REVIEW

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Intradermal injection of platelet-rich plasma for periorbital wrinkles: A review

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ABSTRACT

Background: Intradermal injection of autologous platelet-rich plasma (PRP) is a non-surgical cosmetic procedure that can restore pathologies such as wrinkles in the periorbital area. Over the past decade, this new treatment has gained worldwide acceptance. We aimed to narratively review the effect of intradermal injection of PRP on the improvement of periorbital wrinkles.

Methods: This was a narrative review evaluating PRP treatment of periorbital wrinkles. Literature searching was performed using the keywords (platelet-rich plasma) AND (periorbital wrinkle) to obtain eligible articles. The literature search was performed in the PubMed database. The findings in the included articles were reviewed and described narratively.

Results: Eight studies treating 83 patients (100% female, age range 26-65) were included. PRP treatment of periorbital wrinkles resulted in objective improvement, increased subjective satisfaction scores, and a blinded evaluation of skin appearance renewal. Future studies need to address the limitations of the current literature and include long-term follow-up, randomized controlled trials with low risk of bias and absence of conflicts of interest or industry sponsors.

Conclusion: Objective and subjective assessments show that this treatment is promising for the prevention of periorbital wrinkles

Keywords: anti-aging medicine, intradermal injection, periorbital wrinkles, platelet-rich plasma, skin aging, wrinkles.

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INTRODUCTION

Rejuvenation of the face is still an important focus of cosmetic procedures whether surgical or nonsurgical. The eyes and infraorbital area are parts of the face that are first noticeable by women and men, respectively.[1] The presence of bags under the eyes is the first sign of aging that is easily seen.[2,3] The aging process that occurs in the midface is characterized by the descending of the malar fat pad, descending and loss of sub-orbicularis oculi fat, hollowing of infraorbital rim, and double contour deformity which is caused by lower eyelid-cheek complex separation.[1] The goal of rejuvenation is to restore and reverse these aging signs including fat atrophy, reduction of laxity, hyperpigmentation, and wrinkles.[2]

Periorbital is a thin and highly vascularized area on the face. Therefore, it is challenging to treat.[3] Injection procedure should be performed carefully to avoid injury to branches of several important arteries including maxillary, angular, superior labial, and septal artery.[4] The pathologies in the periorbital area can be treated with surgical and non-surgical treatment. The surgical treatment options include fat transfers, blepharoplasty, and face-lifts. On the other hand, the non-surgical treatment options include injections of hyaluronic acid, micro-needling, chemical peeling, micro-dermabrasion, laser-resurfacing, nifedipine injection, botulinum toxin injection, and carboxytherapy.[3,5,6] The platelet-rich plasma (PRP) has also emerged within the past decade as a treatment option for facial rejuvenation.

In this section, we explained the preparation process of PRP. Firstly, venous blood is collected from the patient and undergoes a centrifugation process. The centrifugation process results in the separation of blood product into a dense (cellular) and less dense supernatant containing platelet, plasma, and protein content. The concentration of platelets in typical PRP is 2 – 5 times higher than the concentration of platelets in the physiological state ranging from 150,000 to 450,000 platelets per µL.[7-9]

The α-granules are secretory granules of platelets that become the source of many growth factors, cytokines, and chemokines.[1] There are many advantages of these molecules including tissue regeneration, wound healing, the proliferation of fibroblast, secretion of hyaluronic acid, formation of granular tissue, angiogenesis modulation, and production of collage.[10,11] The epidermal growth factor, connective tissue growth factor, transforming growth factor β1, vascular endothelial growth factor, and fibroblast growth factor are key molecules in the process of facial rejuvenation.[12,13] It has been reported that the concentration of these key molecules is high in the PRP.[14]

The protocol of centrifugation for PRP is varied. Earlier, PRP is defined to describe the derivation of many platelet concentrates. However, many research has begun to describe the variation

of protocol that gives benefits for certain applications.[7,10,15-17] One or two centrifugations are usually performed and the addition of anticoagulants and activators substrates are also performed.

The addition of platelet activators including thrombin or calcium chloride induces the activation of platelets. Platelets can also be activated slowly by contact with the glass storage tube. This activation of platelets creates a platelet gel with higher viscosity compared to PRP. This platelet gel is called platelet-rich fibrin (PRF) or platelet-rich fibrin matrix (PRFM). As described by their name, PRF and PRFM have a higher density of fibrin matrix compared to PRP.[16,18] The benefits of PRF and PRFM are fast volumization after injection, high content of growth factor, small clots at the injection site, and shorter time of growth factor release.[8,13,19,20]

The selection of layers following centrifugation is also important. The supernatant following centrifugation can be divided into lower and higher layers. The lower layer contains more-dense platelet-rich which is called PRP and the higher layer contains less-dense platelet-poor which is called platelet-poor plasma (PPP). If the buffy coat that is rich with leukocytes is included with PRP, the term would be leukocyte-rich PRP. If the PRP is lacking the buffy coat, then it is termed leukocyte-poor PRP and also termed plasma rich in growth factors (PRGF).[13,18]

Platelet-rich plasma has been an emerging treatment to rejuvenate the periorbital area with minimally invasive methods, especially for periorbital wrinkles. We aimed to narratively review published articles regarding the platelet-rich plasma for periorbital wrinkle treatment.

METHODS

This was a narrative literature review study. The eligibility criteria are determined based on the PICO framework. The population in this review was periorbital wrinkles; the interest was intradermal injection of platelet-rich plasma; the comparator was none; and the outcomes were improvement of periorbital wrinkles. The PICO framework then can be used to create keywords to perform literature searching in the database. The keywords to perform the literature review were (platelet-rich plasma) AND (periorbital wrinkle). The online database that has been used was the PubMed database. Articles that have been written in English that describe the effect of intradermal injection of platelet-rich plasma on periorbital wrinkles were included in this review. We restrict the year of publication to the past 10 years. The included studies were reviewed further and narratively elaborated. In this literature review, we included eight articles that describe the effect of intradermal injection of platelet-rich plasma on periorbital wrinkles

RESULTS

We retrieved eight articles that match with the eligibility criteria. As can be seen in Table 1, we describe the included studies and their patient characteristic. Table 2 provided data regarding administration of PRP and objective treatment outcome between studies.

DISCUSSION

The formation of crow's feet is a normal process of skin aging and photoaging. The lateral orbital skin will produce multiple linear folds that will spread outward from the lateral canthus. Early clinical trials investigating PRP for periorbital wrinkles from 2010 to 2016 lacked a control group but showed that PRP and PRF improved overall skin appearance, wrinkles, firmness/thinning, and color uniformity when measured after 1-3 months. A statistically significant improvement was achieved at follow-up.[2,17,23,24] Except for Mehryan *et al*., these studies are limited by the lack of objective outcomes and unblinded assessment. In particular, Mehryan *et al* found that a single PRP treatment significantly improved color uniformity.[17]

Subsequent clinical trials with different treatments showed that 3-6 treatments significantly reduced the number and volume of wrinkles over 4-6 months.[12,13] This result was also supported by a double-blind randomized controlled trial by Gawdat *et al*.[11] in which improvements lasted six months after treatment stopped. Cameli *et al*.[21] performed an objective assessment of facial areas including crow's feet using multiple devices. He reported that one month after the third treatment, the skin scales, roughness, wrinkles, smoothness, plumpness, transepidermal water loss (an indication of skin barrier function) and skin elasticity have improved. Their findings are supported by an uncontrolled clinical trial by Everts *et al*., which showed sustained improvement within six months after injection. Specifically, Evert *et al*. found that three PRP treatments improved the number and volume of wrinkles, improved skin firmness, and reduced brown spots by 26.3%. PRP also reported reduced overall erythema intensity with unchanged quantity and area of erythema.[12]

Elnehrawy *et al*. provided a subgroup analysis of the skin rejuvenation effect of PRP and found that the effect peaked at eight weeks after a single treatment with greater improvement in nasolabial folds than crow's feet.[23] This difference in the facial location effect was later confirmed by changes in skin thickness observed in ultrasound analysis by Gomez *et al*.[13] Nevertheless, Elnehrawy *et al*.[23] reported that all patients who were treated for fine lines and wrinkles were improved. While only 60 percent of patients who were treated for deep wrinkles experienced improvement. These differences in results can be attributed to the influence and importance of the injection technique.

Injection techniques for the treatment of fine wrinkles are best performed by intradermal injections, while deep wrinkles and volume reduction are best treated at the dermal-subcutaneous interface.[1] Cameli *et al*.[21] use an injection technique called a wave to treat crow's feet, which involves intradermal ponfi injections and then passing a needle through the injection area.

Alternative PRP formulations are an important area of active research. Gómez *et al*.[13] have launched a platelet gel similar to PRGF but with increased viscosity due to proprietary additives. A single injection of this gel provides an immediate volumization. Patient evaluations and blinded photographic and digital 3D topographic evaluations showed continued improvement within four months after treatment. When plated in vitro without tissue plasminogen activator

Table 1. Study and patient characteristic

Author	Design	Sample	Gender	Age in years (mean, range)	Treatment
Yuksel *et al.*[2] (2014)	Uncontrolled clinical trial	I = 10	F = 10, M = 0	50, -	I = Platelet-rich plasma
Gawdat *et al.*[11] (2017)	Split face randomized controlled trial	I = 20 C = 20	F = 20, M = 0	41, 35 – 55	I = Platelet-rich plasma C = Mesotherapy injection
Everts *et al.*[12] (2018)	Uncontrolled clinical trial	I = 11	F = 11, M = 0	51, 47 – 60	I = Platelet-rich plasma
Gomez *et al.*[13] (2018)	Uncontrolled clinical trial	I = 10	Not reported	60.6, 50 – 65	I = Platelet-rich growth factor
Mehryan *et al.*[17] (2014)	Uncontrolled clinical trial	I = 10	Not reported	41.2, 26 – 61	I = Platelet-rich plasma
Cameli *et al.*[21] (2017)	Uncontrolled clinical trial	I = 12	F = 12, M = 0	43.7, 40 – 49	I = Platelet-rich plasma
Hui *et al.*[22] (2017)	Split face randomized controlled trial	I = 13; C = 13	F = 13, M = 0	42.1, 32 – 57	I = Platelet-rich plasma injection and topical + CO_2 laser C = Saline injection + CO_2 laser
Elnehrawy *et al.*[23] (2017)	Uncontrolled clinical trial	I = 20	F = 20, M = 0	36.9, -	I = Platelet-rich plasma

I: Intervention; C: Control; F: Female; M: Male

Table 2. Administration of platelet-rich plasma and the objective treatment outcome

Author	Injection	Follow-up	Assessment Method	Outcomes
Yuksel *et al.*[2] (2014)	3 injections. Q2W	4.5 months	Physician	Improved skin appearance, firmness, sagginess, and wrinkles. No improvement of pigmentation
Gawdat *et al.*[11] (2017)	6 injections. Q2W	2.5 months	Optical coherence tomography measuring device	Increased epidermal and dermal thickness
Everts *et al.*[12] (2018)	3 injections. Q4W	6 months	Device	Decreased brown spot count, decreased wrinkle count, and improved skin firmness
Gomez *et al.*[13] (2018)	1 injection	4 months	Physician	Reduced wrinkles, restored facial volume, softened skin texture, and increased homogeneity
Mehryan *et al.*[17] (2014)	1 injection	3 months	Physician	Improved color homogeneity
Cameli *et al.*[21] (2017)	3 injections. Q4W	3 months	Device and ultraviolet photograph analysis	Improved skin texture, elasticity, smoothness, and barrier function
Hui *et al.*[22] (2017)	1 injection	3 months	Digital image analysis software	Improved wrinkles, texture, and elasticity
Elnehrawy *et al.*[23] (2017)	1 injection	2 months	Physician	Improved wrinkles, nasolabial folds, texture, and homogeneity

(tPA), the gel retained 100% of its weight after two weeks, whereas the gel with the addition of tPA retained 80–92% of its weight.[13] A retrospective study showed that PRF is effective in the treatment of various periorbital diseases, providing a basis for future clinical trials to thoroughly investigate PRF in the treatment of periorbital wrinkles.[1] This can cause significant pain and prevent the patient from continuing treatment, so the use of local anesthesia should be considered.

Although delicate, the periorbital area, including the upper eyelids, can be safely treated with precisely targeted PRP injections.[25] However, crow's feet are unique in the periorbital area in that they can be treated with topical PRP after microneedling. El-Domyati *et al.*[6] reported that this treatment was superior to trichloroacetic acid 15% with microneedling in improving the appearance of crow's feet. Although their clinical trial used blinded clinical assessors and a blinded dermatopathologist for histological analysis, it was limited by a small sample size, and their conclusions were drawn for the whole face and not the periocular region because the subgroup analysis was not performed.[6]

Hui *et al.* evaluated PRP as an adjunct to CO_2 laser in a double-blind split randomized controlled trial and found that PRP treatment at three months was superior to CO_2 laser and saline treatment within three months of follow-up.[22] PRP was significantly superior in improving patient satisfaction scores for wrinkles, skin texture, and skin elasticity, in addition to objective assessments of elasticity and texture. Patients also reported that the duration of erythema, edema, and crusting decreased by an average of half a day after PRP treatment. Blinded assessment by dermatologists and the VISIA Skin Color Analysis System also showed an improvement in wrinkles, but this was not statistically significant.

Elnehrawy *et al*. found that the people who saw the greatest improvement in wrinkles after a single injection of PRP were women under 40.[23] Interestingly, studies of the effects of photoaging treatments have found opposite age correlations, with less photoaged skin being less responsive to PRP.[26] Future research may be aimed at clarifying the results of the limited number of studies that have analyzed improvement by age. Possibilities to consider include pathophysiological differences between photoaging and normal aging, psychosocial factors such as younger age group, disproportionate satisfaction with subjective measures, and age-related considerations such as shallow wrinkles improve more consistently than deeper wrinkles, and the less damaged the skin, the better it responds to treatment.[23]

Although subjective, patient satisfaction is an important and necessary consideration in cosmetic treatment. Our review showed that patients were consistently satisfied with PRP treatment when PRP was applied to the periorbital area. In addition, when PRP is used as an adjunctive treatment, satisfaction is improved compared to control injections and can be combined with other cosmetic procedures. As pain may prevent patients from continuing regular PRP treatment, mechanisms to reduce the burning sensation, such as the use of local anesthesia should be considered. PRP therapy is often followed by a topical application such as PPP or polypropylene film masks, which can enhance the patient experience. Combining satisfaction measures in research is difficult due to the many scales used, and future studies should consider using existing scales, such as the most commonly used 4-category 0-3 scale. [3,11,13,17,21,22,27]

As an autologous product, PRP injections pose minimal risk to patients.[28,29] No study reported hyperpigmentation after infection, allergies, or inflammation, which is supported by a male pattern baldness study that found PRP injections to improve bacterial skin infections.[28] One study reported a slight increase in fine lines in one patient one month after nasolabial fold treatment.[21] Mild side effects of any skin injection include erythema, pain, burning, bruising, swelling, pressure, and tenderness. Adding calcium chloride without the use of a local anesthetic can cause significant enough pain for patients to seek other treatments.[24] However, adding a local anesthetic to PRP causes patients to report no pain.[3]

CONCLUSION

Interest in the use of PRP in cosmetic dermatologic pathology has increased over the past decade. Objective and subjective assessments show that this treatment is promising for the prevention of periorbital wrinkles. Further, randomized controlled trials with high-quality reporting and low risk of bias are needed to investigate the appropriateness of platelet concentrate products for various periorbital pathologies. Finally, randomized controlled trials with long-term follow-up and comparison of platelet concentrate products with non-saline controls are needed to elucidate the long-term improvement of PRP and its role in the treatment of cosmetic periorbital pathologies.

CONFLICT OF INTEREST

The authors declared the absence of a conflict of interest regarding the preparation of this manuscript.

ETHICAL APPROVAL

Not applicable.

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AUTHOR CONTRIBUTION

The author made equal contributions during the preparation of this manuscript and agrees to accept equal responsibility regarding the content of the article.

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