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EFFECTIVENESS OF PLATELETS RICH PLASMA IN SKIN REJUVENATION: A SYSTEMATIC REVIEW

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Mehmet Mustafa Beşirikli
Tashkent State Medical University
besirikli@lomnas.uk

Abstract

A possible noninvasive method for facial rejuvenation is platelet-rich plasma (PRP). The purpose of this systematic literature review is to evaluate the type and standard of published studies assessing PRP's safety and efficacy in facial rejuvenation. A systematic review was conducted using four different databases and grey literature to collect relevant articles through a systematic search, using PRISMA guidelines. Studies on the effectiveness of PRP in facial rejuvenation were included in this review. Risk bias assessment was done using the Newcastle-Ottawa scale. Studies that met predefined criteria regarding patients, interventions, outcomes, comparator, and study design methodology were eligible for inclusion. Despite variations in research design and outcome measures, many of which were subjective, improved results were found in eleven of the twelve studies that were found, including three randomized split-face trials. To consolidate the encouraging findings of the studies found in this systematic review, more randomized controlled trials and associated systematic reviews are necessary. Level I evidence-based medicine studies are also needed to confirm the effectiveness of PRP injections in facial rejuvenation.

Keywords:

Platelet-rich Plasma, rejuvenation, PRP, Aging, Systematic review

INTRODUCTION

The previous five decades have experienced a rise in life expectancy around the world, which has prompted an extensive and interesting search for strategies and treatments to slow down the aging process (Robine, Jagger, Crimmins, Saito, & Van Oyen, 2020). Recent developments in science and technology have made it feasible to reduce the signs of aging. Based on data published by the American Society for Aesthetic Plastic Surgery, the overall number of skin rejuvenation treatments performed since 1997 has increased by almost 300% (Tierney & Hanke, 2009).

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Reversing the aging process using noninvasive or surgical methods is the primary goal of face rejuvenation (Atiyeh, Oneisi, & Ghieh, 2021). The number of patients choosing surgical face rejuvenation surgeries has decreased in recent years, even while the number of cosmetic facial rejuvenation procedures has increased (Banihashemi, Zabolinejad, Salehi, Alamdari, & Nakhaizadeh, 2021). This highlights how crucial noninvasive procedures are to achieving better cosmetic results. Platelet-rich plasma (PRP), a platelet concentrate made from autologous plasma, is one of the noninvasive techniques for face rejuvenation. PRP has been utilized for a number of dermatological issues over the years, including facial rejuvenation (Hersant et al., 2021).

The term PRP was used by hematologists to refer to plasma with a considerable high platelet count as compared to peripheral blood during the 1970s (Arora & Arora, 2021). Earlier at times, it was only used for transfusion purposes in patients with severe thrombocytopenia. However, it has been proven to have a wide range of uses in other medical disciplines (Collins, Alexander, & Barkatali, 2021).

A decade later, maxillofacial surgeons started utilizing it as a platelet-rich fibrin (PRF) because of its fibrin-rich content (Montero, Santos, & Fernández, 2015). It has been considered an important factor for a variety of surgical applications because of its potential to promote cell proliferation and anti-inflammatory properties. PRP was widely accepted and favorable in orthopedic surgery in the years that followed, especially in the treatment of sports-related injuries (Magruder, Caughey, Gordon, Capotosto BS, & Rodeo, 2024). PRP has been used in a variety of specialties outside orthopedics, such as urology, cardiac surgery, gynecology, pediatric surgery, plastic surgery, and ophthalmology (Andia, Rubio-Azpeitia, Martin, & Abate, 2015).

Over 800 bioactive molecules are present in platelet-derived growth factor (PRP), transforming growth factor-β1 (TGF-β1), TGF-β2, basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and epithelial growth factor (EGF), among other mitogenic and chemotactic growth factors released from the alpha granules of activated platelets (Macaulay et al., 2005; Senzel, Gnatenko, & Bahou, 2009). By up-regulating the genes involved in cellular proliferation and differentiation, angiogenesis, and extracellular matrix formation, these components may affect tissue repair and other biological processes (Abuaf et al., 2016; Hom, Linzie, & Huang, 2007).

Utilizing PRP's therapeutic potential in dermatology has gained momentum in recent years, with particular attention focused on wound healing, vitiligo, tissue regeneration, scar revision, and skin rejuvenation. Furthermore, studies have

explored its effectiveness in treating alopecia, providing encouraging paths for hair loss management. This review will concentrate on PRP for skin rejuvenation, an area that the authors are especially interested in.

METHODOLOGY

Study Protocol

This systematic review of available literature was conducted according to the PRISMA guidelines (Preferred Reporting Items for Systemic Reviews and Meta-Analyses) (Takkouche & Norman, 2011).

Studies selection

This systematic review aimed to summarize the effectiveness of PRP in skin rejuvenation. The central question guiding this review was: Does PRP is more effective in skin rejuvenation as compared to other aesthetic surgeries? Formulated in line with the PEOS strategy, the breakdown is as follows: P (population) refers to adults using PRP, E (exposure) denotes those who have used PRP for skin rejuvenation, O (outcome) explores the distribution patterns, and S (study type) focuses on original studies.

During the identification of the articles, duplicates were removed by exporting them to EndNote Basic (ENDNOTE, 2015). Subsequently, the studies were chosen in two stages. Reviewer 1 evaluated titles and abstracts in duplicate, separately, throughout phase 1 to find studies that qualified.

However, the reviewers gave their approval before any research was chosen. When necessary, a second reviewer was invited in to help resolve any disagreements through group discussion. Therefore, abstracts and titles mentioning two things were considered acceptable: (1) the effectiveness of PRP in skin rejuvenation; and (2) the original study. To determine whether the publications had the relevant data for the systematic review, the articles were fully examined during the second evaluation step. We considered the following things as exclusion criteria: (1) lacking information regarding the effectiveness of PRP in skin rejuvenation; (2) a case report; (3) a narrative review study; (4) a systematic review study; (5) a study based on an individual's judgment; and (6) a study which is only based on differential diagnosis.

A Microsoft® Excel Spreadsheet was used to extract and store data and records (Microsoft, Inc., Redmond, Wash., USA).

Search Strategy

A systematic search was done for the relevant literature on the following four databases to retrieve relevant studies: **Scopus:** ("platelet-rich plasma" OR PRP) AND ("skin rejuvenation" OR "skin aging" OR "skin renewal" OR "skin regeneration") AND ("effectiveness" OR "efficacy" OR "outcome" OR "results"),

Web of Science: TS=("platelet-rich plasma" OR PRP) AND TS=("skin rejuvenation" OR "skin aging" OR "skin renewal" OR "skin regeneration") AND TS=("effectiveness" OR "efficacy" OR "outcome" OR "results"), **PubMed/EMBASE:** ("platelet-rich plasma" OR PRP) AND ("skin rejuvenation" OR "skin aging" OR "skin renewal" OR "skin regeneration") AND ("effectiveness" OR "efficacy" OR "outcome" OR "results"), **Google Scholar:** "Platelet-rich plasma" AND "skin rejuvenation" AND "effectiveness". Databases were also searched for published systematic reviews or ongoing systematic reviews on the same topic. Relevant studies were retrieved and stored on ENDNOTE to discard the repeated results.

Data collection

Data were separately extracted by the same reviewer from the chosen articles. Title, authors, name of journal, duration, kind of study, country, age, gender, number of participants, location, and effectiveness of PRP were noted for each included study.

Assessment of Risk Bias

Data extractions were conducted using a standard form, and the full-text articles were assessed according to the New Ottawa scale (NOS) criteria. Publications were given scores on a low, medium, or high scale as a methodological quality indicator based on several variables such as reporting bias, performance, and selection. The inclusion and randomization criterion descriptions were used to score preference for selection. Allocation concealment and descriptions of a control arm were taken into consideration when evaluating performance bias. Biased reporting, industrial sponsorship, partial data management, and selective reporting received different rankings. During several teleconferences, the topics of eligibility limitations and reporting uniformity were covered. A second author considered gaps in the reviewers' scores before selecting a study.

RESULTS

Search Results

We found 1014 studies using the criteria for selecting studies from four different databases, of which 433 were removed as duplicate records when the articles were sorted through Endnote software. After removing duplicates, we found 581 studies, which were all sorted for retrieval.311 studies were not retrieved from the databases due to restricted access and were removed from inclusion in our study. After 270 full-text publications were reviewed for eligibility, 258 of them were rejected based on that these studies did not directly target focus on the effectiveness of PRP in skin rejuvenation. This systematic review turned out to comprise 12 papers in all **(Figure 1)**.

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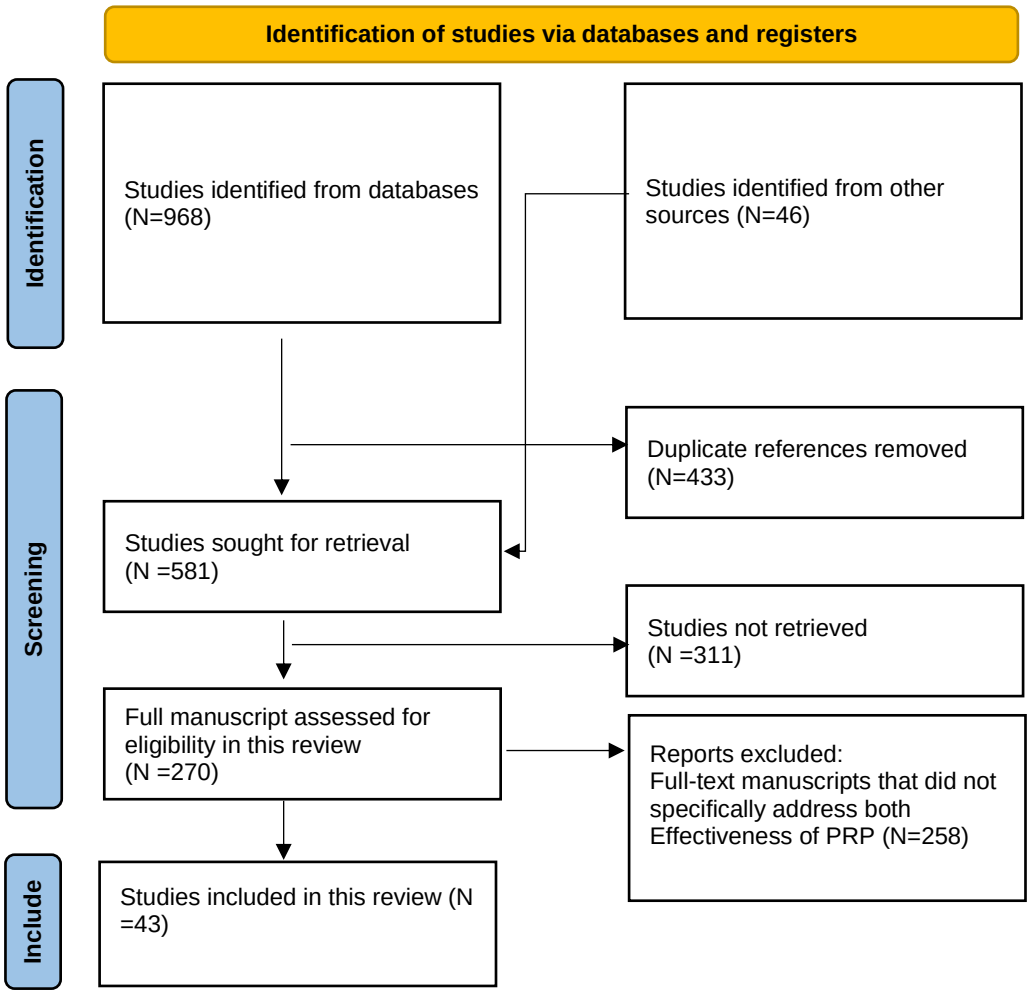

Figure 1: Studies selection using the guidelines of PRISMA

Risk Bias Assessment

When the included studies were assessed for risk bias through the Newcastle-Ottawa scale, it was noted that eight studies showed low-risk bias while the remaining four studies demonstrated moderate risk bias. None of the included studies were recorded to have high-risk bias. The inclusion of observational studies (case-control), which increases the risk of bias because it is unable to randomize the exposure, and the inconsistent nature of the research were the main causes of the low quality of the evidence.

Table 2: Risk of bias assessment in the studies included in the systematic review on the effectiveness of PRP in Skin rejuvenation using the Newcastle - Ottawa Scale (NOS).

Study	Selection	Comparability	Exposure

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	1.	2.	3.	4.	1.	1.	2.	3.
(Díaz-Ley et al., 2015)	★	★			★★	★	★	★
(Mehryan, Zartab, Rajabi, Pazhoohi, & Firooz, 2014)	★	★		★	★	★	★	★
(Sclafani, 2010)	★	★				★	★	★
(Sclafani, 2011)	★	★				★	★	★
(Redaelli, 2010)	★	★	★		★★	★	★	★
(Everts, Pinto, & Girão, 2019)	★	★			★★	★	★	★
(Cameli et al., 2017)	★	★			★	★	★	★
(Elnehrawy, Ibrahim, Eltoukhy, & Nagy, 2017)	★	★			★★	★	★	★
(Kang, Shin, Lee, & Kim, 2014)	★	★		★	★★	★	★	★
(Sevilla, Dhurat, Shetty, Kadam, & Totey, 2015)	★	★	★		★★	★	★	★
(Gawdat, Tawdy, Hegazy, Zakaria, & Allam, 2017)	★	★			★★	★	★	★
(Alam et al., 2018)	★	★		★	★	★	★	

Rating scale: 7 to 9 stars = low risk of bias; 4 to 6 stars = moderate risk of bias; 0 to 3 stars = high risk of bias

Characteristics of included studies

Table 2 reports the inclusion of twelve publications in the qualitative synthesis. Díaz-Ley et al. carried out three treatments of both intradermal and deep dermal injections of AA-PRP in the prospective case series of ten patients, providing histologic investigation in addition to subjective clinical assessment (Díaz-Ley et al., 2015). Collagen volume, fibroblast count, and epidermal and papillary dermal thickness have all statistically significant results. Three patients reported they were "indifferent" to the outcomes, while seven patients reported they were either satisfied or very satisfied with the results.

Mehryan et al. treated ten patients with periorbital wrinkles and dark circles with AA-PRP therapy (Mehryan et al., 2014). After three months, participants' infraorbital dark circles considerably decreased, their wrinkles dramatically improved, and the patients expressed satisfaction with the outcomes.

Sclafani presented the results of 50 patients who had intradermal and subdermal AA-PRP injection therapy for deeper facial wrinkles and folds (Sclafani, 2010). The patients' average follow-up period was 10 months. An average of 1.6 treatments were given to each participant. The majority of patients (90%) reported

continued improvements up to 4 weeks after injection, with the majority noticing improvement 7 days after treatment.

In another study, where 15 female patients were followed up for 12 weeks after receiving a single AA-PRP injection for moderate-to-severe nasolabial wrinkles, Sclafani observed a significant improvement in wrinkle assessment evaluations ($P < 0.001$) (Sclafani, 2011).

In a study conducted by Redaelli et al., 23 patients who received AA-PRP facial injections every month for three months were studied (Redaelli, 2010). By three months, they observed a thirty percent improvement in crow's feet lines and a thirty percent improvement in skin homogeneity and texture. In a case series of 11 patients treated with AA-PRP injections administered monthly for three months with a six-month follow-up, Everts et al. documented a substantial decrease in brown spot counts and total wrinkle appearance scores (Everts et al., 2019). Additionally, there was a notable improvement in skin firmness metrics. At six months, self-assessment revealed an average satisfaction score of over 90%.

In a similar treatment, Cameli et al. administered three ANA-PRP injections on a monthly basis to twelve patients (Cameli et al., 2017). One month following the final treatment session, image analysis revealed an important change in skin texture when compared to the baseline.

Elnehrawy et al. used AA-PRP injection to treat a group of twenty female patients with skin phototypes III and IV (Elnehrawy et al., 2017). Eight weeks following a single injection, AA-PRP injection showed statistically significant improvements in skin homogeneity, texture, and subjective satisfaction among patients as measured by the Wrinkle Severity Rating Scale.

Kang et al. conducted an ANA-PRP versus saline split-face RCT on twenty patients enduring three infraorbital injection therapy sessions at 4-week intervals, with evaluation at baseline and three months following treatment (Kang et al., 2014). This study differs from the case series studies mentioned above. When ANA-PRP was applied to infraorbital skin, wrinkles and skin tone significantly improved as compared to saline treatment.

Sevilla et al. compared GF concentrate (GFC) injections with single-treatment ANA-PRP injections in a split-face trial involving sixty patients (Sevilla et al., 2015). After three months of therapy, both ANA-PRP and GFC exhibited significant progress on the global aesthetic improvement scale. However, a study of the total improvement scores revealed that GFC outperformed PRP by a significant margin ($P < 0.001$).

Gawdat et al. conducted a split-face comparative trial in which they prospectively randomized twenty female patients, five of which had skin types

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Glogau types II and III (Gawdat et al., 2017). Two treatment procedures, AA-PRP or a ready-made GF solution, were assigned at random to either side of the face. Patients weren't aware of which side of their faces received the treatment. Additionally, six months following therapy, the investigators assessed the level of clinical improvement while remaining blind to the assigned treatment. Concerning skin turgor, overall appearance, and improvements in dermal and epidermal thickness, the AA-PRP group exhibited considerably better levels of patient satisfaction and clinical improvements. A prospective split face RCT with 1:1 allocation was also carried out by Alam et al. in which raters and participants were blinded to the side of the face that received an injection of normal saline or ANA-PRP. At six months following a single treatment, the photoaged face skin of the 19 patients showed a considerable reduction in roughness and wrinkles (Alam et al., 2018).

Table 2: Key characteristics of all included studies

Author	Samples size	Study type	Technique for PRR Injection	Condition	Assessment period	Outcomes
(Díaz-Ley et al., 2015)	10	Case series	AA-PRP into the whole face	Photodamage	8 weeks	Increases in epidermis and papillary dermis thickness that are statistically significant and beneficial for photodamage
(Mehryan et al., 2014)	10	Case series	AA-PRP single treatment	Facial wrinkles	3 months	No statistically significant changes in melanin content, stratum corneum moisture, wrinkle volume, or visibility index, but a statistically significant increase in infraorbital color homogeneity
(Sclafani, 2010)	15	Case series	AA-PRP for NLFs	Facial wrinkles	12 weeks	Significant improvements were made to all Wrinkle Severity Rating Scale scores, which can lead to a

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						long-term reduction in deep NLFs.
(Sclafani, 2011)	50	Case series	AA-PRP for fine rhytides and deeper folds	Facial deeper folds	3 months	The majority of patients (90%) reported continuing to improve 2-4 weeks following the injection, with most noticing improvement within 5-7 days of the treatment.
(Redaelli, 2010)	23	Case series	AA-PRP into forehead, periorbital, nasolabial fold and neck for 3 months	Nasolabial folds	1 month	improvements in periocular wrinkles (30%), horizontal neck bands (28%), nasolabial folds (24%), and skin homogeneity/texture (33%).
(Everts et al., 2019)	11	Case series	AA-PRP monthly for 3 months	Facial aging	6 months	Profound skin regeneration as indicated by biometric metrics and validated by the patient's self-rating
(Cameli et al., 2017)	12	Case series	ANA-PRP monthly for 3 months	Facial aging	1 month	Improvements in skin texture were observed in clinical and patient evaluation; there was also a significant improvement in skin barrier function, capacitance, smoothness parameters, and gross elasticity.
(Elnehraw	20	Case series	AA-PRP	Facial	8 weeks	improvements in

y et al., 2017)			single treatment	wrinkles		the Wrinkle Severity Rating Scale, Skin Homogeneity and Texture Scale, Physician Assessment Scale, and Subject Satisfaction Scale that are statistically significant
(Kang et al., 2014)	20	Retrospective cross-sectional	ANA-PRP vs. saline into infraorbital area; three sessions at 4-wk intervals	Facial aging and wrinkles	3 months	When comparing infraorbital skin treated with PRP vs saline-treated skin, there was a noticeable improvement in wrinkles and skin tone.
(Sevilla et al., 2015)	60	Pilot Study	single injection of GFC on the right side of the face and ANA-PRP on the left side of the face	Facial folds	1 year	An examination of improvement scores revealed that GFC was more effective than PRP for the regeneration of nasolabial folds.
(Gawdat et al., 2017)	20	Split face study	AA-PRP vs ready-made growth factor split face study; six sessions at 2-wk intervals	Facial aging	12 weeks	Significant improvements were seen in the skin's turgor and general vitality as well as in the assessment of epidermal and dermal thickness following both processes; patient satisfaction was much higher on the AA-PRP side, and the improvement

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						was more sustained there.
(Alam et al., 2018)	19	Split face randomized study	ANA-PRP vs. normal saline	Facial aging	1 year	Participants evaluated the PRP-treated side as substantially better for texture (P = 0.02) and wrinkles (P = 0.03) after six months following a single treatment.

The physician global assessment score, patient global assessment score, and photographic evaluation were among the endpoint evaluation techniques in addition to clinical evaluation. In certain of the studies that were included in this review, the effectiveness of AA-PRP and/or ANA-PRP was also assessed using the satisfaction surveys and scales that were created from the viewpoints of patients and other observers. PRP injection was found to be clinically effective in eleven out of the twelve studies (92%), which included all three split-face RCTs. The benefits of PRP injection included reduction of dark circles, improvement of wrinkles, improvement of skin homogeneity and texture, improvement of crow's feet lines, reduction of brown spot counts, and improvement of overall appearance.

All studies still showed notable variations in the follow-up length and outcome measures. Clinically, ANA-PRP and/or AA-PRP were used on humans to treat soft-tissue abnormalities of the face, aging signs, elasticity loss, wrinkles, and roughness.

DISCUSSION

It's interesting to note that several studies revealed that PRP was less effective when administered to patients who were older than 60 (Everts et al., 2019; Gawdat et al., 2017; Sevilla et al., 2015). This might be explained by a decrease in GF levels in the platelets extracted from old people, which would be detrimental to the results and tissue reactivity. Another explanation would be that older people are less receptive to PRP injection therapy since they typically have deeper wrinkles and more severe photoaging when they first arrive. This highlights how important it is to select the best patients, plan for their treatment, and control their expectations. The information provided demonstrates how diverse the studies were discovered to be, particularly in terms of the intervention protocol. In particular, when comparing study outcomes, variables such as g force, spin frequency and time, platelet activation, anticoagulant agent, platelet concentration, number of

treatments, and related interval could all have an impact on how effective PRP injection treatment performs (Jo, Roh, Kim, Shin, & Yoon, 2013).

Additionally, variations in the way that blood is drawn and PRP is injected may potentially have an impact on the effects of PRP on viable platelet concentration and the release of growth factors. The type of centrifugation process utilized also affects the final PRP product. Single-spin PRP devices are mostly made of plasma and have a lower ultimate platelet concentration. Therefore, when compared to a buffy coat double-spin PRP sample high in platelets and GFs, which are thought to be essential for tissue regeneration, these devices may show a less significant benefit (Everts et al., 2019).

Regenerative PRP action is directly linked to the process by which accumulated GFs are released from α-granules. GFs are released by activated platelets within 10 minutes of activation, and they continue to emit GFs over the next 7 days of their lives (Dolder, Mooren, Vloon, Stoelinga, & Jansen, 2006). Many activators, such as thrombin, collagen, and calcium chloride, can start the degranulation process during PRP preparation. Still, depending on the substance utilized to induce platelet activation, this procedure may result in considerable differences in GF release (Mazzucco, Balbo, Cattana, & Borzini, 2008). One other aspect of PRP preparation that could affect final platelet concentration is anticoagulation, which may also adversely affect platelet function by changing pH (Araki et al., 2012; Wahlström, Linder, Kalén, & Magnusson, 2007). Four studies (33%) and five studies (42%) used acid citrate dextrose and sodium citrate, respectively, as the anticoagulant; the remaining three studies (25%) did not disclose the exact anticoagulation used.

The twelve studies that were investigated only reported mild localized injection-site reactions instead of any severe or long-lasting side effects from PRP injection therapy. One patient treated with PRP injections for bilateral glabellar wrinkles experienced skin necrosis in the targeted region, optic nerve infarction, and irreversible blindness in the right eye, according to Kalyam et al (Kalyam et al., 2017). This was the only example of a PRP injection that had serious negative effects. Furthermore, before injection, some practitioners have reportedly been known to intentionally modify PRP preparations (Pensato, Al-Amer, & La Padula, 2024). This may involve combining PRP with fillers, which raises the possibility of this kind of adverse reaction. There have been reports of visual problems from several types of periocular cosmetic fillers in the past (Carle, Roe, Novack, & Boyer, 2014; Danesh-Meyer, Savino, & Sergott, 2001; Lazzeri et al., 2012).

Outcome-wise, it is not possible to confirm which facial regions respond better to PRP; only those that have been investigated and recommended have been shown

to respond. Treatment duration is estimated to be between one and ten months. The need for a follow-up treatment depends on the patient's satisfaction and the procedure that was followed. Numerous injection procedures have been used, with a mean duration of 30 days and one to three treatments administered to each patient.

Based on these considerations, the authors believe it is imperative to advise the use of PRP in patients who have been chosen by inclusion and exclusion criteria while adhering to any applicable blood regulations and/or institutional policies in that specific country. Blood disorders (platelet disorders, thrombocytopenia), anti-aggregating medication, bone marrow aplasia, neglected diabetes, malignancy, and sepsis are examples of exclusion criteria. According to prior reports, the inclusion criteria may include wrinkles and dark circles, infraorbital dark circles, deeper wrinkles and facial folds, light-to-moderate nasolabial wrinkles, face rejuvenation, and crow's feet lines.

CONCLUSIONS

PRP can be used alone or in conjunction with additional therapies like laser treatment, fat grafting, subcision, growth factors, and thread lifting to achieve positive results for facial rejuvenation. The results of the analysis are significant, despite the wide range of medical evidence between levels I and IV of evidence-based medicine (level I, RCTs; and level IV, case series), demonstrating the safety and effectiveness of ANA-PRP and/or AA-PRP in face rejuvenation, with a manageable side-effect profile when used appropriately. Large-scale RCTs are required to create uniform protocols because the current processes vary in methodology and treatment approach.

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