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Medical Policy Manual Medicine, Policy No. 77

Autologous Blood-Derived Growth Factors as a Treatment for Wound Healing and Other Miscellaneous Conditions

Effective: January 1, 2025

Next Review: October 2025
Last Review: November2024

DESCRIPTION

Blood-derived growth factors are intended to improve healing of various wounds or surgical sites.

MEDICAL POLICY CRITERIA

Note: This policy is not intended to address Regranex® (becaplermin gel), which is not an autologous platelet-derived growth factor.

Autologous blood-derived growth factors (i.e., platelet rich plasma) are considered **investigational** for all indications including but not limited to:

A. Wounds, including but not limited to:
   1. Acute traumatic or surgical wounds
   2. Chronic non-healing wounds
B. Disorders of joint structures, including but not limited to the following:
   1. Achilles tendinopathy
   2. Degenerative disorders of the joint, including but not limited to cartilage

lesions

3. Dupuytren's contracture
4. Lateral epicondylitis (e.g., tennis elbow, elbow epicondylar tendinosis)
5. Osteoarthritis
6. Patellar tendinosis (jumper's knee)
7. Tendinopathy
8. Traumatic joint injury (e.g., hip fracture, long-bone fracture)

C. Plantar fasciitis

D. As an adjunct to surgical procedures, including but not limited to:

1. Spinal fusion
2. Sinus surgery
3. Maxillofacial and periodontal surgery
4. Arthroplasty (e.g., rotator cuff repair, repair of structures of the knee)
5. Subacromial decompression surgery

E. Injection of ligament tears with any type of blood-derived growth factor, whether from the patient or another source

F. Ophthalmologic conditions or procedures

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Stem-cell Therapy for Peripheral Arterial Disease, Medicine, Policy No. 141
2. Orthopedic Applications of Stem-Cell Therapy, Including Bone Substitutes Used with Autologous Bone Marrow, Medicine, Policy No. 142

BACKGROUND

A variety of growth factors have been found to play a role in wound healing, including platelet-derived growth factors (PDGFs), epidermal growth factor, fibroblast growth factors, transforming growth factors, and insulin-like growth factors. Topically applied autologous PDGFs have been most extensively investigated for clinical use in wound healing. For example, platelets are a rich source of PDGFs, transforming growth factors (which function as a mitogen for fibroblasts, smooth muscle cells, and osteoblasts) and vascular endothelial growth factors.

Autologous platelet concentrate suspended in plasma, also known as platelet-rich plasma (PRP) or buffy coat, can be prepared from samples of centrifuged autologous blood. Exposure to a solution of thrombin and calcium chloride degranulates platelets, releasing the various growth factors. The polymerization of fibrin from fibrinogen creates a platelet gel, which can then be used as an adjunct to surgery with the intent of promoting hemostasis and accelerating healing. In the operating room setting, PRP has been investigated as an adjunct to a variety of periodontal, reconstructive, and orthopedic procedures. For example, bone morphogenetic proteins are a type of transforming growth factors, and thus PRP has been used in conjunction with bone-replacement grafting (using either autologous grafts or bovine-derived xenograft) in periodontal and maxillofacial surgeries. Alternatively, PRP may be injected directly into various tissues. PRP injections have been proposed as a primary treatment of miscellaneous conditions such as epicondylitis, plantar fasciitis, and Dupuytren contracture.

PRP must be distinguished from fibrin glues or sealants, which have been used for many years as a surgical adjunct to promote local hemostasis at incision sites. Autologous fibrin glue or sealants can be created from platelet-poor plasma and consists primarily of fibrinogen. Commercial fibrin glues are created from pooled homologous human donors; Tisseel I® (Baxter) and Evicel® (Omrix) are examples of commercially available fibrin sealants. This policy does not address the use of fibrin sealants.

REGULATORY STATUS

The U.S. Food and Drug Administration (FDA) regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1270 and 1271. Blood products such as PRP are included in these regulations. Under these regulations, certain products including blood products such as PRP are exempt and therefore do not follow the traditional FDA regulatory pathway. To date, FDA has not attempted to regulate activated PRP.

A number of PRP preparation systems are available, many of which were cleared for marketing by FDA through the 510(k) process for producing platelet-rich preparations intended to be mixed with bone graft materials to enhance the bone grafting properties in orthopedic practices. The use of PRP outside of this setting (e.g., an office injection) would be considered off-label.

Examples of PRP preparation services/systems include, but are not limited to:

- The 3C patch system, which according to the FDA is used at the point-of-care for the safe and rapid preparation of PRP gel from a small sample of a patient's own peripheral blood. Then, the PRP gel is topically applied to exuding cutaneous wounds, such as leg, pressure, and diabetic or surgically-debrided wounds.
- Aurix™ (Nuo Therapeutics) (previously AutoloGel™, Cytomedix) and SafeBlood® (SafeBlood Technologies) that are two related but distinct autologous blood-derived preparations that can be prepared at the bedside for immediate application. Both Aurix™ and SafeBlood® have been specifically marketed for wound healing.
- Some devices may be used in the operating room setting, such as Medtronic Electromedic, Elmd-500 Autotransfusion system, the Plasma Saver device, or the Smart PreP device.
- The Magellan® Autologous Platelet Separator System (Medtronic) includes a disposables kit designed for use with the Magellan Autologous Platelet Separator portable tabletop centrifuge.
- BioMet Biologics received marketing clearance through the FDA's 510(k) process for a gravitational platelet separation system (GPS®II), which uses a disposable separation tube for centrifugation and a dual cannula tip to mix the platelets and thrombin at the surgical site.
- The Jen Device (DSM Biomedical) is a compact centrifugal-based system for rapid preparation of PRP from small samples.

- The Amicus Separator System (Fresenius Kabi USA LLC) is a continuous-flow, centrifugal device that draws whole blood, separates the blood into its components, and collects the component of interest. Filtration or plasmapheresis may also be used to produce platelet-rich concentrates.

The use of different devices and procedures can lead to variable concentrations of active platelets and associated proteins, increasing variability between studies of clinical efficacy.

EVIDENCE SUMMARY

The focus of the literature appraisal below is on evidence from randomized controlled trials (RCTs) and systematic reviews.

FORMULA PREPARATION

Several articles described different methods of preparation of autologous PRP and noted variability in platelet concentration and viability depending on the preparation.[1-6] The clinical significance of these differences is unclear.

WOUND HEALING

ACUTE WOUNDS

Systematic Reviews

Imam (2023) published a meta-analysis of 13 comparative studies, including 808 individuals with burn wounds who were treated with PRP (n=413) or standard wound therapy (n=395) with sample sizes ranging from 25 to 100 participants.[7] PRP had a shorter healing time compared to standard therapy (mean difference [MD], -5.80; 95% CI, -7.73 to -3.88; p<0.001) as well as a higher healing rate (OR, 3.14; 95% CI, 2.05 to 4.8; p<0.001) although these pooled estimates had substantial (I^2=93%) and moderate heterogeneity (I^2=42%), respectively. Individuals treated with PRP also had a higher percentage of graft take area (MD, 4.39; 95% CI, 1.51 to 7.26; p<0.001) and a higher percentage of area healed (MD, 12.67; 95% CI, 9.79 to 15.55, p<0.001) compared to standard therapy for burn wounds with a low level of heterogeneity. No differences were observed in the graft take ratio or infection rates which showed low heterogeneity across studies in the pooled estimates. Interpretation of results is limited by risks of bias arising from low overall study quality, small study sizes, heterogenous PRP preparations, limited number of studies included for some comparisons, and short follow-up durations.

Zhu (2023) published a meta-analysis of the effect of PRP on sternal wound healing.[8] 11 studies of 8,961 cardiac surgery patients were included. Patients were either treated with PRP (n=3,663) or control therapies (n=5,298), with sample sizes ranging from 44 to 2000 participants. PRP was found to have a significantly lower rate of sternal wound infection (odds ratio [OR], 0.11; 95% CI, 0.03 to 0.34; p<0.001; I^2, 0%), deep sternal wound infection (OR, 0.29; 95% CI, 0.16 to 0.51; p<0.001; I^2, 32%) and superficial sternal wound infection (OR, 0.20; 95% CI, 0.13 to 0.33; p<0.001; I^2, 0%) compared to patients in the control cardiac surgery groups. The poor quality of included studies, heterogeneous PRP preparations, and heterogeneous cardiac surgeries limit interpretation of the results.

A systematic review by Yao (2020) examined the use of PRP on sternal wounds following cardiac surgery, with a focus on the development of infection.[9] Ten studies (total n=7,879) were included in the review. A meta-analysis of data from retrospective cohort studies showed a lower incidence of infection with PRP compared with control treatment, however no such difference was seen when only RCTs were included in the analysis.

Wang (2014) published a systematic review that evaluated the efficacy of PRP in treatment of acute wounds and included 13 studies (n=982).[10] Wound healing time was shorter in the PRP treated patients compared to the control group, as was the length of hospital stay (MD -1.45, 95% confidence interval [CI] -2.07 to -0.83, p<0.01). Post-traumatic pain level of the PRP group was lower than that of control group (MD -1.26, 95% CI -1.71 to -0.82, p<0.01). Although PRP treatment appears to be beneficial, the evidence remains insufficient to permit conclusions concerning its use as a primary treatment.

Randomized Controlled Trials

Huang (2021) published a meta-analysis of eight RCTs representing 539 patients with burn wounds.[11] The healing rate of burn wounds was improved with PRP (odds ratio 4.43, 95% CI 2.13 to 9.22), yielding a significantly shorter wound healing time (odds ratio -4.23, 95% CI -5.48 to -2.98) compared to conventional dressings for both superficial and deep burn groups. Incidence of adverse events, pain scores, and scar scores was also all improved in the PRP treatment group. Interpretation of results is limited by risks of bias arising from lack of blinding, small study size, heterogenous PRP preparations, and short follow-up durations.

Yeung (2018) performed a prospective RCT to test the efficacy of lyophilized PRP powder (LPRP) on the healing rate of wounds in patients with deep, second-degree burn injuries in comparison with a control group using a placebo.[12] LPRP was dissolved in a solution and applied on deep second-degree burn wounds once per day for four consecutive days. 27 patients with deep second-degree burns were recruited and then those that met eligibility criteria were randomized into two groups. The LRPR group received the intervention (n=15), and the control group received a placebo application (n=12). A concentration of 1.0×10^7 platelets/cm^2 (wound area) was sprayed on the wound evenly. Function was assessed by the percentage of wound closure and bacteria picking out rate at weeks two and three. The mean burn area of control for the LPRP was 75.65 ± 50.72 cm^2 and 99.73 ± 70.17 cm^2 (p=0.013), respectively. In the control group, the original wound area was 25.49 cm^2 at baseline, 23.79 cm^2 (6.67% healed) at week two, and 4.34 cm^2 (86.40% healed) at week three. In the LPRP group, the original wound area was 84.36 cm^2, followed by 23.96 cm^2 (71.59% healed) at week two, and 0.63 cm^2 (99.24% healed) at week three. The wound closure rate at week two in the LPRP group reached nearly 80% and was greater than 90% by week three, showing a significant difference (p<0.05). Alternatively, in the control group, the wound closure rates were 60% and 80% in two and three weeks, respectively. The postoperative infection rate in the LPRP (26.67%) was lower than the control group (33.33%). Neither was significant, statistically.

Marck (2016) reported on a randomized, double-blind, within-patient controlled study in patients with deep dermal to full thickness burns undergoing split skin graft, comparing PRP with usual care.[13] The study randomized 52 patients, 50 of whom received the allocated PRP intervention. There were no significant differences in short term (five to seven days) rates in graft take in the intervention and control areas on each patient. At three, six, and 12 months, there were no significant differences in skin appearance or epithelialization scores.

MULTIPLE TYPES OF WOUNDS

Systematic Reviews

An industry-funded systematic review included 21 studies on PRP gel for cutaneous wound healing, 12 of which were RCTs.[14] There were three main types of wounds, including open chronic wounds, acute surgical wounds with primary closure, and acute surgical wound with secondary closure. Study quality was found to vary considerably, with three studies rated as high quality and six rated as poor quality. The primary outcome measure for this meta-analysis was complete wound healing. Overall, results from the RCTs were mixed, i.e., some trials reported a benefit, but others did not. Of the two RCTs included for acute primary wound closures, one RCT detected a statistically significant difference in complete wound healing for PRP compared to no topical treatment during a short two-week follow-up, but the other RCT found no difference between treatment and control at day 50. There were two RCTs included that addressed acute secondary closure wounds. The PRP group healing rates and wound area and volume reductions were statistically significant compared to controls for both studies.

Randomized Controlled Trials

No published RCTs were identified after the above review.

CHRONIC WOUNDS

Systematic Reviews

A number of systematic reviews of the evidence on PRP have been published. These reviews are heterogenous in whether they pooled data from studies reflecting a variety of wound types[15-18] or focused on specific wound types, primarily diabetic foot ulcers.[19-21]

Deng (2023) published a systematic review with meta-analysis that assessed 22 RCTs (n=1,559) to determine the safety and efficacy of PRP to treat diabetic foot ulcers.[22] PRP significantly increased the overall healing rate of diabetic foot ulcers compared with standard treatment (risk ratio [RR]=1.42; 95% CI: 1.30 to 1.56; p<0.001; I^2=55%). PRP reduced the complete wound healing time of diabetic foot ulcers compared to conventional treatment (MD=-3.13; 95% CI: -5.86 to -0.39; p<0.001; I^2=97.5%) and resulted in a greater reduction in diabetic foot ulcer area (MD=1.02; 95% CI: 0.51 to 1.53; p<0.001; I^2=36%). Amputation rate, reported by three trials, was significantly reduced for the autologous PRP group (RR=0.35; 95% CI, 0.15 to 0.83; p<0.001; I^2=0%). Four studies reported adverse events, and pooled analysis revealed a similar rate of events between the PRP and control groups (RR=0.96; 95% CI, 0.57 to 1.61; p>0.05; 35%). The authors reported no significant publication bias; however, a sensitivity analysis suggested that the pooled outcome assessment for time to wound healing may be affected by considerable inter-study variability. The low number of high-quality of studies available on PRP for diabetic foot ulcers and the low number of studies reporting some outcomes of interest were limitations of this meta-analysis.

Fang (2023) published a meta-analysis of six studies of patients treated with PRP for lower extremity venous ulcers.[23] 294 patients were included, with 148 patients in the PRP group and 146 in the control group. PRP was found to have a greater reduction in elliptical area at the end of treatment compared to the control group (MD=-1.19; 95% CI, -1.8 to -0.058; p=0.0001). The healing rate also favored PRP over the control group (RR=5.73; 95% CI, 3.29 to 9.99; p<0.00001). The reviewers rated evidence quality as moderate. The reviewers suggested that there may be publication bias for both elliptical area at the end of treatment and healing rate.

The Agency for Healthcare Research and Quality (AHRQ) (2020) published a Technology Assessment on Platelet-Rich Plasma for Wound Care in the Medicare Population.[21] This Technology Assessment was requested by the Centers for Medicare & Medicaid Services to inform reconsideration of a National Coverage Decision on autologous blood-derived products for chronic non-healing wounds. The authors, who additionally published a separate systematic review,[24] evaluated evidence in lower extremity diabetic ulcers, lower extremity venous ulcers, and pressure ulcers. Separate meta-analyses were conducted for each wound type. Here the focus is on findings for lower extremity diabetic ulcers and those for the other populations are discussed below. Risk of bias of individual studies was assessed using the Cochrane Collaboration's Risk of Bias 2 tool and rated high in eight RCTs (57.14%), moderate in six RCTs (42.86%) and high in the one observational study (100%). Strength of the body of evidence was rated based on the Evidence-based Practice Center methods guide. The findings of this Technology Assessment indicated that there is moderate-strength evidence that PRP modestly increases complete wound closure and low-strength evidence that PRP may shorten time to wound closure (meta-analysis not feasible). However, due to risk of bias and severe imprecision, evidence is insufficient to draw conclusions about other important outcomes, including wound infection, amputation, pain reduction, and wound recurrence. Important limitations of the literature were described as "inadequate description of offloading and wound care procedures, wound characteristics, PRP formulation techniques, concentration and volume; inadequate length of follow-up, and lack of stratification by comorbidities and other patient characteristics, such as diabetes control, vascular perfusion, and under representation of older adults."

The AHRQ (2020) Technology Assessment on Platelet-Rich Plasma for Wound Care in the Medicare Population described above also evaluated evidence on use of PRP in individuals with lower extremity venous ulcers and individuals with pressure ulcers.[21] For individuals with lower extremity venous ulcers, the evidence included eight RCTs and three observational studies (total n=615). The majority compared PRP to management without PRP. Risk of bias was described as moderate due to randomization and outcome measurement limitations. There were no significant differences between PRP versus management without PRP in complete wound closure (RR 1.49, 95% CI 0.72 to 3.06, five studies, n=250, I^2=29.4%), wound recurrence (RR 0.38, 95% CI 0.09 to 1.57), wound infection (RR 0.79, 95% CI 0.22 to 2.81), or quality of life as measured by the Chronic Lower Limb Venous Insufficiency Questionnaire (weighted MD 10.99, 95% CI -50.5 to 72.5). For the outcomes time to complete wound closure and pain, meta-analysis of two studies was not possible due to insufficient data and findings were mixed between studies on both outcomes. The strength of evidence was rated as 'insufficient' to draw conclusions on all outcomes.

For individuals with pressure ulcers, the AHRQ Technology Assessment (2020)[21] included one RCT and one comparative observational study (total n not reported). The comparator was serum physiological dressing in the RCT and saline dressing in the observational study. Risk of bias of the primary studies was described as moderate, due to limitations in the randomization process and outcome measurement, deviations from intended interventions, and selective outcome reporting. Although both studies found that PRP significantly reduced wound size (strength of evidence=insufficient), neither study evaluated other important outcomes, such as complete wound closure.

Oliveira (2020) also conducted a meta-analysis of cost and effectiveness of studies of PRP for venous ulcers.[25] Based on fewer studies identified from searches only through July 2018, although their findings indicated greater reductions in wound area for PRP, findings were consistent with the ARHQ review in finding no significant difference in complete wound closure (RR 2.54, 95% CI 0.42 to 15.30, four studies, n=156, I^2=69%).

A 2012 Cochrane systematic review included nine RCTs (n=325) on PRP for treating chronic wounds.[16] This review was restricted to studies where PRP was compared with no additional treatment or placebo. Four RCTs included patients with mixed chronic wounds, three included patients with venous leg ulcers, and two RCTs included patients with diabetic foot ulcers. Only one study was considered to be at low risk of bias. After a median treatment time of 12 weeks, there was no significant difference between the PRP and control groups in complete healing of diabetic foot ulcers, venous leg ulcers, or mixed chronic wounds. There was no significant difference in the area epithelialized in three RCTs of mixed chronic wounds. In two RCTs of mixed chronic wounds, there was a significant difference favoring PRP in the wound area that was healed. The two RCTs addressing diabetic foot ulcers utilized two different FDA-approved methods to administer PRP: the Gravitational Platelet Separation System (GPS, Biomet)[26] and Aurix™ (Nuo Therapeutics) (previously AutoloGel™, Cytomedix).[27] The Driver study was a prospective multi-center RCT including 129 patients that were randomized to standard care with PRP or control (saline-gel) dressing for 12 weeks. The group reported that there were significantly more wounds healed by PRP than control treatment (81.3% vs. 42.1%, p=0.036) and time-to-healing was significantly different between groups (p=0.0177). There were several limitations of this study including a significant difference in wound area at baseline between groups and high number of patient exclusions (32 out of 70) due to protocol violations and failure to complete treatment. This study was also determined as having a high risk of bias, in part due to selective reporting. The Cochrane review concluded that there is no current evidence to suggest that autologous PRP is of value for treating chronic wounds.

This Cochrane review was updated in 2016; it added a new RCT, for a total of 10 RCTs (total n=442 patients).[17] Conclusions about the quality of the overall body of evidence were similar to the 2012 review. For the outcome of overall wound healing, autologous PRP did not significantly increase healing compared with standard treatment (RR 1.19, 95% CI 0.95 to 1.50, I^2=27%, low-quality evidence). For wound healing in foot ulcers in people with diabetes, the evidence suggested that autologous PRP might increase healing compared with standard care (RR 1.22, 95% CI 1.01 to 1.49, I^2=0%, low-quality evidence). It was unclear whether autologous PRP increased wound healing compared with standard care for venous leg ulcers (RR 1.05, 95% CI 0.29 to 3.88, I^2=0%, low-quality evidence).

A meta-analysis by del Pino-Sedeño (2019) assessed eight RCTs and two longitudinal-observational studies (total n=525) to determine the safety and efficacy of PRP to treat diabetic foot ulcers.[19] Results indicated PRP significantly increased chronic wound healing compared with standard treatment (RR 1.41, 95% CI 1.08 to 1.84, p=0.01, I^2=51%). Subgroup analysis showed that PRP source affected the proportion of completely healed diabetic foot ulcers (autologous RR 1.21, 95% CI 1.04 to 1.42, p=0.02; allogenic RR 3.20, 95% CI 1.14 to 9.03, p=0.03). PRP preparation method also influenced healing (homemade RR 1.22, 95% CI 1.04 to 1.44, p=0.02; commercial protocol RR 1.13, 95% CI 0.58 to 2.20, p=0.71; blood bank RR 3.20, 95% CI 1.14 to 9.03, p=0.03). The two trials that reported mean time for complete wound healing showed that PRP resulted in quicker healing (MD -11.18 days, 95% CI -20.69 to -1.68, p=0.02, I^2=53%). Overall, the studies reported no significant differences in rates of wound complications or dermatitis, and rates of recurrences were similar between PRP and standard treatment. The authors noted, however, that results of their analysis should be interpreted cautiously because no statistical differences were found in the epithelialized area before and after wound treatment (MD 0.70 cm^2, 95% CI -0.96 to 2.35, p=0.41, I^2=70%). This study was limited by the low number and quality of studies available on PRP for diabetic foot ulcers. Similar results were seen in a meta-analysis by Dai (2020).[28]

A meta-analysis by Li (2019) assessed the efficacy and safety of autologous platelet-rich gel (APG) for topical treatment of diabetic chronic cutaneous ulcers.[20] Their analysis included 15 RCTs with 829 patients. Results indicated that autologous platelet-rich gel had a significant positive effect on healing rate, shorter healing time, and lower risk of infection than conventional treatment. Autologous platelet-rich gel also had a significantly lower incidence of infection when compared with conventional treatment (odds ratio 0.34, 95% CI 0.15 to 0.77, p=0.009). This meta-analysis was limited by a high or unclear risk of bias among the trials, which may indicate the trials were underpowered. Also, some studies had small sample sizes and limited outcome information. Finally, most of the trials were 8 to 12 weeks long and others only two to five weeks, making it difficult to analyze the relationship of time of observation to ulcer healing.

An industry-funded systematic review on PRP gel for cutaneous wound healing (described above), included four RCTs that evaluated complete healing of chronic wounds.[14] Two reported a statistically significant benefit for PRP, and meta-analysis of the four RCTs showed a significant combined effect of PRP for complete healing of chronic wounds. However, two of the four studies were rated as low quality and the other two could not be rated because they were presented only in abstract or letter form. The meta-analysis of the effect of PRP on complete wound healing of chronic wounds was limited by the inclusion of poor-quality studies. There were no high-quality RCTs that showed an improvement in complete healing with PRP.

A 2009 systematic review identified 42 controlled trials on PRP; 20 of these were RCTs and were included in the review.[15] The 20 RCTs included 11 studies on oral and maxillofacial surgery, seven on chronic skin ulcers, and two on surgery wounds. The authors concluded that PRP improved the gingival recession but not the clinical attachment level in chronic periodontitis. Results were inconclusive for the healing of skin ulcers, and there were little safety data. Non-randomized controlled studies were identified but not reviewed for chronic elbow tendinosis, muscle strains, lumbar spinal fusions, and other orthopedic procedures.

Randomized Controlled Trials

Shehab (2023) conducted an RCT of adjunct PRP in addition to compression therapy in individuals with post-phlebitic venous ulcers.[29] Forty patients were randomized to either PRP and compression therapy or placebo and compression therapy. The median number of treatments was six (range three to six). Both participants and outcome assessors were blinded to treatment allocation. The primary outcome, median ulcer surface area, was significantly lower for the PRP group (4 cm^2 versus 10 cm^2; p=0.036) as well as the median volume of ulcers (1 cm^3 versus 3 cm^3; p=0.008). This translated to individuals in the PRP group experiencing a larger drop in ulcer area (74% versus 40%; p=0.008) and volume (81% versus 48%; p=0.013) compared to placebo. Differences in VAS pain scores were observed in favor of the PRP group at both the three-month and six-month follow-ups. Nine patients in the PRP group had complete wound healing, but the authors did not report the rate of complete healing in the control group, and healing time and recurrence were not reported. This study is limited by small sample size.

Hossam (2022) published an RCT that assessed PRP versus standard wound care in healing non-ischemic diabetic foot ulcers.[30] Patients were randomized to receive either PRP injection in the healing edge and the floor of the targeted diabetic foot ulcer or usual standard care with moist dressing with or without collagenase ointment. Total ulcer surface area was calculated in both groups before treatment, immediately after treatment, and every week up to 12 weeks. Study authors found accelerated rates of ulcer area reduction and decreased incidence of wound infections with PRP treatment; however, the difference in the percentage of healed surface between groups lost statistical significance at six, seven, and, eight weeks follow-up. It is unclear whether complete wound healing was achieved in either group.

An RCT by Gupta (2021) of PRP dressing with total-contact casting compared to standard saline dressing for diabetic foot ulcers did not find significant differences in rates of ulcer area reduction or absolute ulcer area reduction between groups over the six-week study period.[31]An RCT of PRP for chronic wounds, by Saha (2020), was published subsequent to the AHRQ review (2020).[32] This single-center, observer-blinded RCT compared PRP plus total contact casting to PRP alone in 118 individuals with trophic ulcers secondary to leprosy. Analyses included 91.5% (n=108) of randomized individuals. Participants were mostly males in their late 40s with trophic ulcer duration of 13.4 months. Reduction in ulcer surface area, the primary outcome, was significantly greater for the PRP group from the first week (38.96% vs 12.46%, p<0.001) through the fifth (and last) week of follow-up (91.10% vs 79.77%, p<0.001). However, healing time and recurrence were not reported and there was no significant difference in complete healing rate.

NONSURGICAL TREATMENT FOR MUSCULOSKELETAL DISORDERS

MUSCULOSKELETAL SOFT TISSUE INJURIES

Systematic Reviews

Masiello (2023) conducted a systematic review and meta-analysis of 33 RCTs (n=2,025) that compared ultrasound-guided PRP injection to control (injection of steroids, saline, autologous whole blood, mesenchymal stem cells, or local anesthetic; dry needling; prolotherapy; or other non-injection intervention) for the treatment of tendinopathy.[33] Tendinopathies included lateral epicondylitis (n=8), plantar fasciitis (n=5), Achilles tendinopathy (n=5), rotator cuff tendinopathy (n=7), patellar tendinopathy (n=3), and carpal tunnel syndrome (n=3). Most trials (n=20) administered PRP as a single injection, but up to four injections were administered in some trials. Few differences in efficacy between control and PRP were found, with the exception of carpal tunnel patients, in whom pain and severity scores were reduced in the short and medium term. Overall mean differences in pain scores were: -0.24 (95% CI, -0.73 to 0.25) for lateral epicondylitis, -3.62 (95% CI, -8.16 to 0.91) for plantar fasciitis, -0.17 (95% CI, -4.25 to 3.90) for Achilles tendinopathy, 0.16 (95% CI, -0.18 to 0.50) for rotator cuff tendinopathy, 0.17 (95% CI, -0.64 to 0.98) for patellar tendinopathy, and -0.24 (95% CI, -0.32 to -0.16) for carpal tunnel syndrome. The evidence was rated as low quality due to risk of bias, imprecision, and inconsistency.

A 2016 health technology review on PRP and autologous blood injections (ABI) was completed by the Washington State Health Care Authority (WSHCA).[34] This review included an assessment of PRP in the treatment of acute muscle injuries. There were four RCTs assessed, one at low risk of bias, two at moderately low risk of bias, and one at moderately high risk of bias. The authors concluded:

> “With respect to primary outcomes, there was low quality evidence of no difference in pain scores between groups (three RCTs); short-term function was better with PRP plus CC [conservative care] compared with CC alone (one

> RCT), however the quality of evidence was insufficient. In the intermediate-term, there was low quality evidence of no difference between PRP plus CC versus saline plus CC in function and pain scores (one RCT each)." … "With respect to secondary outcomes, short-term return to sport results were mixed, with two studies finding better results with PRP plus CC and one finding no difference between groups. One trial reported no difference between groups in short-term recovery and patient satisfaction as well as in intermediate-term symptoms, health-related quality of life, and return to sport. There were no differences between groups in re-injury rates in the short- (two RCTs), intermediate- (one RCT), or long-term (one RCT)."

The WSHCA health technology assessment of PRP identified two RCTs that compared PRP to conservative treatment (dry needling or extracorporeal shockwave therapy) for patellar tendinopathy.[34] One trial was found to be at a moderately low risk of bias and one was found to be at a moderately high risk of bias. The review authors reported no difference between groups for the short-term primary outcome pain and function scores in both trials, based on low quality evidence, and insufficient evidence for intermediate- and long-term primary outcomes.

This health technology assessment also evaluated two small RCTs that compared PRP to a conservative control (saline injection or exercise) in patients with Achilles tendinopathy.[34] The primary outcome of these studies was the Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire evaluating pain score and activity level. One trial, determined to have a low-risk of bias, compared PRP to saline injections in 54 patients, with all patients also participating in a rehabilitation program.[35, 36] No participants were lost to follow-up. The authors found no difference in VISA-A scores between the two groups at six-weeks, six-months, and 12-months follow-up. Return to sports was also similar between groups at six- and 12-months follow-up. The other trial, determined to have a moderately high risk of bias, compared PRP to a 12-week exercise program in a group of 20 patients.[37] This trial also found no significant differences in short-term, intermediate-term, or long-term VISA-A scores. A pooled analysis also showed no significant difference between PRP and controls.

Muthu (2022) conducted a systematic review with meta-analysis of RCTs comparing PRP, autologous blood, corticosteroids, local anesthetics, laser therapy, and surgery for patients with lateral epicondylitis.[38] A total of 25 trials met the eligibility criteria (n=2,040). Results demonstrated that based on data from 22 trials, only leukocyte-rich PRP significantly improved visual analog scale (VAS) pain scores compared to saline control (weighted MD -14.8, 95% CI -23.18 to -6.39); in a subgroup analysis of 14 studies with at least 12 months of follow up, the weighted MD did not reach statistical significance (-7.69, 95% CI -27.28 to 11.90). Based on data from 11 trials, none of the interventions were superior to saline control for improvement in the Disabilities of the Arm, Shoulder and Hand (DASH) score. Treatment ranking based on the P-score approach demonstrated that leukocyte-rich PRP was most likely to be the best treatment amongst autologous blood, corticosteroids, laser therapy, local anesthetics, and leukocyte-poor PRP.

Dai (2021) conducted a systematic review and meta-analysis of RCTs evaluating PRP versus control (saline injection, dry needling, or no treatment) for the treatment of tendinopathy.[39] A total of 13 trials met the eligibility criteria and included patients with lateral epicondylitis (five RCTs), Achilles tendinopathy (four RCTs), rotator cuff tendinopathy (two RCTs), and patellar tendinopathy (two RCTs). Among the 13 RCTs, seven studies were judged to be at low risk of bias and six were found to have a high risk of bias. The meta-analysis demonstrated that PRP was not superior to control for the primary outcomes of change in pain intensity or function at 12 weeks; these trends also persisted at 24 weeks. The authors noted that included trials displayed significant heterogeneity with respect to PRP preparation and patient characteristics, and had important methodological limitations.

Miller (2017) conducted a systematic review and meta-analysis on PRP for symptomatic tendinopathy and included only RCTs with injection controls.[40] The literature search, conducted through November 2016, identified 16 RCTs with 18 groups (some studies included more than one tendinopathy site) for inclusion (total n=1,018 patients). The Cochrane Collaboration tool was used to assess the risk of bias: five studies had an uncertain risk of bias, and 11 studies had a high risk of bias. The median sample size was 35 patients. Tendinopathy sites were lateral epicondylar (12 groups), rotator cuff (three groups), Achilles (two groups), and patellar (one group). Preparation of PRP differed across trials as did the number of injections, with most studies administering one injection and a few administering two injections. Eight of the 18 groups reported statistically significant lower pain scores using PRP compared with control and the other ten reported no differences in pain scores between trial arms. A meta-analysis reported a standardized mean difference (SMD) in pain scores favoring PRP over control (0.47, 95% CI 0.21 to 0.72, I^2=67%).

Fitzpatrick (2016) published a systematic review that assessed the use of PRP for tendinopathy and included 18 RCTs, eight of which were determined to be at low risk of bias.[41] After performing a meta-analysis, the authors concluded that there was "good evidence to support the use of a single injection of [leukocyte-rich] PRP under ultrasound guidance in tendinopathy" and that both "the preparation and intratendinous injection technique of PRP appear to be of great clinical significance." However, there were substantial limitations this analysis. Chiefly, PRP was not directly compared to the control treatment, and instead, improvement from baseline was assessed. Therefore, the placebo effect, along with the expected improvement in untreated patients were not accounted for.

Tsikopoulos (2016) published a meta-analysis of PRP compared with placebo or dry needling in patients with tendinopathy lasting at least six weeks.[42] Minimum length of follow-up was six months. The primary outcome of interest was pain intensity and functional disability was a secondary outcome. Five RCTs met the review's eligibility criteria. Two RCTs addressed lateral epicondylitis, two rotator cuff tendinopathy, and two patellar tendinopathy. Three studies had a saline control group and two compared PRP with dry needling. In a pooled analysis of all five trials, there was no statistically significant difference in pain intensity at two to three months with PRP or placebo/dry needling (SMD -0.29, 95% CI -0.60 to 0.02). The between-groups difference in pain intensity was statistically significant at six months in a pooled analysis of the four studies reporting this outcome (SMD -0.48, 95% CI -0.86 to -0.10). The authors noted that the difference between groups in pain relief at six months was not clinically significant. Three studies reported functional disability levels at three months and a meta-analysis of these studies found significantly greater decrease in function in the PRP group (SMD -0.47, 95% CI -0.85 to -0.09). Functional disability six months postintervention was not addressed in this review.

Balasubramaniam (2015) published a systematic review that included RCTs on PRP for tendinopathy.[43] In contrast to the Tsikopoulos (2016) review, the authors did not limit study inclusion criteria by type of control intervention or postintervention length of follow-up. The authors included four of the five RCTs in the Tsikopoulos (2016) review and five additional RCTs (total of nine). There were four trials on epicondylitis, on rotator cuff tendinopathy, two on patellar tendinopathy, and one on Achilles tendinopathy. Comparison interventions included placebo (three studies), dry needling (two studies), ABI (two studies), extracorporeal shock wave therapy (one study), corticosteroid injections (two studies) (One study included both placebo and corticosteroid control groups). The authors did not pool study findings due to a high level of heterogeneity among studies. In their qualitative analysis of the literature by anatomic site of tendinopathy, they concluded that one study on PRP for Achilles tendinopathy was insufficient to draw conclusions about efficacy. Findings of studies of other anatomic sites were mixed. Some studies showed statistically significantly greater benefit of PRP than controls on outcomes and some did not, or some studies found statistically significantly better outcomes at some time points but not others.

Andia (2014) published a systematic review of PRP in the treatment of painful tendinopathies.[44] They included 13 prospective controlled trials (12 RCTs, one controlled study that was not randomized) with data from 636 patients included in the meta-analysis. The number of studies on various tendinopathies included seven studies on chronic elbow tendinopathy, two on supraspinatus, three on patellar, and one study on Achilles tendinopathy. Nearly all studies used leukocyte-rich PRP, and the PRP preparation protocol was the same in about half of the studies. The number of injections ranged from one (nine studies) to three (one study). Control interventions included physical therapy (one study), extracorporeal shock wave therapy (one study), corticosteroid (three studies), ABI (three studies), saline (three studies), and dry needling (two studies). Risk of bias rated as low in four studies, unclear in three, and high in six. Meta-analysis found that PRP was not better than control interventions in reducing pain at one- or two-month follow-up. A small significant effect in pain reduction was found at three months (weighted mean difference [WMD] -0.61). At one year, the WMD between PRP and control interventions was significant at -1.56. Due to heterogeneity between studies, these findings had low power and precision.

Three other systematic reviews for various tendinopathies found few randomized trials, and no studies of high-quality design.[4, 45, 46] While uncontrolled trials showed promising results, those studies with a control group reported no significant benefit from use of PRP compared with patients who did not receive PRP. These reviews concluded that well-designed, large, long-term, randomized trials with appropriate control groups are needed to determine the impact of PRP for chronic tendinopathies.

A 2014 Cochrane systematic review of platelet rich therapy (PRT) for acute or chronic musculoskeletal soft tissue injuries included randomized and quasi-randomized controlled trials comparing PRT with placebo, ABI, dry needling, or no PRT.[47] Primary outcomes were functional status, pain, and adverse effects. 19 small, single-center trials (n=1,088) were identified, of which 17 were RCTs and two were quasi-randomized trials. Data could be pooled for 11 trials (45% of participants). The outcomes for individual conditions are summarized in the subsections below. The evidence for all primary outcomes was rated as very low quality due to significant methodological limitations. The authors listed the following limitations: the small number of participants in most trials, the heterogeneity in PRP preparation due to the lack of standardization and quantification of the PRP, the method of delivery (e.g., guided by imaging, arthroscope, direct vision, or no guidance), the number of applications of PRT, and the post-operative interventions. The authors noted that the variations in these methodologies reduced the quality of the evidence and concluded that the evidence is insufficient to support the use of PRT for treating musculoskeletal soft tissue injuries.

Randomized Controlled Trials

Several RCTs have been published since the systematic reviews described above, including studies on patellar and gluteal tendinopathies. The patellar tendinopathy study did not find significant differences between PRP and saline injection,[48] while the gluteal tendinopathy study reported that PRP injection resulted in significantly improved pain scores compared with corticosteroid injection.[49] However, study limitations preclude reaching strong conclusions based on this evidence.

LATERAL EPICONDYLITIS

Systematic Reviews

The WSHCA health technology review (previously described) evaluated the use of PRP to treat elbow epicondylitis.[34] It included four RCTs that compared PRP to ABI, and eight RCTs and two cohort studies that compared PRP to other control treatments (steroid injections, anesthetic injections, and dry needling). The authors concluded that there was low quality evidence that PRP resulted in short-term and intermediate-term improvements in function, relative to ABI, low quality evidence that there was no difference in pain between PRP and ABI treatment, in insufficient evidence for long-term outcome comparisons. Regarding studies that compared PRP to other control treatments, the authors concluded that there were no differences in primary short-term outcomes for any of the groups, low quality evidence that PRP improved intermediate-term and long-term function, and long-term pain outcomes compared to controls.

Chen (2021) published a meta-analysis of nine RCTs of PRP for lateral epicondylitis, most of which were also in the WSHCA assessment described above.[50] Patients receiving PRP had improved pain scores at three and six months compared to patients receiving autologous blood, but functional scores did not differ. There was no significant difference in pain or disability scores between PRP and corticosteroids at three months, but at six months, the PRP group was superior. Most differences represented less than a 10% absolute difference for their respective estimated minimal clinically important difference values. The authors concluded that due to “the small number of comparable studies, lack of quantification of specific PRP content, considerable heterogeneity between randomized control trials, and most effect sizes being equivocal,” the use of PRP for this application could be neither supported nor discouraged.

De Vos (2014) published a systematic review of RCTs.[51] The review included seven studies on six RCTs, including three RCTs,[13-15] from the 2014 Cochrane systematic review summarized below. Unlike the Cochrane review, which noted high risk for bias and a number of other methodological limitations in the three RCTs, de Vos (2014) rated them as high quality along with another RCT[52, 53]. The remaining two RCTs[54, 55] were rated as low quality. The control injections in the included studies included corticosteroids, ABI, saline, or needling with bupivacaine. All PRP and control groups reported initial significant symptom improvement. Only one RCT[52, 53], which used a corticosteroid injection in the control group, reported continued significant effect of PRP during the follow-up period; however, the authors of the systematic review noted that corticosteroid injections are harmful in tendinopathy. The authors also noted the following limitations of this review: differences in predefined outcome measures, a high rate of disagreement between the authors on the quality assessment due in part to inadequate descriptions of study methods or results, and pooling of data for quantitative analysis was not possible due to the heterogeneity of the data. The conclusion for this review was that strong evidence exists that PRP injection does not improve pain and/or function in chronic lateral epicondylar tendinopathy compared to other treatment options.

The 2014 Cochrane systematic review on the use of PRP in soft tissue injuries [47] analyzed the three-month outcomes of three RCTs (n=219) for application of PRP as a treatment of lateral epicondylitis. The control groups received ABI in two RCTs[56, 57] and saline[58] in the third RCT. The inclusion criteria, treatment protocols, assessment tools, and post-procedure co-interventions (e.g., rehabilitation) varied between studies. All three RCTs were rated as high risk for bias due to large loss to follow-up. Outcomes were heterogenous, with results from Krogh (2016) and Thanasas (2011) tending to favor PRP therapy, while Creaney (2011) reported outcomes in favor of the control group. However, the authors recommended caution in interpreting the latter report due to the exclusion of some participants who were referred to surgery because of treatment failure. Data could be pooled for the two RCTs with ABI control groups (n=151); no statistically or clinically significant difference in short-term (within three months) function was found between the treatment and control groups. The authors concluded that the evidence was insufficient to determine whether PRP therapy can provide clinically relevant beneficial effects in patients with lateral epicondylitis.

Two systematic reviews with network meta-analyses compared the use of PRP, ABI, and corticosteroid injection. The analysis by Tang (2020) included 20 RCTs and reported that corticosteroid use was associated with greater short-term improvement in pain and function, while PRP was associated with greater long-term improvement.[59] The analysis by Arirachakaran (2016) included the RCTs that were in the deVos review (described above) with one additional RCT, and did not demonstrate a statistically significant difference between PRP and ABI in pain and function measures, except for pressure pain threshold, which showed improvement in the ABI group.[60] Both blood and PRP injections improved outcomes relative to corticosteroid injection in this analysis. The authors noted that those receiving ABI had a higher rate of adverse events than those receiving PRP or corticosteroid injections.

Randomized Controlled Trials

Linnanmäki (2020) compared PRP to autologous blood or saline injection for lateral epicondylitis in a participant- and assessor-blinded randomized trial that included 119 patients.[61] Patients were randomized 1:1:1 to one of the three treatments, and the outcomes assessed were pain (VAS score) and function (DASH score). Outcomes were assessed at 4, 8, 12, 26, and 52 weeks post-injection. No clinically important differences in either VAS or DASH scores were seen at any of the time points, leading authors to recommend against the use of PRP or autologous blood until a clinical benefit is demonstrated in future studies.

Gupta (2019) randomized 80 patients with lateral epicondylitis to receive either PRP or corticosteroid injections.[62] The primary endpoint of the study was change in pain, as measured by the (VAS) at six weeks, three months, and one year. At six weeks, there was greater improvement in pain in the corticosteroid group, while at three months and one year, the PRP group showed significantly greater improvement.

An RCT by Martin (2019) compared tenotomy with PRP to tenotomy with lidocaine in 71 patients with elbow tendinopathy that had failed to improve with conservative treatments. In the 51 patients the provided 20-month follow up data, there were no significant differences in measures of pain and function between groups.

Palacio (2016) published an RCT that randomized 60 patients to one of three treatments: PRP, neocaine, or dexamethasone.[63] The outcomes of this study were the Disabilities of the Arm, Shoulder and Hand and Patient-Rated Tennis Elbow Evaluation questionnaires, which were filled out by patients at baseline and 90 and 180 days after treatment. Nearly 82% of the patients reported some improvement in symptoms, and there were no significant differences in the outcomes between treatment groups.

Gautam (2015) reported a small prospective randomized trial that compared PRP versus corticosteroid injections for the treatment of lateral epicondylitis in 30 patients with recalcitrant LE not responsive to oral medication or non-invasive treatment.[64] At six months post-treatment, both groups were evaluated for measures of pain, elbow performance and residual damage. The PRP treated group had improved outcomes over the corticosteroid group for pain (77% vs. 59%, as measured using the VAS), hand grip strength (40% vs. 21%), and modified Mayo score (26% vs. 8%) and Oxford Elbow Score (50% vs. 16%) for elbow performance.

ORTHOPEDIC INJURIES

Systematic Reviews

Johal (2019) conducted a systematic review and meta-analysis of RCTs on PRP for various orthopedic indications.[65] The meta-analysis evaluated the standardized mean difference in pain at both 3 and 12 months. Systematic review authors used the Cochrane Collaboration risk of bias tool to assess study quality. At 12 months, pain scores were statistically significantly lower for PRP versus its comparators (i.e., steroids, whole blood, dry needling, local anesthetics). However, these results should be interpreted with caution due to important limitations including high statistical heterogeneity (I^2=73%), lack of a clinically significant difference, and moderate to high risk of bias in study conduct.

A systematic review by Franchini (2018) evaluated the use of PRP as a conservative treatment in orthopedics.[66] The review included 36 RCTs, most of which were noted to be fairly small (n=20 to 225). In 19 of these, PRP was compared to local steroid injection. The control treatments in other trials included saline injection (six studies), autologous whole blood (four studies), local anesthetic injection (three studies), and dry needling (three studies). The primary outcomes assessed in the meta-analysis were pain (using the VAS) and function (using any standard validated scale, e.g., the American Orthopedic Foot and Ankle Society Score). Short-term (within three months) and medium-term (four to six months) outcomes were assessed separately. Long-term (12 months) outcomes were not included due to a lack of data from the studies. The meta-analysis indicated that PRP was not associated with short-term improvements in pain or function, and only a marginal benefit was seen with medium-term outcomes. The overall quality of the evidence in the review was rated as very low, and the authors concluded that it did not support the use of PRP as a conservative treatment in orthopedics.

Sheth (2012) published a systematic review that addressed a wide variety of orthopedic indications. This publication included 23 randomized trials and 10 prospective cohort studies that compared PRP with placebo, corticosteroids, or a standard procedure.[67] For most of the studies, the outcome measures differed, but six RCTs (n=358) and three prospective cohort studies (n=88) reported results of PRP using VAS, and these were combined for analysis. These studies assessed injuries to the acromion, rotator cuff, lateral humeral epicondyle, anterior cruciate ligament (ACL), patella, tibia, and spine. Follow-up ranged from six weeks to 24 months. Of 22 RCTs that evaluated functional outcomes, six showed a functional benefit of PRP, 15 showed no difference between PRP and the control, and one showed a significant functional advantage for the control group. Interpretation of this systematic review is limited by the combination of a wide variety of conditions, as well as the lack of standardization of platelet-separation techniques and outcome measures in the primary literature.

Randomized Controlled Trials

No RCTs were identified that were published after the review above.

PLANTAR FASCIITIS

Systematic Reviews

Seth (2023) published a systematic review comparing corticosteroid injections to either PRP or extracorporeal shock wave therapy in patients with plantar fasciitis.[68] The studies were limited to RCTs up to April 2021. 18 studies were included, 12 of which evaluated PRP compared to corticosteroid injections. VAS scores were higher in the corticosteroid group than the PRP group at both three months (MD, 0.62; 95% CI, 0.13 to 1.12; p=0.01) and six months (MD, 1.49; 95% CI, 0.22 to 2.76; p=0.02). Notably, numerical differences between groups were small. Functional outcomes were similar with corticosteroids compared to PRP at three months but worse with corticosteroids at six months (American Orthopaedic Foot and Ankle Society [AOFAS] MD, -11.53; 95% CI, -16.62 to -6.43; p<0.0001). The authors deemed the evidence very low quality, and most studies had either high or unclear risk of bias.

The 2016 WSHCA health technology assessment included five RCTs judged to be at moderately high risk of bias and three prospective cohort studies comparing PRP to control treatments for plantar fasciitis.[34] The control treatments were steroid injection (three RCTs), prolotherapy (one RCT), and extracorporeal shockwave therapy and conservative care (one RCT with both). The reviewers concluded that:

> "With respect to primary outcomes in both the short- and intermediate-term, there was no difference between groups in function or pain scores based on low quality evidence (4 RCTs for each). In the long-term, low quality evidence suggested better function scores with PRP versus steroid (2 RCTs), while there was insufficient quality evidence of more PRP patients achieving function success (one RCT) and better pain scores with PRP versus steroid (one RCT)." … "With respect to secondary outcomes, results were mixed, with one trial reporting no differences between PRP and prolotherapy in short- or intermediate-term disability, and the other trial reporting better long-term symptoms with PRP versus steroid (although there were no differences between groups in the short- or intermediate-term). The cohort studies were all at moderately high risk of bias and compared PRP to steroid injections, with 50 to 60 patients per study. Function was better in PRP patients in the short- (2 studies) and intermediate-term (one study), while results for pain were mixed (some studies showed no difference and some favored PRP) in both the short- (3 studies) and intermediate-term (2 studies). One study reported no difference between groups in short- and intermediate-term symptoms."

Hohmann (2020) compared PRP to corticosteroids for planar fasciitis treatment in a systematic review that included 15 studies.[69] Nine of the studies were reported to have a high risk of bias, and only one was judged to be of high quality. Pooled analyses were performed for the American Orthopedic Foot and Ankle Society (AOFAS) hindfoot score and VAS. While the AOFAS and VAS scores indicated a benefit with PRP treatment at 6 and 12 months, the results should be interpreted with caution based on the high risk of bias and low study quality.

In contrast, a systematic review by Fei (2021), which included 12 RCTs, considered all trials to be of high quality and reported that PRP treatment was associated with lower pain scores at six-months, one-year, and one-and-a-half-years follow-up and with improved American Orthopedic Foot and Ankle Society (AOFAS) scores at one-year follow-up, compared with steroid injection.[70]

A systematic review by Chen (2019), which included many of the same studies as the Hohmann review described above, compared PRP to corticosteroids for plantar fasciitis and included 12 RCTs and four quasi-experimental studies.[71] Outcomes included the VAS pain score and the American Orthopedic Foot and Ankle Society hindfoot score. A meta-analysis found that corticosteroids were associated with reduced pain scores at 1.5 and 3 months, compared with PRP, but this relationship switched at six-months follow-up. There was no significant difference in the American Orthopedic Foot and Ankle Society score between groups throughout the study. Outcomes were not assessed after six months.

Hsiao (2015) published a study that compared the efficacy of autologous blood-derived products, corticosteroids and shock-wave (SW) therapy in the treatment of plantar fasciitis, including seven RCTs and three quasi-experimental studies (n=604).[72] Pair-wise meta-analysis indicated that at three-month follow-up PRP-treated patients had significantly reduced pain (by VAS score) over those treated with corticosteroids. However, PRP treatment was slightly inferior to SW therapy for VAS reduction at six months. The authors concluded that there were no significant between-group differences in VAS reduction at six months and in treatment success (as determined by OR) between the three treatments.

Franceschi (2014) published a qualitative systematic review of the literature on PRP for chronic plantar fasciitis. Eight prospective studies were identified, three of which were randomized. The three single-blinded RCTs had a total of 90 patients and compared treatment with PRP with corticosteroids (n=60) or prolotherapy (n=30).[73] The three randomized studies varied substantially in terms of follow-up time (six weeks, six months, 24 months) and outcome assessed. The two studies that compared PRP and corticosteroid treatment reported statistically significant improvements in the PRP-treatment group, where the study with prolotherapy as a control treatment did not.

Randomized Controlled Trials

Since the 2016 WSHCA health technology review, several RCTs have been published on PRP as a treatment for planar fasciitis. These have compared PRP to low dose radiation,[74] ABI,[75], steroid injection,[76-78] platelet-poor plasma,[79] and saline.[77, 78] In the majority of studies that included a direct comparison between treatments, improvements with PRP were not significantly different from those with control treatments.[74-76, 79] In the trial that compared PRP with steroid and saline controls, improvements in the PRP group were similar to those in the steroid group and both of these groups showed greater improvement than the saline group.[77, 78]

OSTEOCHONDRAL LESIONS AND OSTEOARTHRITIS

Systematic Reviews

Anil (2021) published a systematic review with network meta-analysis to compare the efficacy of nonoperative injectable treatments for knee osteoarthritis.[80] A total of 79 RCTs (n=8,761) were included, and the follow-up ranged from four weeks to 24 months. Intra-articular injectable treatments included PRP, autologous conditioned serum, bone marrow aspirate concentrate, botulinum toxin, corticosteroids, hyaluronic acid, mesenchymal stem cells, ozone, saline placebo, plasma rich in growth factor, and stromal vascular fraction; the publication did not delineate the number of RCTs that specifically evaluated PRP. At 12 months, the treatment with the highest P-Score for the MD in Western Ontario and McMaster Osteoarthritis Index (WOMAC) scale score and VAS score was stromal vascular fraction. However, the MD in WOMAC scale and VAS scores for leukocyte-poor PRP and leukocyte-rich PRP versus saline placebo at 12 months did not reach statistical significance.

Belk (2022) identified six RCTs comparing the efficacy of PRP (n=211) and hyaluronic acid injections (n=197).[81] The mean follow-up was approximately 12 months. In an analysis of four RCTs, PRP and hyaluronic acid groups had similar improvements in VAS score (MD 5.9, 95% CI -0.741 to 1.92) and WOMAC score (MD 0.27, 95% CI -0.05 to 0.59).

Gazendam (2020) identified 11 RCTs (total n=1,353) assessing the efficacy of PRP, corticosteroids, and saline injections in individuals with hip osteoarthritis.[82] Pooled pain and functional outcomes were reported for two-, four- and six-month follow-up. No intervention significantly outperformed saline intra-articular injection at any time point. Clinically significant improvements in pain from baseline were observed for all treatment groups, including placebo.

Trams (2020) published a systematic review that included 38 RCTs (n=2,962) evaluating the effects of PRP on patients with knee osteoarthritis.[83] The meta-analysis focused on the review of 33 blinded studies. Follow-up ranged from six months to two years. Comparators included hyaluronic acid (HA) in 23 studies, placebo (e.g., saline, no injection, physical therapy) in 10 studies, corticosteroids in four studies, and acetaminophen in two studies. Twenty-two studies reported visual analog scale (VAS) pain outcomes for placebo (5 studies), HA (15 studies), and corticosteroids (2 studies). Placebo and HA subgroups showed significant VAS differences in favor of PRP ($p<0.00001$). The corticosteroid subgroup was not significantly different from PRP ($p=0.23$). Six studies comparing single versus multiple injections of PRP showed a significant difference in favor of three PRP injections ($p<0.00001$). Functional outcomes were reported via the WOMAC scale for placebo (nine studies), corticosteroids (one study), and HA (15 studies). Both pooled and subgroup analyses favored PRP ($p<0.00001$). In five studies assessing multiple versus single PRP injections, significant differences in favor of multiple injections were found ($p<0.00001$). Functional outcomes assessed via International Knee Documentation Committee (IKDC) scores were reported in two placebo studies and five HA studies. While a significant difference was found for HA ($p=0.004$), no significant difference was found for placebo ($p=0.24$). Pooled estimates for six studies comparing PRP to corticosteroids, HA, or mesenchymal stem cells found no significant differences in Knee injury and Osteoarthritis Outcome Score (KOOS) sport, quality of life, activities of daily living, symptoms, or pain subscales. The pooled estimates for adverse events showed non-significant differences in favor of the control groups ($p=0.15$). Risk of bias was assessed using Cochrane criteria. One study was at high risk of bias for three domains, two studies were at high risk of bias for two domains, and 12 studies were at high risk of bias for one domain. The most impacted domains were performance bias and reporting bias.

A systematic review and meta-analysis of RCTs by Hohmann (2020) compared PRP with HA for knee osteoarthritis.[84] Twelve studies were included. Funnel plot analysis suggested some degree of publication bias, and more than half of the studies were rated as having a high risk of bias. Outcomes evaluated included WOMAC, IKDC, KOOS, and VAS scores. Of the 12 included studies, 11 had six-month follow-up results and the results of a pooled analysis showed non-significant differences for clinical outcomes between PRP and HA groups. Non-significant clinical outcome differences were also seen in a pooled analysis of the eight studies with 12-month results. Significant differences favoring PRP were found for pain measures (VAS, WOMAC, and KOOS) at six months and 12 months (both p<0.001), however the limitations of the included studies limit the conclusions that can be drawn from the pooled analyses.

Xu (2017) conducted a systematic review and meta-analysis of RCTs comparing PRP with HA (eight trials), or placebo (two trials), for the treatment of knee OA.[85] Risk of bias was assessed using Cochrane criteria. Four studies were assessed as having low quality, three as moderate quality, and three as high quality. Meta-analyses including seven of the trials comparing PRP with HA showed that PRP significantly improved WOMAC or IKDC scores compared with HA at six-month follow-up; however, when meta-analyses included only the two high-quality RCTs, there was not a significant difference between PRP and HA. (Note that WOMAC evaluates three domains: pain, scored from 0 to 20; stiffness, scored from 0 to 8; and physical function, scored from 0 to 68. Higher scores represent greater pain and stiffness as well as worsened physical capability. The IKDC is a patient-reported, knee-specific outcome measure that measures pain and functional activity.) In the meta-analysis comparing PRP with placebo, a third trial was included, which had four treatment groups, two of which were PRP and placebo. This analysis showed that PRP significantly improved WOMAC or IKDC scores compared with placebo; however, only one of the trials was considered high quality and that trial only enrolled 30 patients. All meta-analyses showed high heterogeneity among trials ($I^2 \geq 90\%$).

The 2016 WSHCA health technology review evaluated the use of PRP for osteoarthritis of the knee, hip, and temporomandibular joint (TMJ).[34] Six RCTs and four cohort studies were included that compared PRP with HA. Among the RCTs (two at low, two at moderately low, and two at moderately high risk of bias), there was no difference between groups for short-term pain and function outcomes. Intermediate-term function scores were improved with PRP and intermediate-term pain scores were similar for both groups. While long-term outcomes indicated functional outcomes and pain success were higher with PRP, long-term pain scores were similar for both groups. One RCT, at moderately low risk of bias, compared leukocyte-rich PRP with steroid injection, and found better short- and intermediate-term pain and function scores, thought the quality of evidence was deemed insufficient by the reviewers. Two moderately low risk of bias RCTs compared PRP to saline and found that short- and intermediate-term function and pain scores were better with PRP, which was judged to be low-quality evidence. Finally, two moderately low risk of bias RCTs compared PRP to exercise with and without transcutaneous electrical nerve stimulation. The reviewers reported no clear differences in short- and intermediate term pain and function outcomes, based on insufficient quality evidence.

Kanchanatawan (2015) published a systematic review addressing PRP treatment for knee osteoarthritis (OA), including nine RCTs.[86] When compared to HA or saline controls, PRP treatment had consistently better functional outcomes, but adverse events were not different between groups. Similar results were reported in other systematic review that compared PRP to HA or saline controls.[87-89] In general, the recent systematic review published on the use of PRP treatment for knee OA indicate the studies included are of small sample size, inconsistent study type and variable in the functional outcomes reported. These shortcomings undoubtedly have contributed to the controversial findings of significant improvements due to PRP treatment. Only a few high-quality clinical trials have been published which showed a clinical improvement limited over time and mainly documented in younger patients not affected by advanced knee degeneration. Further RCTs with larger sample sizes and longer follow-up are required to establish with greater certainty if PRP is more effective than other treatment options.

A systematic review of PRP for degenerative cartilage pathology in knee joints included five RCTs, three quasi-RCTs, and eight single-arm prospective series (n=1,543) comparing PRP with HA (four RCTs and two quasi-randomized[90-95]) or saline (one RCT[96]).[97] Meta-analysis of functional outcomes found that the effectiveness of PRP was greater than that of HA and improved over the course of 12 months. Fewer than three injections, single spinning, and lack of additional activators led to greater uncertainty in the treatment effects. PRP also had lower efficacy in patients with higher degrees of cartilage degeneration. Results were consistent when analyzing only RCTs, but asymmetry in funnel plots indicated that significant publication bias was a concern. Similar results were reported by other systematic reviews of knee OA.[98-100] Low level of evidence, small sample sizes, and wide variability in treatment were limitations cited.

Dold (2014) analyzed 10 studies of PRP for treatment of osteochondral pathology.[101] Two studies were RCTs,[95, 102] one was a prospective quasi-randomized comparative study,[103] one was a retrospective comparative study, and six were case series. The review included literature indexed up to October 11, 2012. Most studies were related to degenerative osteoarthritis of the knee or hip (n=570 of 662 joints). In two studies, PRP was applied as an adjunct to surgical treatment; in the remaining eight studies, PRP was delivered by intra-articular injections. The three prospective comparative studies reported superior clinical results with PRP compared to HA for knee osteoarthritis and osteochondral lesions of the talus. However, the data from all included studies suggested that any beneficial effects began to decrease after six months. Evidence was rated as weak mainly due to heterogeneity in PRP preparation and delivery methods, short-term follow-up, and the high risk of bias. The authors concluded that there is no high-quality or conclusive evidence for PRP as a treatment of osteochondral lesions or osteoarthritis. Further data is needed from high-quality RCTs that compare PRP injections to placebo, and surgical treatment with versus without PRP.

Randomized Controlled Trials

Nouri (2022) conducted an RCT that compared PRP to hyaluronic acid in patients with hip osteoarthritis.[104] 105 patients were randomized to receive intra-articular injection of PRP, hyaluronic acid, or a combination two times over two weeks. There were no differences in VAS scores between groups at six months, but WOMAC, Lequesne, and Activities of Daily Living scores were significantly higher in PRP/hyaluronic acid and PRP only groups compared to the hyaluronic acid group. This study is limited by lack of a placebo control and long-term follow-up.

In individuals with knee OA undergoing PRP injections, three RCTs with follow-up durations of at least 12 months have been published subsequent to the above-described systematic reviews.[105-107] All were conducted outside of the United States. Sample sizes ranged from 40 to 200 participants. Two RCTs found statistically significantly greater 12-month reductions in WOMAC scores with PRP versus corticosteroids or celecoxib.[105, 107] The findings of these RCTs should be interpreted with caution due to important study conduct limitations, including potential inadequate control for selection bias and unclear blinding. Additionally, no significant differences between PRP and HA were found in the IKDC subjective score or EuroQol visual analog scale in the longest-term trial with five years of follow-up. In the RCT by Di Martino

(2019), reintervention rates were significantly lower with PRP compared with HA at the 24-month follow-up assessment (22.6% 37.1%, p=0.036), but the difference was not maintained at five years.[106]

Trueba Vasavilbaso (2017) conducted a controlled trial that randomized patients after knee arthroscopy to five injections of Suprahyal/Adant (n=10), four injections of Orthovisc (n=10), three injections of Synvisc (n=10), one injection of PRP (n=10), or standard of care (n=10).[108] All patients received the same rehabilitation protocol. At 18-month follow-up, total WOMAC scores improved most from baseline with Suprahyal/Adant (65% reduction). The next best improvement was seen with PRP (55% reduction), then Synvisc (50% reduction), and Orthovisc (30% reduction). The control group experienced a 15% increase in WOMAC scores.

Dallari (2016) evaluated PRP in 111 patients with hip osteoarthritis.[109] These patients were randomize to one of three treatments: PRP, PRP plus HA, or HA alone. There were three weekly injections for each treatment and follow-up was 12 months. The primary outcome of the trial was change in pain intensity by VAS. Secondary outcomes were the Harris Hip Score, WOMAC index score, the concentration of growth factors in PRP, and the correlation of these factors with clinical outcomes. Clinical outcome assessors were blinded to the treatment type. The PRP group had significantly lower pain intensity than the HA group or the PRP+HA group at six months, and an improved WOMAC score at two and six months, but not at 12 months. There was a moderate correlation between interleukin-10 and variations of the VAS score. (r=0.392, p=0.040).

ADJUNCT TO SURGICAL PROCEDURES

SPINAL FUSION

Systematic Reviews

No systematic reviews were identified.

Randomized Controlled Trials

One RCT was found for use of autologous growth factor concentrate (AGF), including PRP, as an adjunct to lumbar fusion.[110] In this small trial, outcomes for 40 patients who underwent spinal fusion with AGF (n=20) versus without AGF (n=20) were reported. One patient per group was lost to follow-up. No significant between-group differences were found with CT scan at one year, which showed osseous healing in all but one patient. The pain and function outcomes at two years follow-up also showed no significant between-group differences. The authors concluded that use of PRP as an adjunct to spinal fusion was not justified.

SHOULDER SURGERY

Systematic Reviews

Li (2022) published a systematic review and meta-analysis of RCTs comparing PRP and platelet-rich fibrin to control treatments for arthroscopic rotator cuff repair.[111] There were 23 RCTs (n=1,440) included in the review, 16 of which were studies of PRP. Of these, 10 reported on VAS reduction and 12 reported on retear rate. The meta-analysis found that PRP use was associated with significantly decreased rates of retear (15.9% vs. 29.0% for control, p<0.0001), VAS (1.3 vs. 1.6 for control, p=0.01), and Constant score (83.9 vs. 81.2 for control, p=0.0006).

A systematic review by Chen (2020) evaluated the use PRP in the treatment of rotator cuff injuries in RCTs.[112] The analysis included 18 RCTs (total n=1,116), mainly trials that compared the use of PRP during surgical repair to repair without additional treatment in patients with full-thickness tears. For patients who received PRP, Constant scores of patients who received PRP were significantly better short term (weighted MD 2.89, 95% CI 0.89 to 4.90, p<0.01) and long term (weighted MD 2.66, 95% CI 1.13 to 4.19, p<0.01), and VAS scores were improved short term (weighted MD -0.45, 95% CI -0.75 to -0.15, p<0.01). Retears were significantly reduced in the PRP-treated patients, as well. However, none of the measures reached their respective prespecified minimal clinically important differences, and the authors noted that, "limited data, study heterogeneity, and poor methodological quality hinder firm conclusions."

Saltzman (2015) published a systematic review and meta-analyses of PRP at the time of surgery and clinical outcomes in patients undergoing rotator cuff repair.[113] The authors identified seven studies, all published after 2012, that performed pooled analyses of trial data. Studies varied in their outcomes of interest, but all pooled data on the overall retear rate and none found a statistically significant difference in the retear rate in patients with PRP use compared to a control intervention; the relative risks ranged from 0.55 to 0.94, and the odds ratio in one study that reported it was 1.11. One of the meta-analyses included in this review, however, found a significantly lower risk of retear with PRP use when an outlier study was excluded from the analysis.

Zhao (2014) conducted a meta-analysis of eight RCTs (with sample sizes ranging from 28 to 88 and a combined total of 464 patients)[114-121] of arthroscopic full thickness rotator cuff tear repair with or without PRP that were published from 1980 to September 2013.[122] The analysis found that the use of PRP did not result in superior outcomes for any outcomes measures which included rate of retears, pain, function, strength and range of motion as measured with either the Constant or the UCLA shoulder scores. The quality of evidence was graded as low to moderate due to several limitations: the included studies were of small sample size, lack of details of randomization methods in two studies, and quasi-randomization in one study. The conclusion of the analysis was that the evidence did not support the use of PRP in repair of full-thickness rotator cuff tears. Similar conclusions have been reported by other systematic reviews that have looked at the effectiveness of PRP treatment for both large and small to medium rotator cuff tears.[123, 124]

Randomized Controlled Trials

Randelli (2021) published results of a 10-year follow-up of a previous RCT of PRP in arthroscopic rotator cuff repair, which included data for 17 patients who received PRP and 21 control group patients.[125] At the 10-year follow-up, both PRP and control groups experienced improvements in the median (interquartile range [IQR]) University of California at Los Angeles activity score (34 [29 to 35] and 33 [29 to 35] points, respectively) and VAS score (0.34 [0 to 1.85] and 0.70 [0 to 2.45] points, respectively); but the between-group differences did not reach statistical significance. Approximately 37% of the operated patients had a re-rupture in each group. Retears occurred in 6% of the patients who received PRP treatment and 14% of patients in the control group (p=0.61).

A double-blind RCT by Flury (2016) compared intraoperative PRP to local anaesthetic injection in 120 patients undergoing arthroscopic rotator cuff repair.[126] Outcome scores, which included Constant-Murley shoulder score, Oxford Shoulder Score, patient American Shoulder and

Elbow Surgeons score, quick Disabilities of the Arm, Shoulder and Hand score, and EuroQol 5 dimensions, were collected preoperatively, and at 3-, 6-, and 24-months after the procedure. There were no significant differences in any of the outcomes during follow-up, and no differences in adverse events between the groups.

Pandey (2016) published an RCT that evaluated the use of PRP during arthroscopic rotator cuff surgery in 102 patients, with a minimum follow-up of two years.[127] The outcome assessments in this study were VAS score, Constant-Murley score, University of California-Los Angeles score, and American Shoulder and Elbow Surgeons score, along with ultrasound to assess cuff healing. PRP was associated with lower VAS scores at one-, three-, and six-month follow-up, but not after. Constant-Murley scores were significantly improved in the PRP group at 12- and 24-months follow-up, and University of California-Los Angeles score was significantly higher with PRP treatment at 6- and 12-month follow-up. The authors noted that at 24 months, the PRP group had fewer retears and enhanced vascularity. This trial was limited by the lack of blinding of either patients or assessors.

Jo (2015) published an RCT on the use of PRP for arthroscopic repair of medium to large rotator cuff tears and its effect on the speed of healing and the quality of healing. 74 patients were randomized to undergo either PRP-augmented repair (PRP group) or conventional repair (conventional group).[128] At three month follow up there was no difference between the two groups in terms of pain, range of motion, muscle strength, overall satisfaction and function, and other functional scores. However, the retear rate of the PRP group was significantly lower than that of the conventional group (3% vs. 20.0%, p=0.032). At one-year postoperative the cross-sectional area of the supraspinatus muscle was significantly lower in the PRP group versus the conventional group (-36.76 ± 45.31 mm^2 vs. -67.47 ± 47.26 mm^2, p=0.014). The study concluded that the PRP treatment significantly improved the quality of healing, as evidenced by a decreased retear rate and increased CSA of the supraspinatus, but not the speed of healing.

Malavolta (2014) published the results of a prospective, double-blind RCT on PRP in which 54 patients undergoing arthroscopic rotator cuff repair were randomized to either a PRP or a control group (n=27 in each group).[129] At the end of the procedure, which was performed by a single surgeon for all patients, after removal of all arthroscopic fluid and closure of incisions, the PRP group received a liquid preparation of PRP and autologous thrombin. The authors did not specifically describe the intervention performed in the control group, so it is unknown whether they received an injection of placebo or no injection. Both groups showed significant clinical improvement (p<0.001) compared to preoperative baseline measures. However, the only statistically significant outcome difference between the groups during the two-year follow-up was in the UCLA shoulder function scores at 12 months in favor of the PRP group (p=0.46). The lack of a description of the intervention in the control group is a significant limitation of this study. Further, the authors noted that, unlike most RCTs on PRP in rotator cuff repair that included patients with large or complete tears, this study included small- and medium-sized tears, making it difficult to compare data between studies. Other authors have criticized the use of PRP in these less extensive tears which generally have satisfactory clinical outcomes and are, therefore, less likely to show statistically significant differences between control and PRP groups. In addition, the authors noted controversy about the use of liquid rather than solid PRP. The authors concluded that liquid PRP prepared by apheresis and applied with the addition of thrombin did not result in improved health outcomes after arthroscopic rotator cuff repair of small- to medium-size tears. A five-year follow-up of this trial reported similar results.[130]

Two additional small, single-center RCTs have been published subsequent to the systematic reviews described above. Walsh (2018) published a prospective, randomized, single-blinded study evaluating PRP in fibrin matrix as a means to augment rotator cuff repair.[131] In contrast to previous RCTs that have focused on administration of PRP at the time of rotator cuff repair surgery, Snow (2019) published a randomized double-blind trial of delayed delivery of PRP at 10 to 15 days post-surgery.[132] Results of these RCTs are consistent with the systematic reviews in finding no statistically or clinically significant benefit of PRP on multiple outcomes.

KNEE SURGERIES

Systematic Reviews

Lv (2022) conducted a systematic review and meta-analysis of 17 RCTs (n=970) of patients who underwent anterior cruciate ligament (ACL) reconstruction.[133] Compared to controls, PRP improved VAS score (MD, -1.12; 95% CI, -1.92 to -0.31; p=0.007), Lysholm score (MD, 8.49; 95% CI, 1.63 to 15.36) and subjective IKDC score (MD, 6.08; 95% CI, 4.39 to 7.77; p<0.00001) at six months. The authors only considered the difference in pain score to be clinically relevant, and they did not consider any differences between groups at 12 months to be clinically meaningful (VAS MD, -0.47 and subjective IKDC score MD, 3.99). Overall, the evidence was determined to be of moderate quality, and the authors concluded that PRP may provide short-term, but not long-term clinically important pain reduction.

A systematic review by de Andrade (2020) included nine studies evaluating the use of PRP in ACL reconstruction (n=525).[134] No differences were seen on MRI measures of graft ligamentization or tibial and femoral tunnel widening, or on knee laxity. While significant differences were found for Lysholm score and VAS, the authors noted that the differences were small and that there was not sufficient evidence to recommend PRP in this setting.

The systematic review by Trams (2020), described previously, identified 16 RCTs (total n=740 patients) involving knee surgery.[83] Five studies showed no significant overall difference with respect to pain (p=0.43). In four studies reporting IKDC scores, no significant differences were noted (p=0.83). In four studies, no significant differences in functional outcomes as measured by the Lysholm score were reported (p=0.19). Pooled estimates for Tegner scale activity assessments in five studies showed no significant differences (p=0.38) in favor of the control. Twelve studies were deemed to be at high risk of bias in at least one domain.

Figueroa (2015) assessed PRP as an adjunct to ACL reconstruction, including 11 RCTs or prospective cohort studies (n=516 patients).[135] Four studies found significantly faster graft maturation while three found no significant difference. One study showed faster tunnel healing while five showed no benefit. One study showed better clinical outcomes and five showed no improvement in clinical outcomes when using PRP. The largest trial included was by Nin who randomized 100 patients to undergo arthroscopic ACL reconstruction with or without PRP. The use of PRP gel on the graft and inside the tibial tunnel in patients treated with bone–patellar tendon-bone allografts had no discernable clinical or biomechanical effect at two-year follow-up.[136] Similar conclusions were reported by a second systematic review that included fifteen clinical trials (11 RCTs, three prospective comparative studies, and one retrospective comparative trial).[137]

A systematic review by Liddle and Rodríguez-Merchán (2015) addressed the safety and efficacy of PRP treatment for patellar tendinopathy as well as the effectiveness relative to other treatments.[138] This review, which included one RCT and two nonrandomized cohort studies, determined that although adverse outcomes were rare, PRP treatment superiority over other treatments such as physical therapy could not be conclusively demonstrated.

The 2014 Cochrane review[47] of platelet-rich therapies for musculoskeletal soft tissue injuries (described above) identified four trials[136, 139-141] (n=203) on PRP applied to the knee bone tunnels and/or the inner area of the graft during ACL reconstruction. At one-year follow-up, no significant difference was found in International Knee Documentation Committee (IKDC) scores between the PRP and control groups. Two additional trials (n=67) reported mixed results for PRP applied to the patellar tendon donor site during ACL reconstruction.[142, 143] Cervellin (2011) reported significant differences in functional scores in favor of the PRP group at one-year follow-up, and de Almeida (2012) found no significant difference in functional scores at six months follow-up. The studies reported that there were no adverse effects. A variety of methodological limitations were found in these six studies such as the lack of documentation of randomization method and allocation concealment, lack of blinding of participants and/or outcome assessors, lack of calculation of sample size, and short-term follow-up periods. The authors concluded that the available evidence is insufficient to indicate whether the use of PRP resulted in clinically significant outcomes compared to ACL reconstruction without PRP.

Randomized Controlled Trials

One small RCT has been conducted to assess the effects of PRP on outcomes of total knee arthroplasty. This study with 40 patients found no significant differences between the PRP and untreated control groups in bleeding, range of motion, and swelling around the knee joint, muscle power recovery, pain, Knee Society Scores or Knee Injury and Osteoarthritis Outcome Score.[144]

LONG BONE NONUNION

Systematic Reviews

A 2012 Cochrane systematic review found only one small (n=21) RCT[145] of allogeneic bone graft with or without PRP for long bone healing.[146] Three patients (14%) were lost to follow-up. At one-year follow-up, there were no significant between-group differences in patient-reported measures or in objective functional measures (95% CI -7.77 to 9.77). The review concluded that the evidence was insufficient to support clinical use of PRP for long bone healing outside the research setting.

A meta-analysis by An (2021) evaluated autologous bone grafting with and without PRP for long bone delayed union or nonunion.[147] Eight studies were included: six RCTs and two non-randomized controlled trials. Five of the studies (including four RCTs) were performed in China and published in Chinese. All studies but one were rated as having unclear or high risk of bias in at least one domain according to the Cochrane assessment tool and ROBINS-I checklist. Pooled analysis showed that combined treatment with PRP and autologous bone grafting was not significantly associated with a higher ratio of patients with bone healing after treatment compared to autologous bone grafting alone but was associated with a shorter healing time (MD −1.35 months, 95% CI −1.86 to −0.84, $p<0.001$), though there was significant heterogeneity between studies (Cochrane's Q test $p=0.02$, $I^2=58\%$).

Randomized Controlled Trials

Calori (2008) compared application of PRP to recombinant human bone morphogenetic protein-7 (rhBMP-7) for the treatment of long bone nonunions in an RCT with 120 patients and ten surgeons.[148] Inclusion criteria were post-traumatic atrophic nonunion for at least nine months, with no signs of healing over the last three months, and considered as treatable only by means of fixation revision. Autologous bone graft had been used in a prior surgery in 23 cases in the rhBMP-7 group and in 21 cases in the PRP group. Computer-generated randomization was developed to create two homogeneous groups; there were generally similar numbers of tibial, femoral, humeral, ulnar, and radial nonunions in the two groups. Following randomization, the patients underwent surgery for nonunion, including bone grafts according to the surgeon's choice (66.6% of rhBMP-7 and 80% of PRP patients). Clinical and radiologic evaluations by one radiologist and two surgeons trained in the study protocol revealed fewer unions in the PRP group (68%) compared with the rhBMP-7 group (87%). Clinical and radiographic healing times were also found to be slower by 13 to 14% with PRP.

Samuel (2018) conducted a controlled trial in which patients with delayed unions (15 to 30 weeks old) were randomized to two PRP injections at the fracture site at baseline and three weeks (n=23) or no treatment (n=17).[149] The delayed unions were in the tibia (n=29), femur (n=8), forearm (n=2), and the humerus (n=1). The main outcome was long bone union, defined as no pain or tenderness on weight bearing, no abnormal mobility, and bridging at three or more cortices in x-ray. Examinations were conducted every six weeks for 36 weeks or until union. Percent union did not differ significantly between the two groups (78% in the PRP group vs 59% in the control group). Time to union also did not differ significantly (15.3 weeks for the PRP group vs. 13.1 weeks for the control group).

OTHER SURGICAL PROCEDURES

There have been a number of studies on various other surgical procedures. However, there is a lack of well-designed RCTs demonstrating long-term improvement in health outcomes. As a result, no conclusions can be reached regarding the effectiveness and safety of these indications. These studies addressed the following surgical procedures:

- Sinus surgery[150]
- Periodontal surgery[151-153]
- Vascular surgeries[154-156]
- Blepharoplasty[157]
- Urethrotomy[158]
- Tonsillectomy in children[159]
- Microfracture surgery for talar injuries[160]
- Cleft palate repair[161]
- Pleurodesis[162]
- Core decompression of the femoral head[163]
- Repair of talar osteochondral lesions[164]
- Skin graft harvest[165]

OPHTHALMOLOGIC CONDITIONS AND PROCEDURES

Use of PRP has been studied as a treatment of persistent corneal defects[166], symptomatic dry eye[167], chemical burns[168], post-LASIK ocular surface syndrome[169]. Studies are limited to small pilot studies with no control groups. No randomized trials were identified.

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF ORTHOPEDIC SURGEONS

In 2020, the American Academy of Orthopedic Surgeons (AAOS) published guidelines on the management of glenohumeral osteoarthritis, which include the following recommendation:[170]

> "In the absence of reliable evidence, it is the opinion of the work group that injectable biologics, such as stem cells or platelet-rich plasma, cannot be recommended in the treatment of glenohumeral osteoarthritis."

The 2019 AAOS guidelines on the management of rotator cuff injuries state that "limited evidence does not support the routine use of platelet rich plasma for the treatment of cuff tendinopathy or partial tears."[171]

The 2021 AAOS guidelines for the treatment of osteoarthritis of the knee made the following recommendation:[172]

"Platelet-rich plasma (PRP) may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee. (Strength of Recommendation: Limited)" The variability of study findings was noted to have contributed to the low strength of recommendation rating.

AMERICAN COLLEGE OF RHEUMATOLOGY/ARTHRITIS

The 2019 American College of Rheumatology/Arthritis guideline for the management of osteoarthritis of the hand, hip, and knee strongly recommends against platelet-rich plasma treatment in patients with knee and/or hip OA.[173] American College of Physicians

American College of Physicians (ACP) (2015) published guidelines on treatment of pressure ulcers.[174] The guidelines noted that "although low quality evidence suggests that dressings containing PDGF promote healing, ACP supports the use of other dressings such as hydrocolloid and foam dressings, which are effective at promoting healing and cost less than PDGF dressings." This guideline is now listed on the ACP website as "inactive."

ASSOCIATION FOR THE ADVANCEMENT OF WOUND CARE

Association for the Advancement of Wound Care (2014) developed guidelines for pressure ulcers and venous ulcers:[175] Pressure ulcer: growth factors are not indicated at this time (level C evidence – no RCTs available comparing growth factors with A-level dressings). Venous ulcer: platelet derived growth factor has shown no significant effects on venous ulcer healing or recurrence (level A evidence).

NATIONAL PRESSURE ULCER ADVISORY PANEL AND THE EUROPEAN PRESSURE ULCER ADVISORY PANEL

A joint 2014 practice guideline from the National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel, and Pan Pacific Pressure Injury Alliance concluded that "due to insufficient evidence to support or refute the use of [non-recombinant] growth factors in the treatment of pressure ulcers they are not recommended for routine use at this time."[176]

SUMMARY

TREATMENT FOR DIABETIC WOUNDS

There is not enough research to show that platelet-rich plasma (PRP) or autologous platelet-derived growth factor (PDGF) treatment improves health outcomes for patients with diabetic wounds. In addition, there are no clinical guidelines that recommend the use of PRP or PDGF for diabetic wounds. Therefore, the use of PRP or PDGF for diabetic wounds is considered investigational.

TREATMENT FOR INDICATIONS OTHER THAN DIABETIC WOUNDS

For indications other than diabetic wounds, there is not enough research to show that platelet-rich plasma (PRP) or autologous platelet-derived growth factor (PDGF) treatment improves health outcomes for any indication. In addition, there are no clinical guidelines that recommend the use of PRP or PDGF. Therefore, the use of PRP or PDGF is considered investigational for these indications.

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CODES

Codes	Number	Description
CPT	0232T	Injection(s) platelet rich plasma, any tissue including image guidance, harvesting and preparation when performed.

HCPCS	G0460	Autologous platelet rich plasma or other blood-derived product for non-diabetic chronic wounds/ulcers, including as applicable phlebotomy, centrifugation or mixing, and all other preparatory procedures, administration and dressings, per treatment
	G0465	Autologous platelet rich plasma (PRP) or other blood-derived product for diabetic chronic wounds/ulcers, using an FDA-cleared device for this indication, (includes as applicable administration, dressings, phlebotomy, centrifugation or mixing, and all other preparatory procedures, per treatment)
	P9020	Platelet rich plasma, each unit
	S9055	Procuren or other growth factor preparation to promote wound healing

Date of Origin: *November 1999*