Technique: ANA-PRP vs. normal saline Injection: N/A Volume: N/A	N/A	Split-face randomized study	19	N/A	N/A	Acid citrate dextrose	At 6 mo after a single treatment, participants rated the PRP-treated side as significantly more improved compared with normal saline for texture ($P = 0.02$) and wrinkles ($P = 0.03$).

NLFs, nasolabial folds; N/A, not available; PRGF, plasma rich in GFs; GFC, GF concentrate.

and papillary dermal thickness, collagen volume, and fibroblast number has been observed. Seven patients reported being either satisfied or very satisfied with the outcome, whereas the remaining three patients reported being "indifferent" about the outcomes.

Mehryan et al.[19] performed AA-PRP therapy in 10 patients affected by wrinkles and dark circles in the periocular region. After 3 months, infraorbital dark circles of participants were significantly reduced, wrinkles were significantly improved, and patients were satisfied with the results.

Sclafani[20] reported the outcomes observed in 50 patients affected by deeper wrinkles and folds on the face treated with intradermal and subdermal AA-PRP injection, with a mean follow-up of 10 months on average. Participants received an average of 1.6 treatments. Most patients perceived improvement 7 days after the treatment, with the majority (90%) noting continued improvement up to 4 weeks after injection.

In a further study, in which a single AA-PRP injection for moderate-to-severe nasolabial wrinkles in 15 female patients followed up for 12 weeks has been performed, Sclafani[21] reported a significant improvement in wrinkle assessment scores ($P < 0.001$).

In a study performed by Redaelli et al.,[22] 23 patients, who underwent monthly facial injections of AA-PRP for 3 months, were analyzed. They reported a 33% improvement in skin homogeneity and texture and a 30% improvement in crow's feet lines at 3 months.

Everts et al.[23] reported a significant decrease in brown spot counts and total wrinkle appearance scores in a case series of 11 patients treated with AA-PRP injection performed monthly for 3 months with a 6-month follow-up. Skin firmness parameters were also significantly improved, with self-assessment at 6 months revealing an average satisfaction score of greater than 90%.

A similar protocol of three ANA-PRP injections at monthly intervals in 12 patients has been performed by Cameli et al.[24] Image analysis showed a significant skin texture improvement 1 month after the last treatment session compared with baseline.

A group of 20 female patients, with skin phototypes III and IV, were treated with AA-PRP injection by Elnehrawy et al.[3] AA-PRP injection resulted in statistically significant improvements in Wrinkle Severity Rating Scale, skin homogeneity, texture, and subjective patient satisfaction 8 weeks after single-injection treatment.

In comparison to the case series articles described above, Kang et al.[25] performed an ANA-PRP versus saline split-face RCT in 20 patients undergoing three infraorbital injection treatment sessions at 4-week intervals with evaluation at baseline and 3 months after treatment. Infraorbital skin treated with ANA-PRP showed significant improvement in wrinkles and skin tone compared with saline-treated skin.

A split-face study of 60 patients by Sevilla et al.[26] compared single-treatment ANA-PRP injections against GF concentrate (GFC) injections. Both ANA-PRP and GFC showed significant improvement in the global aesthetic improvement scale at 3 months after treatment; however, overall improvement score analysis showed that GFC was significantly superior to PRP ($P < 0.001$).

Gawdat et al.[27] prospectively randomized 20 female patients, five with Glogau types II and III skin, in a split-face comparative trial. Each side of the face was randomly assigned to one of two treatment protocols, represented by readymade GF solution or AA-PRP. Patients were blinded to the assigned treatment for each side of the face. The investigators were also blinded to the assigned treatment and evaluated the degree of clinical improvement 6 months after treatment. Patient satisfaction and clinical improvements (based on skin turgor, overall appearance, and epidermal and dermal thickness improvements) were significantly higher in the AA-PRP group. Alam et al.[28] also performed a prospective split-face RCT with 1:1 allocation in which participants and raters were masked to which side of the face received ANA-PRP or normal saline injection. In the 19 patients enrolled, the photoaged facial skin of those treated with ANA-PRP was found to be significantly less rough and wrinkled at 6 months after a single treatment.

Outcome Evaluation Methods

In addition to clinical evaluation, endpoint evaluation methods included photographic evaluation, physician global assessment score, and patient global assessment score. The satisfaction surveys and scales, taken from the perspective of patients and other observers, were also used to evaluate the efficacy of AA-PRP and/or ANA-PRP in some of the recruited studies. Eleven of the 12 studies (92%), including all three split-face RCTs, reported a clinical efficacy from PRP injection, in terms of increase in epidermal and papillary dermal thickness, collagen volume and fibroblast number, dark circle reduction, wrinkle improvement, improvement for skin homogeneity and texture, improvement in crow's feet lines, decrease in brown spot counts, and global aesthetic improvement.

However, significant differences in outcome measures and follow-up period were noted between all studies. The human clinical autologous use of ANA-PRP and/or AA-PRP regarded the treatment of facial soft-tissue defects, signs of aging, loss of elasticity, wrinkles, and roughness.

Satisfaction Rate

Twelve studies yielded a total of 300 patients, including 119 patients who underwent the split-face control. The overall satisfaction rate was 68% (n = 123 and 58 in case series studies; n = 80 and 39 in split-face studies; two-tailed P = 0.0345).

Limitations

The main weakness of the prospective case series of 10 patients described by Díaz-Ley et al.[18] is the absence of a control group (CG) and thereby an inability to randomize and blind, leading to issues with bias. A small patient cohort and relatively short follow-up time of 3 months also limit the merits of their findings. Again, limitations of the study of Mehryan et al.[19] include the small number of participants, absence of a CG, and relatively short follow-up duration.

Despite the larger patient cohort, in the study by Sclafani,[20] there is considerable variation in treatment protocol, including injection technique, number of treatments, and the interval between treatments. Also, no details about post-treatment evaluation methods are mentioned other than patient satisfaction scores which, in the absence of a CG and blinding, are susceptible to bias. In the second study by Sclafani[21] also, the improvements reported were subjectively assessed only by the treating physician, raising significant issues regarding methodology and validity.

In the study performed by Redaelli et al.,[22] the clinical outcomes were described after only 1 month of follow-up. Everts et al.[23] acknowledge that the results reported in their study were influenced by the small sample size without a CG, eliminating the potential for blinding. Cameli et al.[24] reported a significant skin texture improvement in most patients treated with three ANA-PRP injections at monthly intervals, but a volume increase of fine wrinkles at the injection site was detected in only one patient. The group of 20 patients in the study by Elnehrawy et al.[3] was composed of females with a mean age of 36 and skin phototypes III and IV, leading to potential limitations to the external validity of the study.

In the RCT described by Kang et al.,[25] the allocation concealment was not reported; however, the article stated that clinical assessment was performed by three blinded dermatologists who compared photographs obtained at baseline and the last follow-up. The author acknowledges the small number of patients enrolled as being a limitation to the study result.

No attempt at randomization was performed in the study by Sevilla et al.,[26] with assessors and patients both aware of the protocol (being left face GFC injection and right face ANA-PRP injection), making the study highly susceptible to bias, and limiting the methodologic advantage of having a control arm. The only positive and significant parameter was the patient-treated group represented by 60 people, currently the largest.

Significant analysis has been reported in a prospective, split-face, randomized, double-blind, controlled study performed by Gawdat et al.[27] in which 20 female patients were treated with a readymade GF solution or AA-PRP. Patient satisfaction and clinical improvement were significantly higher in the AA-PRP group. Interestingly, the difference in patient satisfaction might be explained by the more frequent burning sensation reported after GF solution injection, highlighting the importance of comfort and effectiveness when treating patients. The lack of diversity in the participant demographic in addition to the small patient numbers involved were negative factors in a study that has made significant efforts in reducing bias by appropriate randomization and double-blinding.

Methodologically, the study of Alam et al.[28] was designed to minimize bias, both using a randomization sequence identified by means of a computerized random number generator, and by means of allocation concealment. A limitation of this study was that several participants did not complete the follow-up protocol, because of the multiple visits required after just one initial treatment session. Other weaknesses of this study were that ANA-PRP platelet concentration and the centrifugation protocol were not reported. In addition, the method of platelet activation (if any) was not described (for this reason, here it was considered ANA-PRP). Reassuringly, reported adverse events were not significantly associated with either ANA-PRP or normal saline and consisted of localized injection-site reactions including redness, swelling, bruising, pruritus, and skin dryness, all of which resolved in less than 2 weeks after injection.

Critical Assessment of Study Design

The analysis of selected studies highlighted a lack of a standardized and widely shared protocol

on the PRP preparation procedures (AA-PRP versus ANA-PRP; type of activation, centrifugation time and speed, frequency and interval of treatment sessions, and anticoagulation agent), and the injecting technique (nappage, mesotherapy, intradermal, subdermal). In addition, the difficulty in clearly interpreting results was determined by the wide range of the studies analyzed (from case series without a CG to randomized trials).

Side Effects

Only tolerable and temporary pain during and immediately after the procedures and transient edema have been described by some patients during PRP treatment. Minor localized injection-site reactions including redness, swelling, bruising, pruritus, and skin dryness were not rare, but all resolved within 2 weeks of treatment. No major side effects have been displayed.

DISCUSSION

Interestingly, several of the studies identified reported that PRP was found to be less effective if given to patients older than 60 years.[23,26,27] This may be explained by a deterioration in levels of GFs in the platelets derived from the older patients, resulting in reduced tissue response and poorer outcomes. It may also be because older patients are more likely to present with deeper wrinkles and more severe photoaging not amenable to PRP injection therapy. This highlights the importance of appropriate patient selection, treatment planning, and patient expectation management. What is evident from the data presented (Table 2) is that there is considerable heterogeneity between the studies identified, particularly regarding intervention protocol including factors such as *g* force, spin frequency and time, platelet activation, anticoagulation agent, platelet concentration, number of treatments, and the related interval, all of which could influence the efficacy of PRP injection treatment, particularly when attempting to compare study outcomes.[29,30] In addition, individual differences in blood withdrawal and PRP injection technique may also influence the PRP effects in terms of viable platelet concentration and subsequent GF release.[31] The final PRP product is also influenced by which type of centrifugation protocol is used. Single-spin PRP devices have a lower platelet concentration in the final product and consist mainly of plasma. These devices may therefore demonstrate a less significant effect when compared with a buffy coat double-spin PRP sample rich in platelets and GFs deemed vital for tissue regeneration.[23]

The regenerative PRP effect is associated with the degranulation of α-granules containing stored GFs. Activated platelets release their GFs within 10 minutes of activation and continue to secrete further GFs within the following 7 days of their life span.[32] In PRP preparation, degranulation can be initiated by various activators, including thrombin, calcium chloride, and collagen. However, this process may produce significant variations in GF release, depending on the agent used to achieve platelet activation.[33] Anticoagulation in PRP preparation is an additional factor that may influence final platelet concentration but could also negatively impact platelet function through alterations in pH.[34,35] Specifics of anticoagulation used were not reported in 25% of the studies identified, with five (42%5) using sodium citrate and four (33%) using acid citrate dextrose. In the presence of the multiple confounding factors in the studies identified, it is not possible to determine which anticoagulant is associated with increased efficacy.

The 12 studies analyzed did not report any serious or persistent side effects following PRP injection therapy but only minor localized injection-site reactions. Kalyam et al.[36] described skin necrosis in the targeted area, optic nerve infarction, and irreversible right eye blindness in one patient who received PRP injections to treat bilateral glabellar wrinkles. This was the only case of PRP injection followed by major side effects. In addition, it has been reported that some practitioners deliberately modify PRP preparations before injection, which can include the mixing of PRP with fillers,[37] increasing the risk of this type of side effect. Visual complications from various periocular cosmetic fillers have been previously reported.[38–40]

Regarding the outcomes, it has not been possible to affirm which facial regions respond better to PRP, but only in which it has been indicated and tested; the expected longevity of the treatment may be considered to range from 1 to 10 months. The patient's satisfaction and adopted protocol influence the necessity to repeat the treatment. A wide range of injection protocols has been performed, with a mean range of 30 days and one to three treatments for every patient.

On these bases, the authors feel the necessity to recommend the use of PRP in patients selected based on inclusion and exclusion criteria, fully respecting the specific country's institutional rules and/or related blood laws. Exclusion

criteria may be considered blood disease (platelet disorders, thrombocytopenia), antiaggregating therapy, bone marrow aplasia, uncompensated diabetes, cancer, and sepsis. Inclusion criteria may be considered wrinkles and dark circles, infraorbital dark circles, deeper wrinkles and folds on the face, light-to-moderate nasolabial wrinkles, face rejuvenation, and crow's feet lines, as previously reported.

The main recommendations are obtaining an amount of 1×10^6 μL (±20%) of platelets as a minimum level for every procedure, performing exclusively infiltrative (intradermal and/or deep dermal injections) or topical PRP, adopting quality and sterility checks on the sample obtained, and illustrating a detailed informed consent. The current findings should be interpreted considering the strengths and limitations described. Indeed, this systematic review encompasses all articles on PRP used in facial rejuvenation without a language or publishing-time restriction and is comprehensive; however, the analyzed data are subject to the heterogeneity of the included studies (eight case series,[3,18–24] three split-face randomized studies,[25,27,28] and one nonrandomized split-face study[26]), the patient cohort, the PRP preparation methods, the PRP injection protocol, the platelet concentrations, the outcome measures, and the follow-up time, representing bias. Despite differences in study designs and outcome measures, many of which were subjective, 11 of the 12 studies identified showed improved results when PRP was used.

CONCLUSIONS

Analyzed data are substantial, even if with a big range of medical evidence between evidence-based medicine levels of I and IV (level I, RCTs; and level IV, case series), confirming the safety and efficacy of ANA-PRP and/or AA-PRP in face rejuvenation, with an acceptable side-effect profile when performed correctly. Given that the current procedures differ in methodology and treatment technique, further studies (large-scale RCTs) are needed to define standardized protocols.

Pietro Gentile, MD, PhD
Via Montpellier 1
Rome 00173, Italy
pietrogentile2004@libero.it

DISCLOSURE

The authors declare no financial interests or potential conflicts of interest concerning the research, authorship, or publication of this article. The authors received no financial support for the research, authorship, or publication of this article.

ACKNOWLEDGMENT

This work was written totally by Pietro Gentile, MD, PhD, independent mind, exclusively based on scientific results selected and analyzed.

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