Platelet-rich Plasma, Collagen Peptides, and Stem Cells for Cutaneous Rejuvenation

ABSTRACT

In recent years, platelet-rich plasma (PRP), collagen peptides, and stem cells have become popular treatments for cutaneous rejuvenation. Mass marketing to consumers via the internet and social media has attracted the attention of the aesthetics industry to these treatments. However, the studies behind these treatment modalities have not supported the often exaggerated claims of effectiveness that have targeted consumers. It is important for clinicians to understand the evidence behind any new trends, especially in the fast-paced world of aesthetics, where treatments often outpace current medical understanding. Here, we summarize and evaluate the current prominent literature on these popular aesthetic treatments.

KEYWORDS: Aesthetics, dermatology, skincare, aging, PRP, collagen, stem cells

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Many factors, including aging, sun exposure, and acne, contribute to irregularities of facial skin. Over time, skin loses the elasticity and firmness that are characteristic of youthful skin. Exposure to ultraviolet radiation, trauma, smoking, and reactive oxidative species can lead to an accumulation of DNA damage that is harmful to cellular function, protein maturation, and regular physiology.[1–3] Aging is itself associated with decreased melanocytes, fibroblasts, and collagen synthesis in the skin. There is also dysregulation of the stem cell population, which normally helps to repair damaged tissue.[2] Clinically, this can manifest as fine lines and wrinkles, loss of elasticity, dyschromia, epidermal thinning, increased coarseness, and scarring.[3,4] Correction of the signs of cutaneous aging is a common motivator for patients who seek out a dermatologist who specializes in aesthetic treatments. In an effort to combat the signs of aging, various treatment modalities have been developed. Recently, a trend has emerged toward noninvasive techniques for cutaneous rejuvenation. Here, we review the current literature on using platelet-rich plasma, peptides, and stem cells as a means to mitigate aging-related changes of the skin. We selected articles that we considered to be prominent in aesthetic literature and among national aesthetic conferences and important to advancing the aesthetic field forward.

PLATELET-RICH PLASMA (PRP)

PRP is an autologous blood-derived product that contains an increased concentration of platelets suspended in plasma. Its preparation includes centrifuging blood until it separates into layers, with the PRP accumulating at the bottom due to high specific gravity. The PRP contains a platelet concentration that is about 3 to 7 times greater than unaltered plasma.[5,6] This concentration can vary due to differences in preparation methods and blood consistency at the time of collection.

PRP contains chemokines, cytokines, plasma proteins, and growth factors, which can contribute to the acceleration of healing, tissue growth, and generation of hyaluronic acid. The rationale for using PRP is its supratherapeutic amount of these essential healing factors. Platelets store and release platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and transforming growth factor beta (TGFβ).[5] Studies have shown that there are over 800 different types

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of proteins present in PRP.[7] These proteins and growth factors can stimulate stem cells and improve cellular proliferation, differentiation, and regeneration.[8] PRP has become an attractive option for skin rejuvenation and scar attenuation due to its ability to activate fibroblasts and synthesize collagen and other elements of the extracellular matrix.[7,9–12]

Cutaneous rejuvenation. As skin ages, it loses some of its ability to repair its own damage. Because PRP contains the necessary growth factors for healing, it has been studied for use in cutaneous rejuvenation. In one study, 12 women underwent three treatments of intradermal PRP to the forehead, areas affected by crow's feet, cheeks, and nasolabial folds.[9] The effects were measured and analyzed by investigators, imaging, and patient evaluation. All patients completed the study, and no serious adverse events were observed. Imaging and patient evaluations were consistent with improved skin texture. Skin elasticity, barrier function, and smoothness additionally improved. Both clinical and patient evaluations at one month showed some improvements in skin texture and fine wrinkles.[9]

A recent split-face trial evaluated the effects of PRP on photoaged facial skin compared to saline control in 19 male and female participants with bilateral cheek rhytids.[13] Mean photoaging scores rated by two dermatologists showed no significant differences between PRP and saline for fine lines, mottled pigmentation, roughness, and sallowness. However, participant satisfaction with texture, wrinkles, pigmentation, and telangiectasias were greater for the PRP-treated side. It should be noted that participants were blinded to the treatments.[13]

Another study was conducted (N=10) in which PRP was applied to the forehead, malar areas, and jaw using a dermaroller and injected into areas affected by crow's feet.[14] After application, the entire face was draped with PRP-soaked gauze for 30 minutes. The protocol was repeated three times at two-week intervals. Patients performed self-evaluations before and after PRP administration and reported a significant difference in general appearance, skin firmness-sagging, and wrinkle state. However, no difference was reported in pigmentation. According to assessments by three dermatologists, the only significant difference was in the skin firmness-sagging measures.[14]

Acne scarring. While microneedling and laser techniques repeatedly demonstrated efficacy for treating acne scars, PRP has only recently been investigated in combination with these treatments.[5,15,16] Microneedling, also known as percutaneous collagen induction (PCI) therapy, causes small channels of epidermal and dermal injury by puncturing the skin.[17] The damaged collagen gets removed and new growth and remodeling occurs.[18] Because of the damage, PDGF, fibroblasts, and elastic fibers are activated and contribute to neovascularization and neocollagenesis.[19,20] Microneedling can be used to augment drug delivery, and it is thought that the additional upregulation of growth factors associated with PRP might act in synergy with microneedling. Laser resurfacing has also demonstrated efficacy for the treatment of scars. Lasers use thermal energy to selectively destroy tissue and stimulate collagen formation by dermal fibroblasts.[21,22] PRP is thought to improve and accelerate post-treatment recovery.[23,24] PRP can be used topically or intradermally, either before or after microneedling and laser treatments, and it has not consistently been shown to cause any significant adverse effects.[25] Histologic studies following PRP administration have revealed increased collagen bundles and a thicker epidermal layer compared to control.[26]

Intradermal PRP. A recent randomized trial for the treatment of scars included 90 patients separated into three treatment groups.[27] One group received microneedling, another group received intradermal PRP, and the third group received alternating microneedling and intradermal PRP treatments. It should be noted that the PRP was only injected within the scars. All groups demonstrated improvement in scar appearance according to physician assessment. However, combination treatment was associated with the greatest mean improvement score, followed by microneedling, 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.[27]

A 50-patient split-face study evaluated microneedling for acne scars with and without the addition of PRP.[28] Microneedling was performed on the entire face, and each half was treated with either PRP or distilled water. PRP was used in two forms: intradermal PRP was injected within acne scars and topical PRP was subsequently spread over the same half. Both sides of the face showed improvement. However, 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 at study completion, almost all patients reported that PRP led to a reduction in the visibility of acne scars and an improvement in skin roughness.[28]

Intradermal PRP has also been tested with laser techniques. For example, Lee et al[24] conducted a study to examine the effects of PRP after treating acne scars with an ablative fractional resurfacing laser (AFR). Fourteen patients underwent a split-face trial with two treatments of AFR combined with PRP injections on one side and saline injections on the other. 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 with decreased duration was noted. The authors concluded that PRP hastened recovery of laser-induced injury.[24]

A split-face study by Faghihi et al[29] that 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 one month after the first treatment or four 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.[29]

Topical PRP. A split-face trial of 35 patients compared microneedling with and without topical PRP, which is often used in clinical practice.[30] For each side of the face following treatment, a significant improvement of acne scars was reported, 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.[30]

Another randomized split-face trial evaluated microneedling alone or in combination with either topical PRP or trichloroacetic acid (TCA) 15% peels.[31] Both combination treatments demonstrated significant cosmetic improvement in acne scars compared to microneedling alone according to assessments 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 microneedling alone. All groups showed more organized and dense collagen bundles following treatment, but this was more pronounced in the topical PRP group.[31]

Regarding combination of laser treatment and topical PRP, a split-face study was conducted in 30 patients with severe acne scars to evaluate the effects of AFR with and without topical PRP.[23] Although both treatment arms offered improvement, the addition of topical PRP did not have significant added benefit to scar appearance. However, the addition of PRP was associated with decreased erythema, swelling, and pain. The authors suggested that topical PRP could be used to improve both post-procedural downtime and patient satisfaction when used with AFR.[23]

Topical versus intradermal PRP treatment combined with lasers has also been studied. Gawdat et al[32] conducted a 30-patient split-face study to compare intradermal and topical PRP modalities. One group received 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 a significantly better response, shorter downtime, and fewer side effects than laser therapy alone. There were no statistical differences between intradermal and topical PRP in regards to the degree of response and downtime. As might be expected, 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.[32]

Adverse events. There was a single case published on irreversible blindness from glabellar injections of PRP for skin rejuvenation.[33] As with any injections to the glabella, practitioners should exercise caution to prevent cutaneous necrosis and blindness. Overall, there appears to be low risk of serious adverse effects.

Summary. Although the available literature pertaining to the administration of PRP for cutaneous rejuvenation is limited, PRP might be helpful in improving fine lines and skin smoothness. When combined with other treatment modalities, it might offer an additional benefit. Larger studies are needed to fully understand the effects of PRP, as some studies did not have thorough control parameters. In regard to acne scarring, combination treatment with microneedling and AFR appears to be effective. Combining treatments has been shown to be superior in several ways, including clinical outcomes, postprocedural downtime, and patient satisfaction. A single study, however, failed to demonstrate significant clinical improvement after combining AFR with PRP and reported prolonged healing time. A major limitation to drawing any definite conclusions is that these are small studies, and there is still a need for a larger, controlled trial. It is interesting to note that one study found no significant clinical difference between intradermal and topical PRP delivery, and thus, topical PRP might offer a more comfortable patient experience without compromising efficacy. It is also worth mentioning that there is no standardized protocol for obtaining PRP, and no standardized concentration exists. Further studies are needed to determine optimal methods and procedures for collection, treatment, and administration of PRP.

COLLAGEN PEPTIDES

Similar to PRP, oral collagen peptide supplements have been purported to rejuvenate skin, reduce wrinkles, and restore volume and elasticity to sagging skin. Oral collagen supplementation has recently become trendy and has been marketed to consumers as an antiaging remedy. These oral collagen supplements contain bioactive collagen peptides. During the digestive process, these peptides are cleaved into di- and tri-peptides and used by the body as building blocks for proteins. It is thought that the availability of these protein peptides can maintain and increase collagen in the skin. These peptides might also increase hyaluronic acid production by skin fibroblasts, induce the migration of fibroblasts, promote stronger collagen fibrils, and increase water content of the stratum corneum.[34]

Clinical trials. In a study conducted by Asserin et al,[34] collagen peptides were administered orally to patients to compare skin hydration and transepidermal water loss (TEWL) to a control. In the first part of the study, 66 women, who were 40 to 59 years old, were treated daily with either 10g of collagen supplement or placebo for eight weeks. Skin moisture was significantly greater for the treatment group compared to placebo. However, no effect was seen on TEWL. In the second part of the study, 106 women aged 40 to 65 years were treated daily with either 10g of collagen supplement or placebo for 12 weeks. After the study period, measures of echogenicity using high frequency ultrasound revealed significantly greater collagen density in the supplementation group.[34]

A double-blind, randomized, placebo-controlled trial by Kim et al[35] studied the effects of low-molecular weight collagen peptide (LMWCP) on skin hydration, wrinkling, and elasticity. Sixty-four women aged 40 to 60 years were enrolled and treated daily with either 1g of LMWCP or placebo for 12 weeks. Skin hydration was increased in the LMWC-treated group compared to control after six and 12 weeks. Three measures of skin wrinkling were significantly greater in the treatment group (average roughness, skin roughness, smoothness depth), while only a single parameter for skin elasticity was significantly greater.[35]

Another randomized, controlled trial compared various doses of oral collagen hydrolysate (CH) treatment to control.[36] Sixty-nine women aged 35 to 55 years were randomly given either 2.5g of CH, 5g of CH, 2.5g of placebo, or 5.0g of placebo daily for eight weeks. At completion of the study, both CH groups had a significant increase in skin elasticity compared to the placebo groups. However, no significant difference was found between the varying doses of CH. Regarding skin hydration, no significant difference was found between treatment and placebo groups after four weeks. While the study observed positive correlations between CH treatment and both skin moisture and skin evaporation, neither of these measures reached statistical significance.[36]

Unlike the previous study, a double-blind, randomized, placebo-controlled trial by Genovese et al[37] found no significant difference in skin elasticity between treatment and placebo groups. In this study, an oral liquid supplement containing collagen peptides and antioxidants was tested for its antiaging effects. One-hundred-twenty subjects were randomly assigned to consume either 50mL of the supplement or placebo daily for 90 days. No significant difference in skin elasticity between the treatment and placebo groups were detected. However, subjects that had undergone cosmetic procedures during the study period had significantly increased skin elasticity if they were part of the treatment group, which was an unintended treatment outcome.[37]

Summary. The paucity of data relating to oral collagen supplementation should caution clinicians against endorsing any claims made by proponents of such supplements. These limited studies suggest that there might be some benefit for the skin. However, there is no reliable evidence to prove that orally digested collagen becomes preferentially localized to the dermis as opposed to other parts of the body.[38] Additionally, the amino acids required for collagen synthesis can be consumed from a normal diet. Other than collagen, there are many other proteins that contribute to the appearance and properties of skin. Additional clinical studies are needed to understand the cutaneous effects of oral collagen peptide supplementation. As nutritional supplements continue to gain popularity and widespread availability, there remains a need for more rigorous research to validate the purported benefits. It should also be noted that collagen supplements fall under the dietary supplement category and are therefore not regulated by the Food and Drug Administration (FDA). Prior to purchasing supplements, patients should check to ensure that they have been verified by a third-party tester, such as NSF or USP.

STEM CELLS

Stem cells have been marketed as a promising treatment for cutaneous rejuvenation due to their potential for self-renewal and differentiation.[39] In theory, they can heal injured tissue and stimulate growth factors for tissue remodeling. In dermatology, mesenchymal stromal cells (MSCs) are most commonly used, which can consist of either fetal- or adult-associated cells.[40,41] Adult-associated MSCs are more common, which can be derived from adipose tissue (ADSCs) or bone marrow. ADSCs are preferred due to their abundance and ease of isolation. Many available studies have examined the effects of media conditioned with stem cells, which contain various associated proteins and growth factors. They have also investigated the use of defensins, which can activate specific stem cells associated with hair follicles.

Clinical trials. Stem cells have recently been tested in clinical trials to determine their efficacy for aesthetic indications. In an eight-week trial, 48 women with photoaged skin were treated with either amniotic membrane stem cell-conditioned media (AMSC-CM) or normal saline.[42] Each participant underwent three applications of treatment at two-week intervals in conjunction with microneedling in order to increase epidermal penetration. AMSC-CM was associated with significant improvements in clinical measures of wrinkles, pores, spot polarized, and spot UV parameters. However, AMSC-CM did not improve skin tone. Side effects were mild and partially related to the microneedling technique.[42]

A randomized, controlled, split-face trial was conducted in 25 women to evaluate microneedling plus medium conditioned with endothelial precursor cells differentiated from human embryonic stem cells (hESC-EPC-CM) for skin rejuvenation.[43] Subjects received either topical hESC-EPC-CM or saline on each half of the face followed by microneedling to increase penetration. Five treatments were completed at two-week intervals. Clinical assessment demonstrated greater improvement in wrinkles and pore size following hESC-EPC-CM compared to control. Moreover, the melanin index and erythema index were both significantly decreased for the experimental side. The authors concluded that the secretory factors of hESC-EPC-CM can improve clinical signs of skin aging and may have benefit when combined with microneedling.[43]

Stem cells have also been combined with laser therapy to augment cutaneous scarring and rejuvenation efforts. One study enrolled 22 patients in a split-face trial to evaluate the combination of ADSC-conditioned media (ADSC-CM) with AFR.[44] Patients were divided into two groups: nine patients were treated for cutaneous rejuvenation and 13 for acne scars. All subjects underwent three treatment sessions at one-month intervals. After laser treatment, ADSC-CM was applied to half of the face, while the other half was treated with FBS-free DMEM medium as a control. For both groups, the side treated with ADSC-CM had increased patient satisfaction and objective clinical assessment scores. Biophysical analysis demonstrated increased elasticity and skin hydration in addition to decreased TEWL, roughness, and melanin index. Only one subject was evaluated with biopsies, which demonstrated that ADSC-CM increased dermal collagen and elastin density. No significant difference in the erythema index was appreciated between the sides. However, the duration of edema and crusting was reduced in the ADSC-CM-treated side, supporting the notion that stem cell treatment might ameliorate laser side effects. The authors concluded that topical application of ADSC-CM can increase the efficacy of AFR for atrophic acne scars and cutaneous rejuvenation, while also reducing postprocedural downtime.[44]

In another study, 46 women underwent a double-blind, vehicle-controlled trial to assess the effects of a defensin-containing formulation on skin rejuvenation.[45] Alpha and beta defensins are immune peptides that can stimulate LGR6-positive stem cells located in hair follicles. The LGR6 stem cell population typically remains dormant until activated when they can produce new epidermal basal stem cells and keratinocytes. A total of 31 women applied defensin-containing products twice daily for 12 weeks, while 15 women applied vehicle. The treatment arm was associated with significantly increased epidermal thickness and skin evenness. The treatment group also experienced reduced superficial wrinkles, pore visibility, pigmentation, and oiliness.[45]

Summary. The availability of studies examining the use of human stem cells for cutaneous and aesthetic purposes is lacking. Early studies have begun to demonstrate promise regarding the efficacy of stem cells in skin rejuvenation, especially when combined with other treatment modalities, such as microneedling and laser therapy. However, it is too early to determine their exact role. More clinical data are needed in order to fully evaluate their effects and to develop

standardized protocols. Importantly, our understanding of their short- and long-term safety remain limited. We do not yet possess a complete understanding of their cellular and molecular interactions as well as their dynamics with our skin. It is still unclear how they might affect neoplastic cells and tumorigenesis. Despite this, stem cells are often marketed to consumers using exaggerated and unsubstantiated claims, which have continued to fuel their controversial status.

CONCLUSION

The marketing of cosmetic products and aesthetic procedures often outpaces the ability of the scientific community to fully assess the claims of new treatment modalities. PRP application, collagen peptide supplementation, and stem cell therapies for facial rejuvenation have all been recent trends in the ever-growing aesthetics and beauty industry. Consumers and patients continue to inquire about these trendy procedures that they have seen on television, the internet, and/or social media. For clinicians, it is their professional obligation to evaluate the evidence behind any procedure before discussing or recommending them to patients. They must strive to keep pace with current trends and understand the published data behind them.

The evidence thus far for utilizing PRP, collagen peptides, and stem cells for purposes of cutaneous rejuvenation is fraught with mixed results. PRP has the strongest evidence behind its use and can be recommended to patients, especially when combined with other treatment modalities, including microneedling or laser therapy. When recommending PRP, it is important to explain the mixed results, but also to relay that PRP might provide benefit without any additional significant adverse events. Collagen peptide supplementation might offer some level of benefit. Without harmful side effects, it is appropriate to recommend them to interested patients. Regarding stem cells, clinicians should continue to remain cautious before recommending such therapies or procedures. Much remains unknown, and there exists risks, which might outweigh potential benefits.

Overall, these various treatment modalities for cutaneous rejuvenation could benefit from additional larger, randomized, controlled trials in order to better evaluate their safety and efficacy. Until then, clinicians should continue to exercise caution before recommending these rejuvenation therapies.

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