Review Article



# Platelet rich plasma: hope or hype?

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**Abstract:** Platelet rich plasma (PRP) is an autologous product consisting of higher platelet levels than native whole blood. It has been hailed as a safe product with a multitude of potential uses in promoting healing with developing applications in numerous fiends including Dermatology, Plastic Surgery, Orthopedics, and Sports Medicine. It is currently administered in many clinical settings, usually as an adjuvant to other standards of therapy. Despite being a biologic product, PRP treatment is being offered to consumers without regulatory oversight, clear guidelines for its preparation, or evidence for its efficacy. This review provides an overview of PRP and current available evidence for its clinical use. The review was constructed based on searches of PubMed as well as Google, a search engine that is easily accessible by consumers. The authors subsequently chose articles thought to be demonstrative of the breadth of evidence on PRP preparation, common applications, and regulation. PRP has promising therapeutic applications, however, there remains much to be learned about this new and increasingly popular product including indications for use, efficacy, and recommended composition and preparation methods. Standardization of operating procedures, research protocols, and data collection are needed to gather more evidence for all of its potential clinical applications. There is therefore a role for the transfusion medicine community to aid in establishing guidance for current practice to ensure safe, appropriate, and effective use.

**Keywords:** Platelet rich plasma (PRP); autologous blood products; injection therapy; regeneration; rejuvenation

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## Introduction

The science of blood transfusion has been documented as early as the 19th century when an obstetrician attempted vein to vein transfusions to treat postpartum hemorrhage (1). From vein to vein transfusions to collection of whole blood stored in glass bottles to the introduction of plastic storage bags, advances in blood transfusion have allowed fractionation of whole blood to component therapy. Transfusion medicine physicians, blood bank staff, and clinical providers are familiar with the collection, indications, and regulations surrounding the use of red blood cells, platelets, plasma, and cryoprecipitate. However, the larger medical community may be unfamiliar with another frequently administered blood product called platelet rich plasma (PRP). This review aims to break down the enigma of PRP and its associated research and selected applications.

## Methods

Articles on PRP were first published in the 1950s and a PubMed search reveals that there has been an exponential growth in interest and research in the past seven decades (*Figure 1*). Publications on PRP are available in almost every subspecialty of medicine and include original articles,

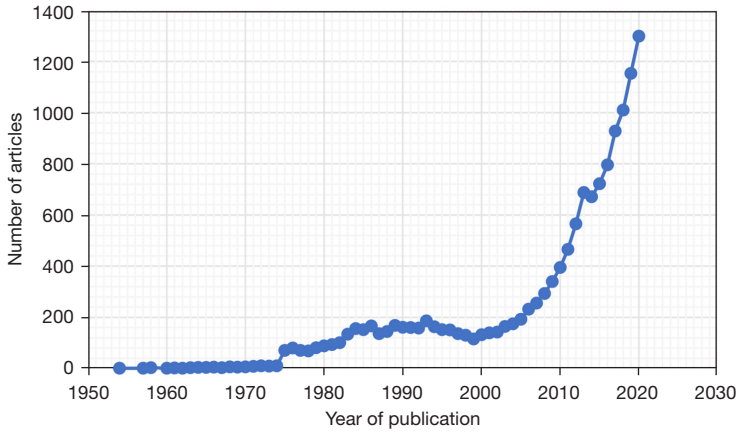


**Figure 1** Number of PubMed search results for "platelet rich plasma" from 1954 to 2020. Search conducted in August 2021.

systematic reviews, and meta-analyses. Select articles were chosen from the literature search and are reviewed here. Online searches of Google and Google Scholar were also performed to guide selected review of popular PRP treatments, as these are search engines that are readily accessible to consumers of PRP. Only English articles were included. The goal is to provide an overview of PRP composition and preparations, some current applications, gaps in knowledge, and areas for future investigation and development.

## Description

PRP consists of concentrated platelets suspended in plasma obtained through the centrifugation of anticoagulated whole blood. All PRP products, by definition, contain a higher platelet concentration than native blood. However, actual concentrations can range from 2 to 12 times baseline concentration with some studies identifying levels as low as 0.52 times baseline despite efforts to standardize preparation methods and protocols (2). There are over 40 commercial systems for PRP preparation aimed at collecting a product that has been hailed as a safe, autologous product with the potential to promote healing (3-5).

Platelets are complex non-nucleated cell fragments containing secretory granules that house multiple chemokines, adhesion molecules, and growth factors that aid in angiogenesis and recruitment of fibroblasts and other cells that are central to collagenesis and healing. These include vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and insulin-like growth factors I and II (IGF-I and IGF-II) (6-8). Upon activation, platelets will release almost all stored growth factors within 1 hour although continued growth factor synthesis will occur until platelet death at around 8 days (9).

PRP encompasses a heterogeneous group of products containing various levels of white blood cells (WBCs) and fibrin and can even be used to describe activation of these products with platelet activators such as thrombin, calcium chloride, or calcium gluconate. PRP can be collected as the serum and buffy coat layers on higher platelet count systems or as the non-cellular component layer using lower platelet count systems (10). This has led to the development of additional classification terminology with a spectrum of pure platelet-rich plasma (P-PRP), leukocyte- and platelet-rich plasma (L-PRP), pure platelet-rich fibrin (P-PRF), etc. (11). WBC content has been observed to vary across PRP preparation methods and the value of including WBCs in PRP formulations has been debated with some support for their role in platelet activation and cell signaling and simultaneous concern for resulting negative inflammatory reactions (12).

*In vitro* studies have shown activated PRP to release platelet-derived growth factor-AB (PDGF-AB) and transforming growth factor-β1 (TGF-β1) with associated heightened proliferation of stem cells and fibroblasts. Cell proliferation, however, varied with activated PRP dose and optimal dosing varied by cell type (13).

Graziani *et al.* [2006] identified the optimal concentration for *in vitro* fibroblast and osteoblast growth to be 2.5 times baseline concentration with adverse effects on proliferation at higher concentrations although this likely differs by product and application (14). Kakudo *et al.* [2008] observed

stimulation of human adipose-derived stem cells and human dermal fibroblast proliferation with 1% and 5% activated PRP with no benefit at the highest studied concentration of 20% (15). It therefore remains unclear whether higher platelet dosages translate into added clinical benefit (9).

Although deemed a safe and generally non-invasive intervention, some suggested contraindications to PRP therapy include platelet dysfunction or critical thrombocytopenia, hypofibroginemia, anticoagulation, hemodynamic instability, sepsis or infection, and chronic liver disease (16).

## Regulation

Unlike blood products that are stored within and distributed by the blood bank, PRP is usually not within the operational scope of most transfusion services. In the United States, PRP products are not regulated, rather, the biologics and medical devices (i.e., centrifuges) used to produce PRP are regulated separately by the Food and Drug Administration (FDA). PRP systems currently have 510(k) clearance based on approval of a predicate device for PRP. PRP was initially intended to be combined with bone graft material for improved handling with all other uses considered to be off-label at this time. Of note, clearance is not synonymous with approval and is not indication-specific (17). The current clearance status for PRP systems does not require clinical data as the autologous, homologous, and minimally manipulated nature of these products deem them low risk biologic products that do not require additional regulation by the FDA. In such a way, PRP products are exempt from quality and other control measures that are common for other biologic products, including its components of platelets and plasma (18-20).

## PRP applications

There has been increasing interest in PRP and its potential uses in the past several decades (*Figure 1*). The main investigated applications have been in the fields of dentistry, orthopedics, and aesthetics with numerous trials conducted for soft tissue injuries, arthritis, dermatologic conditions including scars, hair restoration, and breast augmentation. PRP has seen various administration routes ranging from gel forms applied topically to injections to the site of interest (21). Of note, some products designated as PRP may not meet established definitions (9). A review of all published applications is beyond the scope of the current review and several comprehensive reviews have been published elsewhere (5,22). A summary of orthopedic and cosmetic applications will be outlined to demonstrate the scope of PRP therapies and available data supporting these interventions.

### *Orthopedics and sports medicine*

Rachul *et al.* [2017] investigated media coverage of PRP and demonstrated that 70% were published in newspaper sports sections and over 75% were sports-related stories. Interestingly, of the articles studied, the majority framed PRP as a routine procedure as compared to an experimental therapy (23). Several reviews have been published outlining current data on the effectiveness of PRP for the management of orthopedic conditions including tendinopathy, muscle injury, and arthritis. PRP has been compared to surgical intervention, such as rotator cuff repair, injections (steroid, hyaluronic acid, saline), and physical therapy (17,21,24). These studies tend to use self-report measures such as the visual analogue scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), or other subjective scales that assess for pain and function (17,21,24,25). Return to sport has also been used to determine benefit of these treatments (17).

There has been some support for improvement of pain in lateral epicondylitis (also known as “tennis elbow”) but minimal support for benefit in other soft tissue injuries including chronic Achilles tendinopathy, rotator cuff injury, and anterior cruciate ligament injury (21). Furthermore, the mechanism for these effects has yet to be elucidated since there does not appear to be a correlation with platelet counts or VEGF, PDGF, and EGF levels (26). Jones *et al.* [2018] outlined relevant meta-analyses that have been published on musculoskeletal applications of PRP (17). There is some support for improved pain and function with PRP injections in osteoarthritis (OA) based on meta-analytical studies with more favorable results with knee, but not hip, OA but these trends have not been replicated in all analyses (17). These have shown modest benefits for some indications including tendon or ligament injuries and knee OA with undetermined clinical significance. Meta-analyses of mixed orthopedic injuries, including muscle injuries, have not found quality trials and even those that have been conducted have not shown benefit. Additionally, when some of these analyses excluded trials that were not blinded, purported benefits were no longer statistically significant. Setayesh *et al.*’s

 

2018 review supports the lack of convincing data on effectiveness of PRP therapy for muscle injury buntial improvement in return to sport (24).

### *Dermatology and plastic surgery*

Human studies have shown intradermal and subdermal injection of PRP matrix formed through activation of PRP with calcium chloride to increase angiogenesis, collagenesis, fibroblast activation, and adipocyte stimulation on skin biopsy in healthy volunteers (27). These have led to interest in the regenerative capabilities of PRP for cosmetic enhancements and therapeutic interventions such as skin rejuvenation, treatment of alopecia, scars, and striae distensae in the fields of dermatology and plastic surgery (5,22). PRP has been administered topically, as well as intradermally and many interventions include the addition of PRP to other dermatologic procedures such as microneedling or laser therapy (28-30). Outcome measures have included pathologic specimen evaluation, before and after photographic comparison, and split side controls to control for individual differences (22,26,31).

In efforts to counter the effects of aging and skin damage, the use of PRP with laser therapy have been shown to improve skin elasticity and reduce erythema (32). Similarly, studies have shown a synergistic effect of intradermal and topical PRP with fractional carbon dioxide laser therapy for acne scars (29,30). Beyond elective aesthetic enhancements, PRP has also been studied in hard-to-heal acute and chronic wounds. Dermatology and plastic surgery colleagues are often consulted for reconstructing non-healing wounds which may be a result of underlying diseases or surgery such as cutaneous ulcers and wound dehiscence. Carter *et al.* [2011] published a meta-analysis on PRP-containing gel on wound healing and found that many studies have found this topical form of PRP to be associated with improved wound healing and potentially reduced wound infection rates (33).

In the area of hair restoration, Takikawa *et al.* [2011] demonstrated improvement in hair growth following subcutaneous injection of PRP and potential accentuated effect when used in conjunction with dalteparin and ptomaine microparticle carriers (31). Rodrigues *et al.* [2018] also demonstrated improvement in male-pattern alopecia with PRP injection (26). In contrast, Marwah *et al.* [2014] demonstrated greater improvement in *subjective* rather than objective measures of hair restoration thereby recommending against use of PRP as stand-alone treatment (34).

Although these reviews demonstrate the promise of PRP in many dermatologic applications, the heterogeneity of studies leaves many questions unanswered.

## Controversies

Despite the accumulating body of research on PRP and its applications, the majority of studies are underpowered and unblinded and address efficacy in various ways. There is also a notable lack of standardization of instrumentation, platelet concentration, application methods, and control groups. Additionally, combination therapies such as radiofrequency, fat grafting, and laser therapy make it hard to determine the magnitude of benefit afforded by PRP, especially in studies with no control groups (22). Current trial data is mixed regarding effectiveness of PRP applications and the existing heterogeneity between studies further muddles interpretation of findings. Moreover, sources of variability in the final product can occur at the collection, processing, and administration stages (17).

There remains much to be elucidated about applications for PRP. This includes appropriate dosage, route of administration, and specific conditions for which PRP formulations may be beneficial. Castillo *et al.* [2011] showed a range of required starting whole blood volume from 18 to 55 mL to obtain approximately the same volume of PRP (6 to 7.5 mL) when comparing three commercial PRP systems (35). Further heterogeneity exists based on individual differences in platelet concentration and activity status of donor blood. Intra-individual variation has also been documented in samples obtained from the same individual at different time points despite consistent cell counts (12).

Although the low-risk designation of these products has exempted them from regulation thus far, the provision of therapies of unknown efficacy continues to have ethical and financial implications for patients. PRP treatment costs can vary widely with estimates of $500–$2,500 USD per treatment making PRP therapies more expensive than other evidence-based treatments such as steroid injections with costs often not covered by insurance (17,18). Reimbursement structure for these therapies has also not been delineated (18).

Although the majority of studies assessing efficacy have reported no adverse events, significant adverse events have resulted from PRP use in the clinical setting including transmission of HIV infection during treatment from unlicensed professionals without established universal

precautions to sterilize equipment and prevent the spread of blood-borne pathogens (36).

Ways to ensure efficacy and safety while prioritizing innovation, such as those being developed for regenerative medicine therapies, have been proposed and may be appropriate for the study and regulation of PRP (19). The AABB guidelines, as well as transfusion medicine expertise, would be valuable in assisting with standardization of processing and storage practices. Furthermore, clear discussion with patients about the lack of evidence for these therapies and the resulting lack of data on efficacy, procedure details and risks, and lack of guidelines on recommended frequency of administration are crucial components of informed consent for these therapies (20). Emphasis on adequate and standardized reporting of PRP characteristics as outlined by Fadadu *et al.* [2019] who describe minimal parameters of platelet concentration, relative concentration compared to whole blood, WBC concentration and differential, and growth factor concentrations, as well as specific procedures including baseline platelet count, centrifugal force and time, and use of activators are also necessary to ensure useful data collection that can be used to guide future use (3).

## Conclusions

The use of PRP is pervasive in academic and community practice, and often without involvement of transfusion medicine or laboratory services. Some studies show promise but further investigation into the precise mechanisms of PRP activity and its effects is warranted. Being an autologous product, PRP has a favorable safety profile but it deserves further research with oversight, standardization, and quality control to fortify evidence of any potential benefits or lack thereof. This is an opportunity for transfusion or laboratory medicine specialists to engage with colleagues who want to perform research or administer PRP to ensure patient safety and benefit, as well as prevent harm.

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