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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

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

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.

Platelet-rich plasma 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 (eg, 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 RCTs and systematic reviews (SRs).

FORMULA PREPARATION

Several articles described different methods of preparation of autologous platelet-rich plasma, 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

Wang (2014) published a SR that addressed the efficacy of PRP in treatment of acute wounds in 13 studies (N=982).[7] Wound healing time was shorter in the PRP treated patients compared to the control group, as was the length of hospital stay (mean difference [MD]: -1.45, 95% 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

No published RCTs were identified after the above SR.

MULTIPLE TYPES OF WOUNDS

Systematic Reviews

An industry-funded SR included 21 studies on PRP gel for cutaneous wound healing, 12 of which were RCTs.[8] 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 address 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 SR.

CHRONIC WOUNDS

Systematic Reviews

Cochran (2016) updated their 2012 review and added one new RCT.[9] The authors concluded that while PRP may improve healing of diabetic foot ulcers, this is based on only low-quality evidence from two small RCTs, and that well-designed clinical trials are needed.

A 2012 Cochrane SR included nine RCTs (N=325) on PRP for treating chronic wounds.[10] 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)[11] and Aurix™ (Nuo Therapeutics) (previously AutoloGel™, Cytomedix).[12] 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.

An industry-funded SR on PRP gel for cutaneous wound healing (described above), included four RCTs that evaluated complete healing of chronic wounds.[8] 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 SR identified 42 controlled trials on PRP; 20 of these were RCTs and were included in the SR.[13] The 20 RCTs comprised 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

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.[14] The study randomized 52 patients, 50 of whom received the allocated PRP intervention. There were no significant differences in short term (5-7 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.

Escamilla Cardenosa (2016) published an unblinded RCT comparing PRP and saline for venous ulcer treatment.[15] The study included 61 patients (n=102 ulcers) who were randomized to weekly application of a PRP dressing (n=31 patients, 55 ulcers) or to weekly wet-to-dry dressing changes with saline (n=30 patients, 47 ulcers) over a 24-week period. The average percentage healed area in the PRP group was 67.7% (vs 11.2% in the control group; P=0.0001). PRP group members had greater reductions in pain with the intervention.

NONSURGICAL TREATMENT FOR MUSCULOSKELETAL DISORDERS

MUSCULOSKELETAL SOFT TISSUE INJURIES

Systematic Reviews

A 2016 health technology review on PRP and autologous blood injections (ABI) was completed by the Washington State Health Care Authority (WSHCA).[16] 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 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 longterm (one RCT)."

There are a number of other SRs of studies on PRP for treating mixed tendinopathies. These included trials on tendinopathies of the Achilles, rotator cuff, patella and/or lateral epicondyle (tennis elbow). Recent (i.e. 2014 to present) SRs of RCTs and/or nonrandomized studies are described next.

Tsikopoulos (2016) published a SRs of PRP compared with placebo or dry needling in patients with tendinopathy lasting at least 6 weeks.[17] Minimum length of follow-up was 6 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, 2 rotator cuff tendinopathy, and 2 patellar tendinopathy. Three studies had a saline control group and 2 compared PRP with dry needling. In a pooled analysis of all 5 trials, there was no statistically significant difference in pain intensity at 2 to 3 months with PRP or placebo/dry needling (standardized mean difference [SMD], -0.29; 95% confidence interval [CI], -0.60 to 0.02). The between-groups difference in pain intensity was statistically significant at 6 months in a pooled analysis of the 4 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 6 months was not clinically significant. Three studies reported functional disability levels at 3 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 6 months postintervention was not addressed in this review.

Balasubramaniam (2015) published a SR that included RCTs on PRP for tendinopathy.[18] 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 (n=three), dry needling (n=two), ABI (n=two), extracorporeal shock wave therapy (n=one), corticosteroid injections (n=two) (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 1 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 SR of PRP in the treatment of painful tendinopathies.[19] 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 was considered to be 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.

A 2014 Cochrane SR 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.[20] Primary outcomes were functional status, pain, and adverse effects. Nineteen 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

Wang (2015) reported a prospective controlled study of PRP treatment after supraspinatus repair to determine the treatment's ability to improve early tendon healing and functional recovery.[21] Sixty patients underwent arthroscopic double-row supraspinatus seven and fourteen. Structural healing and integrity, assessed at 16 weeks by MRI, were similar between the PRP-treated and control groups. Measures of function recovery (assessed at weeks six, twelve and sixteen) were also similar between the treated and control groups.

LATERAL EPICONDYLITIS

Systematic Reviews

The WSHCA health technology review (previously described) evaluated the use of PRP to treat elbow epicondylitis.[16] 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.

de Vos (2014)published a SR of RCTs.[22] The review included seven studies on six RCTs, including three RCTs[13-15] from the 2014 Cochrane SR 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 (214) rated them as high quality along with two other RCTs[23,24]. The remaining two RCTs[25,26] 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[23,24], which used a corticosteroid injection in the control group, reported continued significant effect of PRP during the followup period; however, the authors of the SR noted that corticosteroid injections are harmful in tendinopathy. The authors also noted the following limitations of this SR: 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 SR on the use of PRP in soft tissue injuries [20] 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[27,28] and saline[29] 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 Krogh and Thanasas tending to favor PRP therapy while Creaney 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 ($\leq$ 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.

A SR and network meta-analysis compared the use of PRP, ABI, and corticosteroid injection.[30] This analysis included the RCTs that were in the deVos review (described above) with one additional RCT. The network analysis did not demonstrate a statistically significant difference between PRP and ABI in pain and function measures, with the exception of pressure pain threshold, which showed improvement in the ABI group. Both blood and PRP injections improved outcomes relative to corticosteroid injection. The authors noted that those receiving ABI had a higher rate of adverse events than those receiving PRP or corticosteroid injections.

Randomized Controlled Trials

Palacio (2016) published a RCT that randomized 60 patients to one of three treatments: PRP, neocaine, or dexamethasone.[31] 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 (CS) injections for the treatment of lateral epicondylitis (LE) in 30 patients with recalcitrant LE not responsive to oral medication or non-invasive treatment.[32] 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 CS group for VAS for pain (77% vs. 59%), 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 Review

Sheth (2012) published a SR 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.[33] 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 a visual analog score (VAS) and 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 SR 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 published RCTs were identified after the above SR.

ACHILLES TENDINOPATHY

Systematic Reviews

The WSHCA health technology assessment (previously described) evaluated two small RCTs that compared PRP to a conservative control (saline injection or exercise) in patients with Achilles tendinopathy.[16] 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.[34,35] No participants were lost to follow-up. The authors found no difference in VISA-A scores between the two groups at 6-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.[36] 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.

Other SRs evaluated only the RCT above which compared PRP to saline injection[34], including the previously described 2014 Cochrane SR[20], the Andia review[19], and a SR by Di Matteo.[37] The Di Matteo review also included nonrandomized studies and concluded that, the encouraging findings in case series were not found in the placebo-controlled RCT.

Randomized Controlled Trials

A small RCT has been published since the SR.[38] This trial included 24 patients with chronic Achilles tendinopathy that were randomized to either PRP or saline injections. After 3 months follow-up, there was no significant difference in the primary outcome of VISA-A score change. Results after the 3-month follow-up could not be attained due to the large dropout of 75% of patients in the PRP group and 33% in the saline group after this point.

OTHER TENDINOPATHIES

Systematic Reviews

Miller (2017) conducted a systematic review and meta-analysis on PRP for symptomatic tendinopathy and included only RCTs with injection controls.[39] The literature search, conducted through November 2016, identified 16 RCTs, with 18 groups (some studies included >1 tendinopathy site) for inclusion (total N=1018 patients). The Cochrane Collaboration tool was used to assess the risk of bias: 5 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 (3 groups), Achilles (2 groups), and

patellar (1 group). Preparation of PRP differed across trials as did the number of injections, with most studies administering 1 injection and a few administering 2 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 standard mean difference (SMD) in pain scores favoring PRP over control (0.47; 95% confidence interval [CI], 0.21 to 0.72; I^2=67%).

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.[16] 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.

Fitzpatrick (2016) published a SR that assessed the use of PRP for tendinopathy and included 18 RCTs, 8 of which were determined to be at low risk of bias.[40] 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.[41]

Three other SRs for various tendinopathies found few randomized trials, and no studies of high-quality design.[4,42,43] 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 SRs concluded that well-designed, large, long-term, randomized trials with appropriate control groups are needed to determine the impact of PRP for chronic tendinopathies.

Randomized Controlled Trials

No published RCTs were identified after the above SR.

PLANTAR FASCIITIS

Systematic Review

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.[16] The control treatments were steroid injection (3 RCTs), prolotherapy (1 RCT), and extracorporeal shockwave therapy and conservative care (1 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 (1 RCT) and better pain scores with PRP versus steroid (1 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 (1 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."

Hsiao (2015) published a study that compared the efficacy of autologous blood-derived products, corticosteroids (CS) and shock-wave (SW) therapy in the treatment of plantar fasciitis, including seven RCTs and three quasi-experimental studies (N=604).[44] 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 CS. 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 odds ratio) between the three treatments.

Franceschi (2014) published a qualitative SRs 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).[45] 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 (RCTs)

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,[46] ABI,[47], steroid injection,[48,49] and saline.[49] In the majority of studies that included a direct comparison between treatments, improvements with PRP were not significantly different from those with control treatments.[46-48] 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.[49]

OSTEOCHONDRAL LESIONS AND OSTEOARTHRITIS (OA)

Systematic Reviews

Xu (2017) conducted a systematic review and meta-analysis of RCTs comparing PRP with hyaluronic acid (8 trials), or placebo (2 trials), for the treatment of knee OA.[50] 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 7 of the trials comparing PRP with hyaluronic acid showed that PRP significantly improved Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) or International Knee Documentation Committee (IKDC) scores compared with HA at 6-month follow-up; however, when meta-analyses included only the two high-quality RCTs, there was not a significant difference

between PRP and hyaluronic acid. (Note that WOMAC evaluates 3 domains: pain, scored from 0-20; stiffness, scored from 0-8; and physical function, scored from 0-68. 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≥90%).

The 2016 WSHCA health technology review evaluated the use of PRP for osteoarthritis of the knee, hip, and temporomandibular joint (TMJ).[16] Six RCTs and four cohort studies were included that compared PRP with hyaluronic acid (HA). Among the RCTS (two at low, twos 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 SR addressing PRP treatment for knee osteoarthritis (OA), including nine RCTs.[51] 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 SRs also comparing PRP to HA or saline controls.[52-54] In general, the recent SRs 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 SR of PRP for degenerative cartilage pathology in knee joints included five RCTs, three quasi-RCTs, and eight single-arm prospective series (N=1543) comparing PRP with HA (four RCTs and two quasi-randomized[55-60]) or saline (one RCT[61]).[62] 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 other SRs on knee OA.[63-65] Low level of evidence, small sample sizes, and wide variability in treatment were limitations cited.

Dold analyzed 10 studies of PRP for treatment of osteochondral pathology.[66] Two studies were RCTs[60,67], one was a prospective quasi-randomized comparative study,[68] 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 (RCTs)

Trueba Vasavilbaso (2017) conducted a controlled trial that randomized patients after knee arthroscopy to 5 injections of Suprahyal/Adant (n=10), 4 injections of Orthovisc (n=10), 3 injections of Synvisc (n=10), 1 injection of PRP (n=10), or standard of care (n=10).[69] 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.

Cole (2017) published a RCT comparing hyaluronic acid (HA) with platelet-rich plasma (PRP) for the treatment of knee osteoarthritis. Patients received either HA (n=50) or PRP (n=49) and were evaluated using varied measures before treatments and four additional times over the next year. In addition, synovial fluid was evaluated for anti-inflammatory markers before treatment and 12 and 24 weeks after. The authors reported there was no difference between treatments with HA or PRP, based on the WOMAC score (the primary outcome measure), but other measures favored PRP. This trial was limited in size.

Duymus (2017) published a randomized study comparing outcomes of treatment with platelet-rich plasma (PRP), hyaluronic acid (HA) or ozone gas for 102 patients with knee osteoarthritis.[70] Group one received two does or PRP. Group two received HA one time. Group three received four doses of ozone gas. Evaluations took place before treatment and at one, three, six and twelve months after. Although the authors noted PRP relieved pain more than HA and ozone gas, this study was limited in size.

A double-blind RCT of PRP versus HA for the treatment of osteoarthritic knee pain was conducted in a Spanish National Health Care System hospital.[71] The trial included 53 patients, with evaluations at 3- and 6-months after treatment. Both the PRP and HA groups had improvements in pain scores and functional measures. PRP appeared to be more effective than HA in patients with lower osteoarthritis grades. There was no statistically significant differences in knee pain between the treatment groups.

Another recent double-blind RCT compared PRP to corticosteroid injection in 41 participants.[72] Outcomes, including knee injury and osteoarthritis outcome score (KOOS), 20-meter walk test, active and passive ranges of motion (ROM), flexion contracture and pain (VAS) were assessed at baseline and 2- and 6-months after treatment. The group receiving

PRP had greater improvements in pain, activities of daily living, walk test, and quality of life compared to the group receiving corticosteroids. Neither treatment improved ROM or flexion contracture.

A trial by Simental-Mendia (2016) compared PRP to control acetaminophen in 65 patients with early knee osteoarthritis.[73] In this study, 32 patients were randomized to acetaminophen (500 mg/8 h) and 33 received three injections of leukocyte-poor PRP (once every 2 weeks). The outcomes assessed included pain by VAS, function, WOMAC index, and self-reported health (SF-12). The authors reported a greater improvements in pain, function, and self-reported health with PRP treatment. However, this study was not blinded and included only patient-reported outcomes, indicating a substantial risk of bias.

Dallari (2016) evaluated PRP in 111 patients with hip osteoarthritis.[74] These patients were randomize to 1 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 he 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 6 months, and an improved WOMAC score at 2 and 6 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 SRs were identified.

Randomized Controlled Trials (RCTs)

One RCT was found for use of autologous growth factor concentrate (AGF), including PRP, as an adjunct to lumbar fusion.[75] In this small trial, outcomes for 40 patients who underwent spinal fusion with AGF (n=20) versus without AGF (n=20). 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 Review

Saltzman (2015) published a SRs and meta-analyses on PRP at the time of surgery and clinical outcomes in patients undergoing rotator cuff repair.[76] The authors identified 7 studies, all published after 2012, that performed pooled analyses of trial data. SRs 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 1 study that reported it was 1.11. One of the meta-analyses included in the Saltzmann review,

however, found a significantly lower risk of retear with PRP use when an outlier study was excluded from the analysis.

Zhao conducted a meta-analysis of eight RCTs (with sample sizes ranging from 28 to 88 and a combined total of 464 patients)[77-84] of arthroscopic full thickness rotator cuff tear repair with or without PRP that were published from 1980 to September 2013.[85] 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 SRs that have looked at the effectiveness of PRP treatment for both large and small to medium rotator cuff tears.[86,87]

Randomized Controlled Trials (RCTs)

A recent double-blind RCT compared intraoperative PRP to local anaesthetic injection in 120 patients undergoing arthroscopic rotator cuff repair.[88] 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.

Another RCT published in 2016 evaluated the use of PRP during arthroscopic rotator cuff surgery in 102 patients, with a minimum follow-up of two years.[89] 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 1-, 3-, and 6-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 a 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. Seventy four patients were randomized to undergo either PRP-augmented repair (PRP group) or conventional repair (conventional group).[90] 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).[91] 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 2-year followup 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.

Everts (2008) reported a rigorously conducted, small (n=40) double-blinded RCT of platelet and leukocyte-rich plasma (PLRP) gel following open subacromial decompression surgery in a carefully selected patient population.[92] Blood was drawn from all patients after induction of anesthesia to maintain blinding. PLRP with autologous thrombin was injected into both the subacromial intracapsular space and the subcutaneous layer covering the incision during wound closure. Postoperative examinations at 1, 2, 4, and 6 weeks were performed by independent evaluators; unique patient identifier codes were used to maintain patient and investigator blinding. Neither self-assessed nor physician-assessed instability were improved. Both subjective pain and use of pain medication were significantly lower in the PRP group across the six weeks of measurements. For example, at two weeks after surgery VAS scores for pain were lower by about 50% in the PLRP group (close to four in the control group and close to two in the PLRP group) and only one patient (5%) was taking pain medication compared with 10 (50%) control patients. Objective measures of range of motion showed clinically significant improvement in the PLRP group across the 6-week assessment period. Significantly more patients in the PLRP group reported improvements in activities of daily living such as ability to sleep on the operated shoulder at four weeks after surgery and earlier return to work. This RCT was limited by the small number of patients and by the very short-term follow-up period. In addition, it is unclear whether the results can be generalized to the broader population of patients requiring subacromial decompression surgery. These short-term data must be validated in larger, long-term RCTs.

KNEE SURGERIES

Systematic Reviews

A 2015 qualitative SRs by Figuera assessed PRP as an adjunct to ACL reconstruction, including 11 RCTs or prospective cohort studies (N=516 patients).[93] 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 2-year follow-up.[94] Similar conclusions were reported by a second SRs that included fifteen clinical trials (11 RCTs, 3 prospective comparative studies, and 1 retrospective comparative trial.[95]

A SRs by Liddle and Rodríguez-Merchán addressed the safety and efficacy of PRP treatment for patellar tendinopathy (PT) as well as the effectiveness relative to other treatments.[96] This review, including one RCT and two nonrandomized cohort studies, determined that although adverse outcomes were rare, that PRP treatment superiority over other treatments such as physical therapy could not be conclusively demonstrated.

The 2014 Cochrane SR[20] of platelet-rich therapies for musculoskeletal soft tissue injuries (described above) identified four trials[94,97-99] (N=203) on PRP applied to the knee bone tunnels and/or the inner area of the graft during ACL reconstruction. At 1-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.[100,101] Cervellin reported significant differences in functional scores in favor of the PRP group at 1-year follow-up. Almeida 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 (RCTs)

One small RCT has been conducted to assess the effects of PRP on outcomes of total knee arthroplasty (TKA). 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.[102]

LONG BONE NONUNION

Systematic Reviews

A 2012 Cochrane SR found only one small (n=21) RCT[103] of allogeneic bone graft with or without PRP for long bone healing.[104] Three patients (14%) were lost to followup. At 1-year followup, 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.

Randomized Controlled Trials (RCTs)

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.[105] 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.

OTHER SURGICAL PROCEDURES

There were several additional articles 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[106]
- Periodontal surgery[107,108]
- Incision site wound closure in vascular surgeries[109-111]
- Blepharoplasty[112]
- Tonsillectomy in children[113]
- Microfracture surgery for talar injuries[114]

OPHTHALMOLOGIC CONDITIONS AND PROCEDURES

Use of PRP has been studied as a treatment of persistent corneal defects[115], symptomatic dry eye[116], chemical burns[117], post-LASIK ocular surface syndrome[118]. Studies are limited to small pilot studies with no control groups. No randomized trials were identified.

PRACTICE GUIDELINE SUMMARY

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE (NICE)

NICE (2016) updated its guidance on the prevention and management of diabetic foot problems.[119] The guidance states that neither autologous platelet-rich plasma gel nor platelet-derived growth factor should be offered in the treatment of diabetic foot ulcers.

NICE (2014) issued guidance on use of platelet-rich plasma for osteoarthritis of the knee.[120] NICE concluded that current evidence on platelet-rich plasma injections for osteoarthritis of the knee raises no major safety concerns; however, the evidence on efficacy is inadequate in quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. In addition, physicians should ensure that patients understand the uncertainty about the procedure's efficacy, be aware of alternative treatments, and be provided with clear written information.

AMERICAN COLLEGE OF PHYSICIANS

American College of Physicians (ACP) (2015) published guidelines on treatment of pressure ulcers.[121] 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.”

ASSOCIATION FOR THE ADVANCEMENT OF WOUND CARE

Association for the Advancement of Wound Care (2014) developed guidelines pressure ulcers and on venous ulcer[122,123]: 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.”[124]

AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS (AAOS)

The 2013 AAOS guidelines were unable to recommend for or against growth factor injections and/or PRP for patients with symptomatic osteoarthritis of the knee. The inconclusive recommendation was based on a single low-quality study with conflicting findings.[125] The 2010 AAOS guidelines did not recommend the use of PRP as first line treatment for rotator cuff tear until more evidence is available (including the surgical scenarios). This recommendation was due to the absence of convincing evidence and in light of the associated out of pocket cost.[126]

SUMMARY

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 for any indication is considered investigational.

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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 for chronic wounds/ulcers, including phlebotomy, centrifugation, and all other preparatory procedures and administration, per treatment
	P9020	Platelet rich plasma, each unit
	S9055	Procuren or other growth factor preparation to promote wound healing

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