Capsule Summary

- Platelet-rich plasma has garnered interest in alopecia, acne scarring and skin rejuvenation but several studies have documented benefits in refractory skin ulcers as well as vitiligo.
- Activated platelet-rich plasma should be considered as adjunctive therapy to optimize outcomes in vitiligo and skin ulcers refractory to standard wound care.
Article type: Review article

Title: “Platelet-rich plasma and its utility in medical dermatology - A systematic review”

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Abstract: The field of dermatology has seen numerous therapeutic innovations in the past decade with platelet-rich plasma (PRP) recently garnering significant interest particularly in alopecia, acne scarring and skin rejuvenation. In other conditions of dermatology, such as chronic wounds and vitiligo, PRP has been investigated but has received less attention. The objective of this literature review was to focus on conditions of medical dermatology and to consolidate the available evidence of platelet-rich plasma for the practicing dermatologist. This review evaluates the literature up to October 31, 2018, and a search was conducted in the PubMed database for “platelet-rich plasma” or “platelet releasate” or “platelet gel” or “platelet rich fibrin” or “PRP” and “dermatology” or “skin” or “cutaneous” or “wound” or “ulcer.” Fourteen articles met the inclusion criteria for this review. In studies representing 1b-4 grades of evidence according to the Centre for Evidence-Based Medicine, Oxford, platelet-rich plasma significantly improved wound healing in chronic diabetic ulcers, venous ulcers, pressure ulcers, leprosy ulcers, acute traumatic wounds and ulcers of multifactorial etiologies. Two studies also documented benefits of adjuctive PRP in stable vitiligo. Platelet-rich plasma warrants further investigation as it represents a potential therapeutic adjunct or alternative with a favorable side effect profile.
**Legend:**

65 AA-PRP: activated, platelet-rich plasma
66 AA-L-PRP: activated, leukocyte and platelet-rich plasma
67 AA-P-PRP: activated, pure or leukocyte-poor, platelet-rich plasma
68 AA-uPRP: activated, undefined, platelet-rich plasma (unknown if leukocyte-rich or -poor)
69 Ca²⁺: calcium
70 Cl⁻: chloride
71 CO₂: carbon dioxide
72 g: gravity
73 L-PRF: leukocyte and platelet-rich fibrin
74 mL: milliliter
75 µL: microliter
76 min: minutes
77 MMP: matrix metalloproteinase
78 NA-PRP: non-activated, platelet-rich plasma
79 NA-L-PRP: non-activated, leukocyte and platelet-rich plasma
80 NA-P-PRP: non-activated, pure or leukocyte-poor, platelet-rich plasma
81 NA-uPRP: non-activated, undefined, platelet-rich plasma (unknown if leukocyte-rich or -poor)
82 NB-UVB: narrow-band ultraviolet B light
83 PDGF: platelet-derived growth factor
84 PRP: platelet-rich plasma
85 P-PRP: pure or leukocyte-poor, platelet-rich plasma
86 PRF: platelet-rich fibrin
87 Rpm: revolutions per minute
Introduction

Platelet-rich plasma (PRP) is a plasma fraction that contains a greater concentration of platelets relative to whole blood, typically three to seven-fold the mean platelet concentration in whole blood. Platelets contain alpha granules and upon their activation, secrete growth factors, adhesion molecules and chemokines that interact with the local environment to promote cell differentiation, proliferation and regeneration.

The production of PRP begins with collecting 10–60 mL of whole blood on the day of treatment. Anticoagulants, like acid citrate dextrose or sodium citrate, are added to prevent ex vivo coagulation and premature secretion of the alpha granules. The blood is then centrifuged to separate cell types based on specific gravity according to Stokes’ law (Figure 1).

In the single-spin method, the lower portion of the plasma layer is collected as platelet-rich plasma. To increase the platelet concentration of PRP, the plasma and superficial buffy coat are isolated and a 2nd centrifugation can be performed. Dohan Ehrenfest, et al., defined the methods to isolate leukocyte-rich and leukocyte-poor PRP in the single spin and 2-spin techniques (Figure 2). In pure PRP (P-PRP), only the most superficial buffy coat is collected with the lower plasma portion whereas the entire buffy coat is collected in leukocyte-rich PRP.

Calcium or thrombin can be added prior to administration creating autologous activated PRP (AA-PRP) while nonactivated autologous PRP (NA-PRP) utilizes host dermal collagen and thrombin as endogenous activators. Alternatively, leukocyte and platelet-rich fibrin gel (L-PRF) can be produced when the blood is centrifuged without anticoagulant, allowing natural platelet activation and fibrin clot development to ensue prior to topical application. The variations in processing are important to describe as they impact the
structure, growth factor and cell concentrations of the platelet product (Figure 3). PRP is generally considered safe with minimal side effects and few contraindications.

[INSERT FIGURE 3]
Methods

The objective of this literature review was to focus on conditions of medical dermatology outside of alopecia, acne scarring and skin rejuvenation, and consolidate the available evidence of platelet-rich plasma for the practicing dermatologist. To identify the evidence up to October 31, 2018, a search was conducted in the PubMed database for “platelet-rich plasma” or “platelet releasate” or “platelet gel” or “platelet rich fibrin” or “PRP” and “dermatology” or “skin” or “cutaneous” or “wound” or “ulcer.” The 547 identified search items were investigated further to include those that specified the method of autologous PRP or PRF preparation and delivery. Given the paucity of large, prospective studies available but also in efforts to limit bias, a sample size of less than 20 patients and rates of subject dropout >15% were set as exclusion criteria. Other exclusions were non-human research, studies not available in English, studies of postsurgical wounds, or studies investigating homologous PRP or other stem cell products added into the PRP. The reference lists of relevant articles were also searched for potentially appropriate publications. Fourteen studies investigating ulcers were identified that fulfilled the inclusion criteria. Due to the heterogeneity of studies and widely variable outcome measures, comparison between platelet-rich plasma treatments and subsequent statistical analysis could not be performed. The quality of each individual study was evaluated and levels of evidence were assigned according to the Centre for Evidence-Based Medicine, Oxford.

[INSERT FIGURE 4]
Medical Dermatology: Ulcers

Chronic wounds are among the most common medical conditions affecting the general population, impacting nearly 15% of Medicare beneficiaries with an estimated annual cost of $28-96 billion. Prior studies have evaluated the role of platelet-rich plasma in chronic ulcer therapy and showed mixed results. Earlier studies are difficult to interpret as the description of the PRP isolation method or delivery technique is often unspecified or ambiguous. Other studies were limited by high rates of patient dropout. The current evidence for the use of PRP in medical dermatology is reviewed with focus on the study’s quality, the various PRP protocols utilized as well as evaluations of treatment response.

Skin ulcers of multifactorial etiology

De Leon, L.M., et al. conducted a large, observational multicenter case series in 200 patients with refractory chronic wounds of a variety of etiologies. AA-P-PRP gel was applied topically once or twice a week. After a mean of 2.8 PRP applications over 2.2 weeks, 86.3% of the wounds responded with an area reduction of 47.5% while 90.5% of the wounds had a 63.6% volume reduction. Specifically pressure, diabetic, and venous ulcers achieved significantly greater response compared to ulcers of other etiologies (p= 0.016).

Pinto, et al. studied a prospective cohort of 44 patients with lower extremity ulcers recalcitrant to 3 months of standard wound care. Weekly topical NA-L-PRF yielded complete resolution in every patient with small venous ulcers (<10cm²), diabetic foot ulcers or complex multifactorial wounds. 10/15 large venous ulcers (>10cm²) achieved full closure after a mean 12.6 treatments. At 3 months, all patients with venous ulcers reported complete alleviation of severe pain that previously required analgesics.

Acute traumatic wounds

Kazakos, et al. conducted an open-label, randomized, controlled trial of 59 patients with acute traumatic wounds (open fractures, closed fractures with skin necrosis, and frictional burns) not requiring flap coverage. Compared to Vaseline gauze, topical AA-uPRP gel weekly for 3 weeks produced early
improvements in wound surface area throughout follow-up starting at week 1 (p=0.003) as well as lower pain scores at week 2 (p=0.002) and week 3 (p<0.001).

207 Chronic diabetic ulcers

208 Saad Setta et al.\textsuperscript{19} conducted an open-label, randomized controlled trial in 21 patients with chronic diabetic ulcers >12 weeks in duration. Patients randomized to twice a week treatment with topical AA-L-PRP gel had a faster mean healing time (11.5 weeks) compared to platelet-poor plasma (17 weeks; p<0.005). Li, et al.\textsuperscript{20} performed a single-blinded, randomized, controlled trial of 117 patients with chronic diabetic ulcers. Patients were randomized to either 12 weeks of standard wound care alone or combined with topical AA-L-PRP gel every 2 weeks if the wound area had not reduced by ≥80%. In the 12-week treatment period, 39/59 (66.1%) only required 1-2 PRP gel treatments while 20/59 (33.9%) required 3-5 treatments. Greater improvements in healing grades (p<0.05) as well as time to healing (p<0.05) were noted with activated platelet gel. Ahmed, M., et al.\textsuperscript{21} evaluated the role of topical AA-L-PRP gel compared to antiseptic iodine ointment dressings in an open-label, controlled trial of 56 diabetic patients with chronic foot ulcers. Treatment was applied twice a week until complete healing, occurrence of infection, or treatment period end at 12 weeks. PRP produced greater healing rates at 2 and 4 weeks (p= 0.003 and p=0.044, respectively). But healing rates slowed at 8 weeks which, the authors speculated, could be due to receptor down regulation induced by persistently elevated growth factors. Nevertheless, at 12 weeks, PRP’s benefits persisted with higher rates of complete healing (86% versus 68% of controls; p= 0.041) and lower rates of infection (P= 0.011).

224 Mohammadi, et al.\textsuperscript{22} conducted a prospective cohort study of 70 diabetic patients with chronic diabetic foot ulcers. Topical AA-uPRP gel applied weekly for 4 weeks significantly decreased mean ulcer area to 51.9% of baseline (p=0.008).

229 Game, et al.\textsuperscript{23} recently published large, multicenter, single-blinded, randomized controlled trial comparing weekly applications of NA-L-PRF (LeucoPatch\textsuperscript{®}) to standard wound care in 269 patients with hard-to-heal diabetic foot ulcers. Although 18% of subjects dropped out in the per protocol analysis, we included this
study as all of the outcomes were evaluated in an intention-to-treat (ITT) analysis. In this ITT population, only 3 patients dropped out. At 20 weeks, 34% L-PRF group ulcers completely healed vs. 22% of ulcers in the standard wound care (OR 1.58, p=0.0235). Time to healing was significantly shorter (p=0.0246) and the improvement in ulcer area was significantly greater (p=0.0168) with L-PRF treatment.

Pressure ulcers

Ramos-Torrecillas, J., et al. conducted an open-label, randomized, clinical trial in 100 patients with pressure ulcers for >8 weeks. Patients were randomized to either: standard care only, a single dose of topical AA-uPRP on day 0, two doses of AA-uPRP on day 0 and day 15, or two doses of AA-uPRP plus hyaluronic acid on day 0 and day 15. At 36 days, ulcer areas were significantly improved in every treatment group when compared to standard care only (p=0.001). Among the treatment groups, 2 doses of PRP/hyaluronic acid produced greater healing compared to 1 dose of PRP alone (p<0.001). Associations with reduced ulcer healing included statin use (p≤0.001) as well as higher peripheral blood platelet concentration (P≤0.01). Two possibilities for this association are excessively elevated local platelet concentrations or PRP’s sustained induction of myofibroblast differentiation. It suggests that an upper therapeutic threshold exists and further investigation is warranted to identify the most optimal PRP product.

Venous ulcers

Moneib, H.A., et al. performed an open-label, randomized, controlled study in 40 patients with chronic venous leg ulcers of >6 months’ duration comparing compression therapy alone to combination with weekly topical AA-L-PRP gel for 6 weeks. The AA-L-PRP gel significantly improved the mean ulcer area at 6 weeks (67.6% vs. 13.7% of controls, p= 0.0001). Complete healing of ulcers was achieved in 35% of patients who received AA-L-PRP gel.
patients treated with PRP compared to 0 controls. All patients treated with PRP claimed a decrease in the pain, pruritus and burning associated with the ulcer.

**Leprosy ulcers**

Over 2 million people worldwide experience complications due to leprosy including sensory loss leading to trophic ulcers. PRP may contribute to peripheral nerve regeneration as well healing of ulcers secondary to neuropathy.

Anandan et al. evaluated weekly topical AA-L-PRP for a maximum of 6 sessions for neuropathic ulcers in 50 leprosy patients. At 3-month follow-up, 92% of subjects showed complete re-epithelialization within 6 treatment sessions and a mean healing time of 4.38 weeks. There was no statistical significance in the rate of wound healing with PRP based on patients’ spectrum of disease.

**Stable Vitiligo**

Ibrahim et al. explored the use of AA-P-PRP combined with narrow band-UVB phototherapy (NB-UVB) for vitiligo. Sixty patients with symmetric vitiligo, stable for >12 months, underwent NB-UVB alone on the left side while combination therapy with intradermal AA-P-PRP injections was performed on the right side. Patients received phototherapy twice a week and PRP injections every 2 weeks for a maximum of 4 months. At 3 months post-treatment, 2 independent dermatologists noted excellent response (>75% repigmentation) in 55% of the lesions treated with PRP. In contrast, 75% of the lesions treated with phototherapy alone displayed only mild improvement (<25% repigmentation) and none achieved >50% repigmentation (p<0.001). At 7 months, 50% of the controls showed recurrent depigmentation while none of the PRP-treated lesions relapsed.

Abdelghani et al. performed an open-label, prospective, randomized, controlled trial evaluating the efficacy of AA-P-PRP, fractional ablative CO2 laser and NB-UVB in 80 patients with stable vitiligo for 12 months. Patients were randomly assigned to one of four treatments: 1) fractional CO2 laser; 2) Intradermal AA-P-PRP; 3) combination fractional CO2 laser and intradermal AA-P-PRP or 4) combination of
fractional CO2 laser and NB-UVB. Three months after the final treatment, evaluation by 2 blinded
dermatologists noted that combination of CO2 laser with PRP achieved improved repigmentation compared
to the combination CO2 laser and NB-UVB. When combined with CO2 laser, >75% repigmentation was
seen in 40% of PRP-treated patients compared to 5% in NB-UVB-treated patients.

Taken together, the above studies highlight that PRP, when used adjunctively in combination with NB-
UVB or CO2 laser therapy, can produce better outcomes in treating stable vitiligo. Larger, randomized
controlled trials with longer follow up are required to validate these findings.
Discussion

This review highlights the utility of PRP in treating ulcers of multiple etiologies across 12 studies with a cumulative 1051 patients (Grade of Evidence 1b-4). 10/12 reviewed studies utilized activated PRP while 2 studies used L-PRF. 6/12 studies investigated leukocyte and platelet-rich plasma while 3 studies used undefined PRP (leukocyte content not reported). But the only study achieving Grade 1b evidence utilized NA-L-PRF applied weekly to diabetic foot ulcers. These articles demonstrate that topical activated PRP or NA-L-PRF applied once to twice a week over 3-6 weeks improves wound healing and support a potential standardized regimen for PRP treatment in ulcers. In addition, symptomatic improvement in pain may be noted after PRP treatment.

The reviewed studies utilize a wide range of centrifugation speeds limiting the ability to propose an optimal technique for collecting PRP. In vitro, the highest platelet capture efficiency while preserving platelet function was noted in a 1st spin at 160g x 10 minutes and an 2nd spin at 250g x 15 minutes. But an optimal PRP platelet concentration may exist. Fibroblastic proliferation and hyaluronic acid production appear greatest with PRP containing 2-4 fold the peripheral platelet concentration whereas angiogenesis decreases as platelet concentrations rise above 1.5 million platelets/µL.

In this review, we excluded many earlier studies documenting benefits from PRP of other sources (allogeneic or recombinant), PRP method or treatment not described, or those with higher rates of dropout and selection bias. Recombinant PDGFs have been associated with the development of various malignancies in the diabetic population but this has not been reported with autologous PRP. In addition, an autologous source would avoid any potential risk for transmissible diseases or graft versus host disease. PRP is generally considered safe but is not without potential risk. A recent report has documented vascular compromise and irreversible blindness after PRP injections for periorbital rejuvenation. This risk may be far lower in the treatment of chronic ulcers and vitiligo as the use of PRP is off the face and most studies utilized a topical preparation. Nonetheless, dermatologists should proceed with the appropriate caution and technique during injections of PRP.
There are a variety of advantages that platelet-rich plasma may provide in regards to wound healing. PRP has also been shown to display local microbicidal effects.\textsuperscript{49–52} PRP appears to facilitate healing in ulcers as it alters the MMP and cytokine expression within 2 weeks after topical application of AA-L-PRP.\textsuperscript{53} While leukocyte inclusion in PRP may contribute to inflammation due to the induction of NFκβ,\textsuperscript{54,55} 6/12 studies successfully treated ulcers with L-PRP. This argues against concerns of high concentrations of leukocytes in PRP producing a deleterious inflammatory effect on wound healing. There are no head-to-head studies comparing L-PRP and P-PRP in ulcers thus it is unclear if one preparation is more efficacious. This remains an avenue for future investigation.

Finally, recent literature has elucidated the role of platelets in modulating local T-cell immunity through TGF-β.\textsuperscript{56} With its proliferative and immunomodulating effects, platelet-rich plasma could be beneficial in T-cell-mediated diseases like vitiligo. We identified 2 studies using adjunctive AA-P-PRP in the treatment of stable vitiligo (Grade of evidence 2b).\textsuperscript{35,36} In the total of 140 patients investigated, combining intradermal AA-P-PRP injections at 2-3 week intervals to CO\textsubscript{2} laser or NB-UVB produced superior outcomes with earlier and more complete repigmentation.
Conclusion

PRP presents an attractive option for treatment-resistant, chronic ulcers, which remain a significant economic burden in healthcare today. Additionally, it could be considered as adjunctive therapy to minimize the use of systemic medications associated with unfavorable side effect profiles, such as analgesics and opioids. Additionally, adjunctive PRP appears to improve repigmentation when treating stable vitiligo.
Capsule Summary

- Platelet-rich plasma has garnered interest in alopecia, acne scarring and skin rejuvenation but several studies have documented benefits in refractory skin ulcers as well as vitiligo.
- Activated platelet-rich plasma should be considered as adjunctive therapy to optimize outcomes in vitiligo and skin ulcers refractory to standard wound care.
References


46. Govindarajan, B. *et al.* Malignant Transformation of Human Cells by Constitutive Expression of


FIGURES

Figure 1: Separation of cell types by specific gravity via centrifugation.

Figure 2: Pure PRP versus leukocyte-rich PRP in a single-spin (softspin) technique or a two-spin technique.

Figure 3: Differences in platelet-rich products

Figure 4: Literature review of PRP in medical dermatology.

Table 1: Medical Dermatology
<table>
<thead>
<tr>
<th>Author (year) &amp; study design</th>
<th>Study Groups</th>
<th>PRP preparation</th>
<th>Outcomes &amp; Follow-up</th>
<th>Grade &amp; Adverse events</th>
</tr>
</thead>
</table>
| De Leon, J.M., et al. (2011) | The AA-P-PRP gel was applied once or twice a week depending on wound characteristics and physician’s judgement. | -20mL of blood collected  
- Centrifuged for 60 seconds (unknown speed).  
- Activator: ascorbic acid and calcified thrombin  
- AA-P-PRP gel applied topically to wound | -After a mean of 2.8 PRP gel treatments over 2.2 weeks:  
-86.3% of the wounds responded with a reduction of 47.5% in area  
-90.5% of the wounds had a 63.6% reduction in volume  
-9.5% of the wounds healed completely  
-Specific wounds achieved significantly greater response: pressure, diabetic, and venous ulcers (p: 0.016).  
Mean follow-up: 2.2 weeks (0.4-11 weeks) | 4  
No side effects reported. |
| Pinto, et al. (2018) | A large, multi-center, case series of 200 patients with chronic ulcers refractory to standard wound care therapy | -20mL of blood collected  
- Centrifuged for 60 seconds (unknown speed).  
- Activator: ascorbic acid and calcified thrombin  
- AA-P-PRP gel applied topically to wound | -All 17 small venous ulcers (≤10 cm², mean baseline area of 4.9 cm²) reached closure after a mean 6.3 PRP applications.  
-10/15 large venous ulcers (>10cm², mean area 27.9 cm²) achieved full closure after a mean 12.6 PRP gel applications.  
-All 10 diabetic foot ulcers reached full closure after a mean 6.8 PRP gel applications.  
Follow-up: 1 year | 2b  
No adverse events were recorded. |
| Kazakos, K., et al. (2009) | Weekly topical application of NA-L-PRF membranes until wound closure. (Compression therapy added for VLU, DFU, and multifactorial wounds.) | -9 mL glass-coated plastic tubes without anticoagulant in the Intra-Spin™ system  
-1st spin: 2700 rpm x 12 min  
-NA-L-PRP gel was gently compressed to obtain 1.0 mm thick membranes | -Improvements in surface area were statistically greater in the PRP group compared to control at 1 week (p:0.003), 2 & 3 weeks (both p<0.001).  
-The control group also displayed significantly higher pain scores at the 2nd and 3rd week (p:0.002, p<0.001, respectively).  
Follow-up: mean 6 months (2.5-21 months) | 2b  
No adverse reactions noted. |
| Saad Setta, et al. (2011) | 1) conventional therapy of washing wounds, necrotic debridement and Vaseline gauze dressing every 2 days (32 patients)  
2) conventional therapy plus topical AA-uPRP gel weekly for 3 weeks (27 patients) | -Biotec’s PRP Fast system, unknown volume of blood with acid citrate dextrose,  
-1st spin: 3200rpm x 20 min  
-Activator: autologous thrombin at a 1:10 ratio.  
-AA-uPRP gel applied topically. | -Number of PRP sessions required to achieve 80% surface area improvement:  
-39/59 (66.1%): 1-2 doses  
-18/59 (30.5%): 3-4 doses | 2b  
No reported side effects. |
| Li, L., et al. (2015) | 1) AA-L-PRP gel applied followed by Vaseline gauze then dressing twice a week (12 patients).  
2) PPP applied followed by Vaseline gauze and dressing twice a week (control; 9 patients). | -10mL of blood with citrate dextrose.  
-1st spin: 1007g x undefined time  
-2nd spin: 447g x undefined time  
-the lower 20% isolated as L-PRP and the upper 80% as PPP.  
-Activator: bovine thrombin (0.2ml per 1ml PRP) and 10% CaCl₂ (0.1ml) | The mean healing time was 11.5 weeks for PRP patients and 17 weeks for the control (p<0.005).  
Follow-up: every 1 week until healed or 20 weeks | 2b  
No reported side effects. |
<table>
<thead>
<tr>
<th>Author (year) &amp; study design</th>
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<tbody>
<tr>
<td>trial of 117 patients with refractory diabetic cutaneous ulcers</td>
<td>PRP gel every 2 weeks if 80% improvement was not achieved (59 patients)</td>
<td>-1&lt;sup&gt;st&lt;/sup&gt; spin: 313g x 4 min, -2&lt;sup&gt;nd&lt;/sup&gt; spin: 1252g x 6 min -Activator: thrombin and Ca&lt;sup&gt;2+&lt;/sup&gt; gluconate in a 10:1 ratio</td>
<td>-Kaplan-Meier time-to-healing from ITT population was significantly less in the PRP group at 36 days versus 45 days in the control (p value: 0.021). Follow-up: 12 weeks</td>
<td>identified.</td>
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<tr>
<td>Ahmed, M., et al. (2017)&lt;sup&gt;21&lt;/sup&gt;</td>
<td>1) AA-L-PRP gel applied twice weekly (28 patients) 2) Antiseptic ointment dressing (28 patients)</td>
<td>-20mL of blood collected -1&lt;sup&gt;st&lt;/sup&gt; spin: 1,500rpm x 5 min -2&lt;sup&gt;nd&lt;/sup&gt; spin: 3,500rpm x 5 min -The pellet was diluted in 3mL of plasma to make L-PRP -Activator: 2mL 10% CaCl&lt;sub&gt;2&lt;/sub&gt; and 2mL homologous thrombin -Platelet count of PRP gel: 1-1.2 x 10&lt;sup&gt;6&lt;/sup&gt; platelets/µL.</td>
<td>-PRP produced a significant increase in number of ulcers healed (p&lt;0.003) at 2 weeks and a significantly higher healing rate at 4 weeks (p&lt;0.044). -At 12 weeks, complete healing seen in 86% compared to 68% of control group (p&lt;0.041). -The use of the platelet gel showed a lower rate of wound infection (P&lt;0.011). Follow-up: 12 weeks</td>
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<td>Mohammadi, MH, et al. (2017)&lt;sup&gt;22&lt;/sup&gt;</td>
<td>After debridement and washing of the ulcer, 2mL/cm&lt;sup&gt;2&lt;/sup&gt; of AA-uPRP followed by a non-absorbing wet dressing applied weekly for 4 weeks.</td>
<td>-27mL of blood with 3mL of sodium citrate anticoagulant: -1&lt;sup&gt;st&lt;/sup&gt; spin: 2000g x 10 min at 24°C -Activator: 2mL of 25mM CaCl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-At 4 weeks, mean wound area significantly decreased by 51.9% when treated with PRP weekly (p=0.008). -The correlation between the initial wound area and healed time by week was 0.22 which was not significant (p&gt;0.05). Follow-up: 4 weeks</td>
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<td>Game, F., et al (2018)&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Randomized to one of 2 groups: 1) Standard wound care including off loading (137 patients) 2) standard care plus weekly L-PRF application (132 patients)</td>
<td>-18mL of blood drawn into LeucoPatch® Device -1&lt;sup&gt;st&lt;/sup&gt; spin: 20 min according to automated programming -L-PRF was placed leukocyte side down onto the ulcer -ulcers &gt;5cm&lt;sup&gt;2&lt;/sup&gt; received 2 patches</td>
<td>-34% of 132 L-PRF group ulcers completely healed vs. 22% of 134 ulcers in the standard care group (OR 1.58, p=0.0235) -Time to healing was shorter in the L-PRF group (p=0.0246). -Ulcer area was significantly reduced in the L-PRF group (p=0.0168). Follow-up: 26 weeks</td>
<td>1b</td>
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<td>Ramos-Torrejillas, J., et al. (2015)&lt;sup&gt;24&lt;/sup&gt;</td>
<td>1) standard care only (control; 25 ulcers) 2) 1 dose of AA-uPRP on day 0 (34 ulcers) 3) 2 doses of AA-uPRP on day 0 and day 15 (25 ulcers) 4) 2 doses of AA-uPRP + hyaluronic acid on day 0 and day 15 (40 ulcers)</td>
<td>-20mL of blood with 3.8% sodium citrate. -1&lt;sup&gt;st&lt;/sup&gt; spin: 460g x 8 min -Activator: 10% CaCl&lt;sub&gt;2&lt;/sub&gt; to generate AA-uPRP.</td>
<td>At 36 days: -All 3 treatment groups achieved a significant % reduction in ulcer area in comparison to the control group (p≤0.001). -Among the treatment groups, 2 doses of PRP/hyaluronic acid produced greater healing compared to 1 dose of PRP alone (p≤0.001). -There was no infection noted in any ulcer - Inverse correlations with ulcer healing were seen with statin use (p≤0.001) and peripheral blood platelet count (P&lt;0.01). Follow-up: 36 days</td>
<td>2b</td>
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<tr>
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<td>Singh, R., et al. (2017)&lt;sup&gt;28&lt;/sup&gt;</td>
<td>For 5 weeks: -One ulcer was treated with bi-weekly PRP dressings (AA-L-PRP gel), then non-absorbent Vaseline gauze -Control ulcer was treated with daily saline dressings</td>
<td>-30mL of blood with citrate phosphate dextrose adenine at 1:9 ratio. -1&lt;sup&gt;st&lt;/sup&gt; spin: 2000rpm x 10 min -2&lt;sup&gt;nd&lt;/sup&gt; spin: 2000rpm x 5 min -Activator: 10% CaCl&lt;sub&gt;2&lt;/sub&gt; at ratio of 6:1 (PRP: CaCl&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>-AA-L-PRP treated wounds had higher percent of surface area healed compared to controls (57.94% vs. 2.36%). -AA-L-PRP treated wounds had significant decrease in wound surface area compared to baseline, unlike control wounds (p&lt;0.001 vs. p=0.924). Mean Follow-up: 7 months</td>
<td>4 PRP patients noted declines in hemoglobin</td>
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<tr>
<td>Moneib, HA, et al. (2017)&lt;sup&gt;29&lt;/sup&gt;</td>
<td>1) weekly topical AA-L-PRP gel x 6 weeks with compression and dressing (20 patients) 2) conventional compression and dressing x 6 weeks (20 patients; control)</td>
<td>-10mL of blood with acid citrate dextrose. -1&lt;sup&gt;st&lt;/sup&gt; spin: 277g x 10 min -2&lt;sup&gt;nd&lt;/sup&gt; spin: 277g x 5 min -Activator: 0.1mL Ca&lt;sup&gt;2+&lt;/sup&gt; gluconate for each 1mL of PRP</td>
<td>At 6 weeks: -Improvement in mean ulcer area was significantly greater in PRP vs control (67.6% vs 13.7%, respectively; p&lt;0.0001). -Complete ulcer healing was 35% in PRP vs 0% in control. Follow-up: 6 weeks</td>
<td>2b No adverse effects noted.</td>
</tr>
<tr>
<td>Anandan, V., et al. (2016)&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Topical AA-L-PRP and occlusive dressings with sterile gauze weekly for a maximum of 6 weeks or until complete ulcer healing</td>
<td>-10mL of blood with acid citrate dextrose at ratio of 10:1.5. -1&lt;sup&gt;st&lt;/sup&gt; spin: 2000rpm x 10 min -2&lt;sup&gt;nd&lt;/sup&gt; spin: 3000rpm x 10 min -Activator: 10% CaCl&lt;sub&gt;2&lt;/sub&gt; at ratio of 10:1 (PRP:CaCl&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>-92% (46/50) of patients showed complete ulcer healing. -88% achieved complete healing within 4 weeks, 8% within 3 weeks. -Mean time for ulcer healing was 4.38 weeks. Follow up: 6 weeks</td>
<td>4 No adverse events noted.</td>
</tr>
<tr>
<td>Ibrahim, ZA, et al. (2016)&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Twice a week NB-UVB to the left side of the body (control side) while the right side with NB-UVB plus intradermal injection of PRP every 2 weeks for 4 months or resolution</td>
<td>- 10 to 20 ml of blood with sodium citrate (10:1). -1&lt;sup&gt;st&lt;/sup&gt; spin: 3000 rpm x 7 min -2&lt;sup&gt;nd&lt;/sup&gt; spin: 4000 rpm x 5 min -Activator: 0.1mL CaCl&lt;sub&gt;2&lt;/sub&gt; for each 1mL of AA-P-PRP</td>
<td>-After 4 months: -75% of PRP lesions had a good or excellent response (&gt;50% repigmentation; compared to 0 controls). -At 7 months, the PRP side showed no relapses while 50% of the controls relapsed. Follow-up: 7 months</td>
<td>2b Injection pain:50%, bruising: 15%.</td>
</tr>
<tr>
<td>Abdelghani, R., et al. (2017)&lt;sup&gt;33&lt;/sup&gt;</td>
<td>4 treatments of: 1) fractional CO2 laser every 2 weeks 2) intradermal AA-P-PRP every 3 weeks 3) fractional CO2 laser, every 2 weeks followed by AA-P-PRP 1 week later 4) fractional CO2 laser every 2 weeks followed 1 week later with twice weekly NB-UVB</td>
<td>-10-20 mL of venous blood was collected in tubes containing sodium citrate as an anticoagulant -1&lt;sup&gt;st&lt;/sup&gt; spin: 252g x 10 min -2&lt;sup&gt;nd&lt;/sup&gt; spin: 448g x 10 min -P-PRP activated with 0.1 mL of CaCl&lt;sub&gt;2&lt;/sub&gt; per 0.9 mL of PRP and then injected intradermally.</td>
<td>At 3 months following the final treatment: -PRP + laser produced the best results with &gt;75% repigmentation in 40% patients and &gt;50% repigmentation in 60% patients. -There was a statistically difference in repigmentation grade and VAS among the 4 groups (P value = .000). Follow-up: 5 months</td>
<td>2b Erythema resolved within 24 hours after laser and NB-UVB</td>
</tr>
</tbody>
</table>
Figure 1: Separation of cell types by specific gravity via centrifugation.
Figure 2: Pure PRP versus leukocyte-rich PRP in a single-spin (softspin) technique or a two-spin technique.
<table>
<thead>
<tr>
<th>Platelet product</th>
<th>Anticoagulant</th>
<th>Activation</th>
<th>Fibrinogen polymerization</th>
<th>Fibrin architecture</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRP</td>
<td>Added prior to centrifugation</td>
<td>Endogenous</td>
<td>Low</td>
<td>None</td>
</tr>
<tr>
<td>Activated PRP</td>
<td>Added prior to centrifugation</td>
<td>Exogenous activation with Ca(^+)/thrombin</td>
<td>Low-moderate</td>
<td>Weak</td>
</tr>
<tr>
<td>(or gel)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRF</td>
<td>None</td>
<td>Exogenous activation without additive</td>
<td>High</td>
<td>Strong</td>
</tr>
</tbody>
</table>

Figure 3: Differences in platelet-rich products
Figure 4: Literature review of PRP in medical dermatology

* Given the paucity of large, prospective studies available but also in efforts to limit bias, a sample size of less than 20 patients and rates of subject dropout >15% were set as exclusion criteria.

+ One included study had a drop out rate of 18% in the per-protocol analysis but the objective measurements were evaluated in an intention-to-treat analysis which included all but 1.25% of recruited subjects.