Efficacy of platelet rich plasma (PRP) on skin rejuvenation: A systematic review

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Background: With the increase in life expectancy, middle aged and elderly people comprise a substantial percentage of the population worldwide. Since aging often manifests itself in the human skin, skin rejuvenation methods have gained a lot of popularity. Current medical modalities such as botulinum toxin injection, fillers, and laser therapy can provide symptomatic relief of skin aging signs without the ability to induce changes at a cellular level. In recent years, Platelet Rich Plasma (PRP) therapy has been emerging as a revolutionary treatment with the ability to induce cell growth in the skin, which results in retarding and reversing the aging process. Therefore, this study was conducted to determine the efficacy of PRP therapy in skin rejuvenation.

Methods: A comprehensive search was conducted using PubMed, Google Scholar, and Cochrane Library. Articles published only in English from 2000 to 2015 were included. The keywords used were platelet rich plasma, PRP, skin rejuvenation, skin aging, skin, platelet rich plasma therapy.

Results: A total of ten articles were retrieved and included for analysis. Eight studies showed improvement of the skin wrinkles. The other two studies reported improvements in the nasolabial fold. Clinical assessments were based on patient satisfaction or feedback questionnaire, pre- and post-treatment photography, and skin biopsy. The results showed a significant improvement in the skin appearance, elasticity, texture, and homogeneity.

Conclusion: In conclusion, PRP therapy is an effective and safe treatment for skin rejuvenation with no significant difference in varying techniques of PRP preparation and injection.

Keywords: platelet concentrates; platelet rich plasma; skin rejuvenation
damaged skin contains unorganized collagen fibrils and undergoes elastic degeneration. To summarize, the primary goals of medical aesthetic treatments are to minimize the facial volume loss and reduce the appearance of wrinkles, as they are among the most obvious changes of the aged skin. Wrinkle formation in the aging skin occurs due to the degeneration of the collagen fibers and deposition of the elastic content of the skin. These changes lead to damage to the dermal extracellular matrix due to the impairment of the structural integrity. The skin resilience is also reduced. Currently, there are a number of methods for skin rejuvenation including laser, light and other energy-based treatments, chemical peeling, and other non-ablative methods. All of these methods result in a more youthful appearance but each has its own advantages and disadvantages. Dermal fillers (DF) and botulinum injections are quick and effective treatments to eliminate the wrinkles. Both present no downtime, but DF injection may result in short-term effects such as necrosis and skin irregularities and botulinum injection may cause undesired muscle paralysis. Laser therapy and chemical peeling are other treatment options which may result in side effects such as skin burning and alteration of the skin color, particularly in patients with a darker skin type. Recently, regenerative dermatologic treatments have been added to the regimen to further enhance the clinical results and minimize the downtime. Studies have shown that application of a mixture of growth factors may stimulate collagen synthesis and epidermal thickening, which improves the skin tone, minimizes the wrinkles, and repairs other signs of facial aging. In this regard, Platelet Rich Plasma (PRP) therapy for skin rejuvenation is performed by injecting the patient’s own platelet and fibrin into the skin. It has been reported to activate and stimulate cell proliferation and collagen synthesis, minimize the wrinkles, and improve the overall skin appearance.

PRP is a product of the whole blood that has a high concentration of platelets. It contains a number of different growth factors and other cytokines that are released through degranulation and stimulate healing of hard and soft tissues. Seven growth factors and three adhesion molecules have been shown to have higher concentrations in PRP compared to the whole blood, thus accelerating cell regeneration at the site of injection as well as during its topical application. Despite the fact that PRP is a widely used terminology and abbreviation, it can be further classified based on harvesting techniques of platelet from the whole blood i.e. pure platelet-rich plasma (P-PRP), leukocyte- and platelet-rich plasma (L-PRP), pure platelet-rich fibrin (P-PRF) (also known as PRFM), and leukocyte- and platelet-rich fibrin (L-PRF). Its classifications are also crucial factors of consideration as they are closely associated with the success rate of platelet therapy. The platelet-rich fibrin matrix (PRFM) is formed by adding a small amount of calcium chloride (CaCl₂) to PRP to initiate fibrinogen cleavage and fibrin polymerization. The PRFM can be injected within 10 to 12 minutes after adding CaCl₂ using a 30-gauge needle. If the mixture is kept for a longer time, polymerization of the fibrin yields a gel or solid fibrin clot.

Even though the efficacy of PRP for skin rejuvenation remains uncertain, it is widely used in medical aesthetics with many physicians making promising claims. This calls for thorough evaluation of several possible complications such as the risk of rejection, infection, and allergic reactions. In this regard, this study was conducted to review the clinical evidence in order to determine the efficacy of PRP therapy for skin rejuvenation.

METHODS

A systematic literature review was conducted. Electronic databases such as Cochrane library, PubMed, and Google Scholar were searched for relevant literature. The included keywords were platelet rich plasma, PRP, skin aging, skin rejuvenation, skin lines, skin texture, skin wrinkle, topical PRP, topical platelet rich plasma, platelet rich plasma injection, and platelet rich plasma therapy. Randomized clinical trials (RCT), retrospective studies, case studies, and case reports published in English from 2000 to 2014 were included. Data were extracted from the selected literature using a research table. Details such as the sample size, duration of the study, patient, intervention, comparison, outcomes and study design (PICO) of the reviewed papers were also noted. Pre-procedure and post-procedure cares, assessment methods, outcomes, and complications of the studies were summarized in the tables and analyzed.
RESULTS

The search was initiated from PubMed using the mentioned keywords. The initial results showed several articles on “platelet rich plasma”. Then, individual searches were conducted for keywords, such as “aging skin”, “skin wrinkles”, and “skin rejuvenation”. Thereafter, a combination of keywords was used. Two research articles were chosen to be included in this study. No related article was found on Cochrane library. Meanwhile, the use of the keywords individually or in combination to search Google Scholar resulted in 474 articles on platelet rich plasma. A manual search was performed using a combination of keywords. Abstracts of the articles with relevant titles were screened. Research articles were included upon fulfillment of all inclusion criteria. Upon completion of the literature search, ten articles were extracted from PubMed and Google Scholar involving a total of 675 participants. The details of included articles are shown in Table 1. Comparison of the results and side effects of the studies are listed in Table 2. The details of PRP preparation including starting blood, methodology of PRP preparation, and the technique of PRP injection are listed in Table 3. All platelet concentrates were used for skin rejuvenation. Nine studies recruited 653 patients for PRP monotherapy whilst 11 patients received PRP therapy in combination with laser and another 11 patients were controls. Sixty-five patients in two studies received PRP therapy in combination with laser and another 11 patients were controls. None of the patients withdrew or refused follow up in all studies. PRP was activated prior to injection in 8 studies with the exception of one study in which PRP was injected for 37 participants without activation. However, the details of PRP preparation and activation were not clearly explained in one study on 30 participants conducted by Banihashemi et al. 9.

DISCUSSION

PRP therapy is widely used for various medical conditions such as repair and regeneration of the bone and cardiac cells. However, variations in the preparation of PRP and treatment methodology
<table>
<thead>
<tr>
<th>Author/Study design</th>
<th>Title</th>
<th>Problem/Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Shin et al. 13</td>
<td>Platelet-Rich Plasma Combined with Fractional Laser Therapy for Skin Rejuvenation</td>
<td>Korean women with skin phototypes IV–V)</td>
<td>Combined topical application of PRP (3ml) and fractional laser treatment or fractional laser treatment alone</td>
<td>Study group who undergone combination of PRP and laser treatment with control group who had only laser treatment</td>
<td>PRP combined with fractional laser increased subject satisfaction and skin elasticity and decreased the erythema index.</td>
</tr>
<tr>
<td>Sclafani 14</td>
<td>Safety, Efficacy, and Utility of Platelet-Rich Fibrin Matrix in Facial Plastic Surgery</td>
<td>Patients with fine rhytids &amp; deep folds, acne scar, volume-depleted midface region</td>
<td>Intradermal and subdermal or preperiosteal plane injection of activated PRP (0.3ml to 2.5ml)</td>
<td>Pre and post treatment</td>
<td>Most patients were satisfied with the results of their treatments although 1 patient felt that there was limited or no improvement after 2 treatments. No swelling was observed lasting longer than 5 days, and minimal bruising was noted lasting for 1 to 3 days.</td>
</tr>
<tr>
<td>Amgar et al. 15</td>
<td>Using objective criteria to evaluate cosmetic effects of platelet rich plasma</td>
<td>Class II or III on the Glogau scale of photobageing (Moderate to advanced wrinkle)</td>
<td>Intradermal injection of PRP (without CaCl2) (4ml) into the lower part of the face</td>
<td>Pre and post treatment</td>
<td>An average of 24% improvement in the anisotropy coefficient after the third week. The TEWL and micro-relief parameters also improved significantly.</td>
</tr>
<tr>
<td>Redallei et al. 16</td>
<td>Face and neck revitalization with platelet-rich plasma (PRP): clinical outcome in a series of 23 consecutively treated patients.</td>
<td>Patients with skin wrinkle in face and neck</td>
<td>Intradermal injection of activated PRP (4ml)</td>
<td>Pre and post treatment</td>
<td>A good improvement of skin texture and elasticity, a volume increase at the injection site of nasolabial folds, forehead scars almost disappeared, acne scars were also treated with very good results. No serious and persistent side effects were detected.</td>
</tr>
<tr>
<td>Zenker 17</td>
<td>Platelet-rich plasma (PRP) for facial rejuvenation</td>
<td>Patient with wrinkle and loose skin in face and neck</td>
<td>Intradermal, superficial and deep dermal injection of PRP (4-6ml)</td>
<td>Pre and post treatment</td>
<td>The results obtained were age-dependent. The younger patients (less than 35 years) were found to respond more quickly. Their main indication was skin rejuvenation and the prevention of skin aging. For this group, treatment every 12 to 24 months was sufficient. Patients up to 45 years required a second treatment 9 to 12 months after the first one, as well as annual booster injections.</td>
</tr>
<tr>
<td>Sclafani 18</td>
<td>Platelet-rich fibrin matrix for improvement of deep nasolabial folds</td>
<td>Patients with deep nasolabial folds</td>
<td>Intradermal injection of activated PRP (4ml)</td>
<td>Pre and post treatment</td>
<td>Maximal correction and significant long-term diminution of deep nasolabial folds with significant reduction in the mean WAS score. No patient noted any fibrosis, irregularity, hardness, restricted movement, or lumpiness.</td>
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Table 2. Comparison of sample size, participants' age, assessment methods and outcomes.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Age range (mean=)</th>
<th>No. of injection sessions</th>
<th>Duration of follow up</th>
<th>Assessment method (s)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banihashemi et al.</td>
<td>30</td>
<td>35-55 years (45.1)</td>
<td>two sessions with 3 months interval</td>
<td>3 and 6 months follow up</td>
<td>Personal judgment of patients and observation of before and after treatment photography by the physician and a dermatologist unaware of the order of photos</td>
<td>Best effects of PRP in rejuvenation were specified to improvement of periorbital darkness and decreasing skin wrinkles</td>
</tr>
<tr>
<td>Kapoor</td>
<td>50</td>
<td>30-63</td>
<td>3 treatment sessions 1 month apart</td>
<td>1 month after last injection (overall 4 months)</td>
<td>Comparing photographs from pre and post treatment, patient satisfaction score, physician satisfaction score</td>
<td>PRP is effective especially in small wrinkles and improves skin texture and elasticity</td>
</tr>
<tr>
<td>Mehrryan et al.</td>
<td>10</td>
<td>26-61 years (41.2)</td>
<td>One</td>
<td>1 week, 1 &amp; 3 months</td>
<td>Melanin content of the infraorbital, epidermal stratum corneum hydration, global assessment by 3 independent and blinded investigators using before and after photographs, patient satisfaction</td>
<td>Platelet-rich plasma may have the potential to improve the infraorbital dark circle in terms of color homogeneity of the region.</td>
</tr>
<tr>
<td>Mikhail and El-Esawy</td>
<td>20</td>
<td>30-55 years (41.2)</td>
<td>3 sessions with one month interval</td>
<td>1 month after last session of injection</td>
<td>Patient satisfaction score &amp; facial wrinkle scale for objective and subjective evaluation, and patient examination</td>
<td>PRP is an effective treatment in skin rejuvenation without serious side effects.</td>
</tr>
<tr>
<td>Shin. et al.</td>
<td>11 case subjects + 11 controls</td>
<td>30–56 years (43.7)</td>
<td>3 sessions after fractional Laser at 4-weeks intervals</td>
<td>before the first treatment and 1 month after the last session</td>
<td>Subjective satisfaction scale, improvement score according to blinded investigators (using standardized photography), biophysical measurements, and skin biopsies.</td>
<td>PRP with fractional laser treatment is a good combination therapy for skin rejuvenation. Keratinocyte and fibroblast proliferation and collagen production can explain the capacity of PRP to increase dermal elasticity.</td>
</tr>
<tr>
<td>Sdafani</td>
<td>50</td>
<td>23-72 (51.3)</td>
<td>average of 1.6 injections (range, 1-5 treatments)</td>
<td>3-30 months for a mean of 9.9 months</td>
<td>Serial photographs taken before and 3 and 12 months after a single treatment, patient satisfaction questionnaire</td>
<td>Autologous PRP treatment is a well-tolerated, excellent choice for use in the face.</td>
</tr>
<tr>
<td>Amgar et al.</td>
<td>37</td>
<td>40-60</td>
<td>Two sessions of injections</td>
<td>1, 3 or 4 months session</td>
<td>Biometric parameters, including anisotropy, transepidermal water loss (TEWL), micro-relief, and hydration</td>
<td>A good anti-aging effect was observed after one PRP treatment which could last for up to 10 months. An additional predictor for a PRP treatment was found to be the initial hydration status of the skin. PRP repairs the skin characteristics which need repair more effectively and may be used as an anti-aging prophylactic method for other characteristics.</td>
</tr>
<tr>
<td>Redallei et al.</td>
<td>23</td>
<td>28-70 years (47)</td>
<td>3 times</td>
<td>4 months</td>
<td>Comparing the pre and post treatment photography, by evaluating the spider improvement for 8 parameters of nasolabial folds, horizontal neck bands, skin micro-relief, homogeneity, texture and tonicity, snap test, crow's feet lines, final patient's satisfaction questionnaire, by the physician's impression</td>
<td>An easy-to-use and well tolerated technique that can be performed favorably in all small skin wrinkles, as well as in skin texture and elasticity. Good results in skin homogeneity. Objective clinical results were good. Patient satisfaction was very high.</td>
</tr>
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</table>
such as effective concentration of platelet, mode of delivery, and application, direct injection or activation prior to injection need to be carefully investigated to achieve optimum, desired and consistent results. Inconsistency of practice and methodology in PRP therapy makes the standardization of this treatment method very challenging. Here, we discuss different variables present in PRP therapy for skin rejuvenation according to the findings from the selected articles. These studies focused on satisfying the need for alternative and safe skin rejuvenation methods either by injection or topical use of PRP alone or in combination with other aesthetic modalities. On the other hand, the present review critically evaluated the outcome of these studies to shed light on the safety and efficacy of PRP therapy for skin rejuvenation. The study design, age range of participants, number of injection sessions, duration of follow-up, technique of PRP application, and assessment methods were extracted from each study and compared.

In the selected articles, a study by Amgar et al. evaluated the effect of PRP without any activation prior to injection and a study by Shin et al. used PRP gel. The other eight studies used CaCl₂ for PRP activation. Thereafter, the resultant PRFM was injected to enhance skin rejuvenation. Since all of these studies reported some degrees of improvement for different skin conditions, it can be concluded that both activated and non-activated PRP demonstrate positive effects on skin regeneration. In line with this finding, Zandim et al. reported that 10% CaCl₂ was a suitable activating substance for platelets but PRP could also be injected without prior activation. It is believed that a high percentage of platelets can be fully activated after injection via routine procedures in the human body. In this review, PRP was used for wrinkle treatment in eight studies while the other two articles reported PRP treatment for the nasolabial fold (NLF). Restoration of the facial appearance using Botox and dermal fillers is considered safe and non-invasive. However, the application of the patient’s own blood products such as PRP might be more desirable compared to Botox and dermal fillers. In addition, other skin characteristics such as periorbital darkness, skin texture and elasticity, acne scars, transepidermal water lost (TEWL), and skin homogeneity were also

<table>
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<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Age range</th>
<th>No. of injection session</th>
<th>Duration of follow up</th>
<th>Assessment method(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zenker</td>
<td>17</td>
<td>18-46 years</td>
<td>2-4 times, depend on age</td>
<td>3, 6, 12, and 24 months</td>
<td>Comparison of pre and post treatment photography; NLFs were rated by the treating physician before and after treatment using WAS and patients rated their appearance at each visit using the Global Aesthetic Improvement Scale.</td>
</tr>
<tr>
<td>Sclafani</td>
<td>18</td>
<td>30-56 years</td>
<td>4</td>
<td>1, 2, 6, and 12 weeks after treatment</td>
<td>PRP can provide significant long-term improvement in the volume of deep NLFs without the use of foreign materials.</td>
</tr>
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Table 2. (continued).
assessed after PRP therapy in the selected studies. All the studies reported a significant improvement in the skin texture and removal of the skin wrinkles. Both patients and physicians were satisfied with the outcomes. The results were also significant for the improvement of wrinkles when patients received a combination of PRP and laser therapy. In a study by Shin et al., a combination of fractional laser therapy and platelet concentrates produced better results when compared to mono-therapy with fractional laser. Fractional laser produces a micro thermal zone in the skin, which can increase the penetration depth of the platelet concentrate. Combination therapy was also reported to have better results in another study. Since topical application of PRP accelerates skin rejuvenation, it can be considered a superior method of application.

As for the NLF, two selected studies showed that PRP had no effect on enhancing the skin volume, but improved the appearance of the NLF. The most common treatment for NLF augmentation is the injection of the dermal fillers which may lead to side effects such as granulomatous reaction, skin necrosis, and unwanted misplacement. In contrast, platelet-rich fibrin matrix therapy showed no side effects. In these two studies, side effects such as over-volumization, skin irregularity, and skin necrosis were not reported.

The age range of the study population was 23 to 72 years old. Both genders were included; however, females were the dominant group. Only one study conducted by Amgar et al. mentioned that improvement in the skin rejuvenation was age dependent and suggested the frequency as well as the intervals of PRP injection in each age group. It can be postulated that the age dependent results of PRP therapy might be associated with tissue repair mechanisms which are anticipated to work better in younger age groups. The regenerative capability of most tissues gradually declines with age due to both age-dependent changes in tissue-specific stem cells and also alterations of the environmental signals stimulating stem cells for tissue maintenance and repair.

Although there were no reports on the effect of age on skin rejuvenation in PRP therapy, age-dependent alterations in cellular responses to PRP therapy was previously reported in tissue engineering related researches. Some animal studies have shown a decrease in the expression of growth factor receptors due to aging. More specifically, a significant decrease has been observed in the expression of TGF-beta.
receptor 1, FGF receptor, and VEGF receptor 2; and a less significant decrease has been noted in the expression of TGF-beta receptor 3 and PDGF receptor. An exception was VEGF receptor 1, a regulator of VEGF receptor 2 which did not show any age-dependent changes. These findings suggest that the decrease in the expression of growth factor receptors is a likely reason for the reduced PRP action with an increase in age. On the other hand, age-dependent skin fibroblast dysfunction, such as the reduced production of type I procollagen, is seen in aged fibroblasts. Laboratory studies conducted to stimulate the growth of fibroblasts have found that younger fibroblasts show a better response to growth factors. As fibroblasts are the main targets in PRP therapy, it is important to record whether the effect of this treatment is more prominent at a young age. In other words, it is necessary to investigate whether the duration of the beneficial effects of PRP therapy on skin improvement is longer in younger patients.

Other variables in these studies were the volume of the starting whole blood, single or double centrifugation, and the amount of injected PRP, number of sessions, use of ordinary test tubes or commercial tubes, and the method of injection. Since the normal platelet count has a wide range in humans, even if equal volumes of whole blood are used, the final concentration of platelets in PRP varies from one patient to another patient. However, none of the selected studies reported the final platelet concentration in PRP at the time of injection. It could be the primary reason for the difference in outcome in different patients in the same study who undergo the same treatment protocol because the injection of the same volume but different concentrations of PRP results in various amounts of growth factors and cytokines. Although the ideal concentration of platelets in PRP therapy is not identified, some studies have reported that concentrations 4 to 6 times more than the whole blood are sufficient to provide the benefit of PRP therapy. The higher concentration of platelet, up to 20 fold, had been reported to be obtained from whole blood. Generally, the composition of PRP and its preparation influence the cellular response of tissues and regulate its overall outcome in tissue repair.

One of the main limitations of the selected studies was their sample size except for one study that recruited 418 participants. The lack of a control group was a significant weakness of most studies. Only one study had matched case and control groups of 11 subjects.

A wide range of outcome assessments were used including the patient and physician satisfaction scale, blind clinical assessment, and the biophysical parameters of roughness, elasticity, and skin hydration, as well as erythema and melanin index. Biopsy and immunohistochemistry for matrix metalloproteinase were also carried out. However, most of these assessments were subjective, making it difficult to establish a sound comparison. However, all different assessment methods confirmed satisfactory results.

No study showed serious or permanent side effects. A burning sensation was a common finding in patients after the injection, which resolved without any treatment. It could be associated with adding calcium chloride to activate PRP. In addition, no study reported hyperpigmentation, hypopigmentation, serious infection, or hematoma. Based on the results of these studies, PRP therapy is a safe treatment method to improve the skin texture and remove the skin wrinkles.

With increased interest in using non-synthetic materials in different medical applications, PRP has attracted a lot of attention, especially in medical aesthetics which always deals with non-disease settings. Based on the results of this review, PRP therapy is a less invasive method compared to plastic surgery which demonstrated positive anti-aging effects on the skin. It is a simple technique which has favorable effects on all small skin wrinkles, skin texture, elasticity and homogeneity. Despite the existence of several PRP injection techniques, no significant differences have been reported. It is a safe treatment method for all skin types. The incidence of hyperpigmentation or hypopigmentation was not reported. This study showed PRP could be considered a safe, promising and effective method of skin rejuvenation. The results were significant when patients received a combination of PRP and laser.

The small sample size and lack of control group were the main limitations of the selected studies. Furthermore, the assessment method was not the same in all studies. As objective assessment of the wrinkles and skin texture is not easy to perform, most assessments are subjective and observation...
is often the only evaluation, which calls for multi-centered well-controlled studies with larger sample sizes and longer follow-ups. Objective assessments should also be incorporated to confirm the efficacy and safety of PRP therapy in skin rejuvenation.

REFERENCES


