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Review Article

Platelet-Rich Plasma in Management of Common Orthopaedic Conditions: A Systematic Review with Discussion of Cost Analysis

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Abstract

Background: Novel non-operative management methods for various orthopaedic conditions is something that orthopaedic surgeons continue to seek. Platelet-rich plasma (PRP) has seen increasing orthopaedic applications over the past 5 years. There is a lack of reliable, evidence-based information to guide orthopaedic clinicians in making decisions that consider both patient outcomes as well as cost-related efficacy of PRP application.

Hypothesis/Purpose: PRP will not demonstrate a significant cost-effective advantage over alternative management options.

Study Design: Systematic Review.

Methods: Utilizing MeSH keywords, the PubMed and National Institute for Health Research Centre for Reviews and Dissemination databases were utilized, with minimal qualifiers, to identify studies investigating PRP application in knee osteoarthritis, total knee arthroplasty, tendinopathy, ligament pathology, and tear or rupture, repair, and reconstruction of ligaments or tendons.

Results: For all of the conditions investigated, studies included supported or refuted the clinical utility of PRP. Some studies found evidence of a significant advantage from PRP use over alternative interventions, but quality and bias of included studies were a major limiting factor. Others qualified the advantage as specific to certain time points or due to other factors unrelated to the effect of PRP. A significant portion of the studies found no statistical evidence of superiority of PRP over other interventions. However, the majority of studies found that PRP did, at the least, result in improved findings compared to baseline measures.

Conclusions: A cost analysis is not possible given the inconclusive evidence and lack of cost information. Stronger, high-quality studies with low risk for bias must be conducted, and standardization must be completed in all aspects of studies comparing PRP efficacy in order to strengthen recommendations made based on the evidence. Given the current level of evidence, if cost information could be obtained, a cost-minimization analysis may be best suited to highlight cost-effectiveness of PRP compared to alternatives.

Clinical Relevance: Consideration of cost with respect to outcomes can help physicians and patients make clear, evidence-based and fiscally-responsible decisions regarding the use of PRP for common musculoskeletal problems.

Keywords: *Platelet-Rich Plasma; Cost Analysis; Tendinopathy; Knee Osteoarthritis; Tendon Rupture*

Abbreviations

OA: Osteoarthritis; TKA: Total Knee Arthroplasty; LE: Lateral Epicondylitis; DALY: Disability-Adjusted Life Year; QOL: Quality Of Life; NSAID: Non-Steroidal Anti-Inflammatory Drug; HA: Hyaluronic Acid; PRP: Platelet-Rich Plasma; VEGF: Vascular Endothelial Growth Factor; PDGF: Platelet-Derived Growth Factor, TGF-B: Transforming Growth Factor-B; CBA: Cost-Benefit Analysis; CUA: Cost-Utility Analysis; QALY: Quality-Adjusted Life Year; CEA: Cost-Effective Analysis; CMA: Cost-Minimization Analysis, RCT: Randomized Controlled Trial; SR: Systematic Review; MA: Meta-Analysis

Introduction

Novel non-operative management methods for various orthopaedic conditions is something that orthopaedic surgeons continue to seek. Biologics that utilize endogenous biochemical pathways are one of the greatest areas of interest for both clinicians and investigators [15]. Common among these problems are tendinopathies (non-ruptured tendon injuries), knee osteoarthritis (OA), total knee arthroplasty (TKA) post-operative healing, and augmented recovery for tendon repair and ligament reconstruction [17].

Tendinopathy is commonly encountered, yielding over two million visits to physicians in the United States in 2001. Overuse injuries, including rotator cuff (RC) tendinopathy or lateral epicondylitis (LE), comprise nearly 30 - 50% of all sports-related injuries as well as almost 50% of all work-related illnesses in the United States [23]. Knee OA comprises 83% of total OA cases globally and is among the top ten non-communicable diseases globally leading to an increased number of years lived with disability and life lost (disability-adjusted life years; DALYs). Outcomes typically result in reduction of quality of life (QOL) and physical disability [9].

Currently, tendinopathies are managed with exercise therapy and non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids [2]. Conservative management of knee OA includes pain-relieving medications or injection therapies, such as intra-articular corticosteroids or synthetic hyaluronic acid (HA). However, these methods have shown limited time of effectiveness and adverse reactions, respectively [7,9]. Recent interest in augmenting regeneration or healing of native musculoskeletal soft tissue (bone, cartilage, ligament, and tendon) may lead to a shift in current treatment paradigms [15,34]. TKA is generally reserved for treatment of severe OA [9].

Among biologics, platelet-rich plasma (PRP) is considered to be the most common means of facilitating tissue regeneration [34]. Platelets have a defined role in coagulation, inflammation, and immune regulation. Factors released by platelets include vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor-β (TGF-β). These promote tissue remodeling, wound healing, and angiogenesis. Platelets also have analgesic properties. PRP is an autologous blood product that contains much higher platelet concentrations than those of whole blood [17,36]. Several studies have demonstrated the prospective benefits PRP can produce in enabling cellular growth and regeneration of musculoskeletal soft tissues [34].

Autologous PRP has seen increasing orthopaedic applications over the past 5 years [17]. Clinical use of PRP ranges back to the 1990's, when it was deployed as an adjuvant for bone healing following spinal injury and plastic/reconstructive surgery [8]. With its recent spike in usage for commonly-encountered orthopaedic conditions, investigations into its treatment utility have concurrently increased [34]. Many studies demonstrate that PRP can yield improvement in both clinical and physical measures from baseline as well as against alternative methods; yet in many cases, the differences between study groups are not significant. Nonetheless, it is still a highly sought after intervention by patients and is recurrently utilized by physicians [15]. PRP has seen popularization partly due to successful, albeit short-term, demonstrations of success with professional athletes and sports medicine [25].

There is a lack of reliable, evidence-based information to guide orthopaedic clinicians in making decisions that consider both patient outcomes as well as cost-related efficacy of PRP application [15]. Many physicians lack strong backgrounds in economic analysis, while most economists and policy-makers have insufficient clinical proficiency. Recent estimates suggest that nearly 33% of US healthcare expenditure is due to misuse, underuse, or overuse. Cost analyses are commonly misconstrued as a cold-accounting exercise that prioritizes fiscal responsibility over patient well-being. Rather, they can help clinicians identify the treatment modality that yields "the most good per additional expense." By employing treatments that are both clinically- and cost-effective, physicians' interventions can simultaneously maximize benefits to patients as well as to healthcare expenditure [35]. This is especially vital with respect to PRP, given that the market valuation of PRP was approximately $45 million in 2009 and is believed to surpass $120 million by 2016 [15].

Cost analyses consider all of the direct costs incurred by the patient as well as the indirect treatment costs, such as facility and equipment costs, etc., and evaluate them in relation to various outcome measures. Common methods include cost-benefit analysis (CBA; outcome = value of outcomes), cost-utility analysis (CUA; outcome = generic outcomes, such as quality-adjusted life years (QALYs)), cost-

effective analysis (CEA; outcome = any clinical outcome), and cost-minimization analysis (CMA; an outdated method that bridges cost analyses and CEAs) [35].

The goal of this investigation is to compare PRP treatment with current standards of treatment for several common musculoskeletal problems. This may best be accomplished by conducting a cost analysis. The aim is to quantify and compare cost-effectiveness and/or utility in terms of patient costs and QALYs, or other similar composite outcome measures more suitable for orthopaedic conditions. It is likely that PRP will ultimately prove to be a cost-ineffective treatment when compared to standard and alternative management options of the orthopaedic conditions evaluated in this study.

Materials and Methods

Two primary databases were selected: PubMed and the National Institute for Health Research (NIHR) Centre for Reviews and Dissemination (CRD) database. Both databases utilize MeSH keyword searches, allowing for standardized search development. Searches were performed between November 15 and November 22, 2014 as well as between March 8 and March 20, 2016. Search strategies utilized are outlined below.

PubMed

MeSH Terms Utilized	*Search String/Query*	*Additional Filters Utilized*	*Results Obtained/**Results Included***	*Study Types*
"Tendinopathy," "Platelet-Rich Plasma," "Costs and Cost Analysis"	(("Tendinopathy"[Mesh]) AND "Platelet-Rich Plasma"[Mesh]) AND "Costs and Cost Analysis"[Mesh]	NO filters utilized (to broaden search)	**0/0**	N/A
"Tendinopathy," "Platelet-Rich Plasma," "Humans"	"Tendinopathy"[Mesh] AND "Platelet-Rich Plasma"[Mesh] AND ((Clinical Trial[ptyp] OR Review[ptyp]) AND "2009/11/25"[PDat] : "2014/11/23"[PDat] AND "humans"[MeSH Terms])	Limited Date Range to 11/25/09 – 11/23/2014	**40/5**	RCT or SR (PRP application) – **4** Comparative measures utilized (Pain, Activity, Cost, QALY, etc.) – **1**
"Tendinopathy," "Platelet-Rich Plasma," "Costs and Cost Analysis," "Humans"	("Tendinopathy"[Mesh] OR "Platelet-Rich Plasma"[Mesh]) AND "Costs and Cost Analysis"[Mesh] AND ("2004/11/26"[PDat] : "2014/11/23"[PDat] AND "humans"[MeSH Terms])	Limits on Article Type removed	**11/3**	RCT or SR (Cost-Effectiveness of PRP related to TKA) – **1** Cost analysis of PRP application to unrelated condition (Diabetic Cutaneous Ulcers) – **2**

Table 1: *Tendinopathy-specific search results.*

MeSH keyword searches were utilized. No sub-categories of any MeSH keywords were selected due to the already limited number of available studies related to the subject matter. Unless otherwise specified, a defined set of filters or limits were utilized for all searches. Article types were restricted to "Clinical Trial" and "Review." No limits were selected to text availability. Publication dates were restricted to

within the last ten years. Species were restricted to "Humans." In order to ensure studies of adequate or superb quality were selected, each result was reviewed to determine relevance and study strength. Inclusion criteria were randomized controlled trials (RCTs) or systematic reviews (SRs) and meta-analyses (MAs) related to application of PRP to select orthopaedic conditions, cost analyses evaluating PRP use as treatment for select orthopaedic conditions, and/or studies utilizing other comparative measures to evaluate PRP use (pain, activity levels, costs, QALYs, standardized questionnaires or scales). Other studies included involved models that evaluated cost-effectiveness of PRP application to related or unrelated medical conditions to help serve as a reference of comparison for this investigation. Search summaries are outlined in the tables below.

MeSH Terms Utilized	*Search String/Query*	*Additional Filters Utilized*	*Results Obtained/**Results Included***	*Study Types*
"Platelet-Rich Plasma," "Osteoarthritis, Knee," "Humans"	"Platelet-Rich Plasma"[Mesh] AND "Osteoarthritis, Knee"[Mesh] AND ((Clinical Trial[ptyp] OR Review[ptyp]) AND "2004/11/26"[PDat] : "2014/11/23"[PDat] AND "humans"[MeSH Terms])	N/A	24/**5**	RCT or SR (PRP comparative studies) – **5**

Table 2: *Knee OA-specific search results.*

MeSH Terms Utilized	*Search String/Query*	*Additional Filters Utilized*	*Results Obtained/**Results Included***	*Study Types*
"Ligaments," "Tendons," "Platelet-Rich Plasma," "Humans"	("Ligaments"[Mesh] OR "Tendons"[Mesh]) AND "Platelet-Rich Plasma"[Mesh] AND ((Clinical Trial[ptyp] OR Review[ptyp]) AND "2004/11/26"[PDat] : "2014/11/23"[PDat] AND "humans"[MeSH Terms])	N/A	72/**12** Preference given to studies with follow-up longer than 6 months and study group size of at least 30 patients (n>30)	RCT, Cohort, or Case Studies – **9** SR – **3**

Table 3: *Ligament and Tendon-related search results.*

NIHR CRD

Searches were restricted to the National Health Service Economic Evaluation Database (NHS EED). Included categories were "Cochrane review," "Cochrane-related review record," "CRD assess," "CRD assessed economic evaluation (bibliographic)," and "CRD assessed economic evaluation (full abstract)." Both MeSH searches and Keyword searches were utilized in order to identify relevant studies in this database.

The first search conducted was a "MeSH Search." The keyword utilized was "Platelet-Rich Plasma." This searched all of the databases within the NIHR CRD. Forty-five results were obtained, and three studies were selected utilizing the inclusion criteria previously described.

The second search conducted was a "Keyword Search." The keywords utilized were "Platelet rich plasma" and "Cost." For both terms, "Any Field" was selected. The search query was as follows: ((platelet rich plasma) AND (cost)) and ((Cochrane review: ZDT) OR (Cochrane related review record: ZDT) OR (Economic evaluation: ZDT and Bibliographic: ZPS) OR (Economic evaluation: ZDT and Abstract: ZPS)) IN NHSEED. Five results were obtained, and two studies were selected due to their assessment of cost-effectiveness and/or comparative efficacy of orthopaedic PRP application against standard/alternative methods.

Results and Discussion

Results

After removing duplicates and filtering out studies of non-orthopaedic conditions, 23 studies were selected. These include ten studies related to knee OA and TKA, seven studies related to tendinopathy and ligament pathology, and six studies pertaining to repair/reconstruction of tendon and ligament ruptures/tears. Results are outlined below as well as in Table 4. Levels of evidence are defined in Table 5.

First Author	Publication Date	Study Design	Level of Evidence	Study Population
Knee OA and TKA				
Rayegani, SM [29]	2014	RCT	1	62 patients
Filardo, G [14]	2012	RCT	1	109 patients
Cerza, F [5]	2012	RCT	1	120 patients; 1:1 ratio.
Say, F [32]	2013	Prospective study	2	90 patients
Khoshbin, A [20]	2013	SR	2	6 Level 1 & 2 studies, n = 577 patients
Anitua, E [1]	2014	SR	5	91 citations, 5 eligible: 2 RCTs, 2 Prospective Studies, 1 retrospective analysis.
Bernasek, TL [3]	2012	Retrospective review	3	400 patients
Chang, KV [7]	2014	SR & MA	5	8-single arm studies, 3-quasi-experimental studies, 5 RCTs (n = 1543)
Dold, AP [12]	2014	SR	5	10 studies
Raeissadat, SA [27]	2013	Observational Study	4	60 patients
Tendinopathy and Ligament Pathology				
Kesikburun, S [19]	2013	RCT	1	40 patients (18-70 y/o)
de Jonge, S [11]	2011	RCT	1	54 patients (18-70 y/o)
Krogh, TP [22]	2013	RCT	1	60 patients
Gosens, T [16]	2012	Prospective study	2	36 patients
Krogh, TP [21]	2013	SR + Network MA	5	17 trials (n = 1381)
Coombes, BK [10]	2010	SR	5	41 studies → n = 2672
Sadoghi, P [31]	2013	SR	5	14 manuscripts included
Tendon and Ligament Rupture/Tear, Repair and Reconstruction				
Jo, CH [18]	2013	RCT	1	48 patients
Ruiz-Moneo, P [30]	2013	RCT	1	63 patients
Cervellin, M [4]	2012	Prospective RCT	1	40 young athletes
Randelli, P [28]	2011	Prospective RCT	1	53 patients
Chahal, J [6]	2012	SR + Quantitative Synthesis	3	5 studies: 2 RCT, 3 Non-randomized, comparative control groups) → n = 261
Podesta, L [26]	2013	Case Series	4	34 athletes

Table 4: *Summary of included studies organized by musculoskeletal problem.*

Level	Description
Level 0	Preclinical studies- including experimental studies and animal models
Level 1	Randomized Controlled Trials
Level 2	Non-randomized controlled trials- a prospective (pre-planned) study with a predetermined eligibility criteria and outcome measures
Level 3	Observational studies with controls- includes retrospective, case-control studies and cohort studies
Level 4	Observational studies without controls- include cohort studies without controls, case series without controls, case studies without controls
Level 5	Systematic reviews and meta-analyses

Table 5: *Levels of Evidence.*

Knee OA and TKA

Several RCTs were included in this evaluation of PRP application for knee OA and TKA, demonstrating varied results. None of these trials included consideration of cost when evaluating outcomes. Outcome measures and questionnaires commonly utilized included, but were not limited to, the Western Ontario and McMaster University's Arthritis Index (WOMAC), SF-36, and Knee Injury and Osteoarthritis Outcome Score (KOOS).

WOMAC score evaluation was common to some of these RCTs. Rayegani., *et al*. [29] designed an RCT (n = 62) following an experimental group prescribed with therapeutic exercise and two courses of leukocyte rich PRP (LR-PRP) at four-week intervals. The control group underwent exercise only. Patients completed WOMAC and SF-36 questionnaires at baseline and six months following treatment protocols. Mean total WOMAC scores showed significant improvement at six-month follow-ups ($p < 0.05$, paired t-test). All three WOMAC parameters within each group showed improvements at six months, whereas the mean difference of WOMAC subgroups between the two study groups was significant only for pain (Table 6). The physical and mental components of the SF-36 for LR-PRP recipients also showed significant improvements over controls.

Parameters	Baseline	6 months	p (Intra-group)	p (between groups)
Pain				
PRP	9.13 ± 3.72	4.2 ± 3.08	0.001	0.006
Control	7.12 ± 3.67	5.16 ± 4.5	0.007	
Stiffness				
PRP	2.3 ± 1.76	0.83 ± 1.28	0.001	0.17
Control	1.67 ± 1.64	0.83 ± 1.31	0.014	
Functional Capacity				
PRP	31.86 ± 9.81	14.1 ± 9.12	0.001	0.09
Control	25.03 ± 17.25	13.93 ± 13.4	0.001	

Table 6: *Changes in WOMAC sub-group scores at baseline and following six-month follow-up for both groups (paired T-test used, $p< 0.05$) [29].*

Cerza., *et al.* [5] conducted an RCT comparing the clinical response of HA and PRP in two groups of patients affected by knee OA. Patients (n = 120) were equally randomized into two study groups (HA or PRP). The PRP group received four intra-articular PRP injections (5.5 mL of autologous conditioned plasma (ACP)). The HA group received four intra-articular injections of HA (20 mg/2 mL). Unblinded

physicians administered all injections once weekly for four weeks. WOMAC scores were obtained prior to treatment as well as 4, 12, and 24 weeks following the first injection. The PRP group showed steady significant improvement in WOMAC scores through the entire measurement period compared to the HA group (HA/65.1 vs. ACP/36.5; $p < 0.001$). The PRP group also outperformed the HA group in clinical outcomes. Both groups showed improvement compared to baseline.

Filardo., *et al.* [14] compared PRP and HA injections for treatment of knee OA or chondropathy while also conducting a pre-treatment prospective evaluation. Patients (n = 109) were randomly divided into two groups (HA, n = 55; PRP, n=54). This RCT required patients to be at least 18 years old, have at least a four-month history of chronic pain or swelling, and demonstrate radiographic findings consistent with OA (Kellgren-Lawrence score < 3). Three weekly injections were administered in a blinded fashion. Patients were evaluated pre-treatment and at two, six, and twelve months following intervention. Measurement outcomes included International Knee Documentation Committee (IKDC) score, EQ-Visual Analog Pain Scale (EQ-VAS), TEGNER, KOOS, and changes in range of motion and knee circumference; adverse effects were noted. No significant difference between the two treatment groups was found, despite both showing significant clinical improvement ($p < 0.05$) compared to baseline at all follow-up evaluations. IKDC, EQ-VAS, TEGNER, and all KOOS sub-categories (symptoms, pain, activity of daily life (ADL), sport, and QOL) showed continuous, significant improvement in scores throughout the evaluation period for both groups without demonstrating any inter-group difference (Table 7). PRP recipients did show increased post-injective pain reaction ($p = 0.039$), however the overall adverse effects observed were mild.

Measure	Baseline	2 Months	6 Months	12 Months
IKDC	50.2 ± 15.7	62.8 ± 17.6	64.3 ± 16.4	64.9 ± 16.8
PRP	47.4 ± 15.7	61.4 ± 16.2	61.0 ± 18.2	61.7 ± 19.0
HA				
TEGNER				
PRP	2.9 ±1.4			3.8 ±1.3
HA	2.6 ± 1.2			3.4 ± 1.6

Table 7: *IKDC and TEGNER scores at baseline and at 2, 6, and 12 months following treatment (p<0.05, compared to baseline intra-group measurements).*

Other study designs chosen included prospective studies, meta-analyses (MAs) and systematic reviews, retrospective reviews, and observational studies without controls.

Say., *et al.* [32] conducted a prospective study in order to compare PRP and HA for the treatment of knee OA. Patients with mild or moderate degenerative arthritis were selected (n = 90) and divided into one of two groups (n = 45; PRP or HA). The PRP group received one intra-articular injection, whereas the HA group received three intra-articular doses. KOOS and VAS measures were utilized, with measurements taken at baseline, three- and six-month follow-ups. KOOS score and VAS measures for the PRP group were significantly better than those of the HA group at both follow-ups (Table 8). Costs of the manual PRP application utilized in this study (approximately $10, compared to several hundreds of dollars for automatic devices and kits) were also lower than that of the HA group (cost not reported).

Measures	PRP	HA	p-value
KOOS			
Baseline	46 ± 16.2	43.8 ± 8.6	0.404*
3-month	76.9 ± 7.5	68.6 ± 3.7	0.02*
6-month	84.4 ± 6.2	73.2 ± 4.6	0.001*
VAS			
Baseline	7.3 ± 1.6	7 ± 1.3	0.234**
3-month	2.3 ± 1.6	4.1 ± 1.3	0.001**
6-month	1.7 ± 1.4	3 ± 1	0.001**

Table 8: *KOOS and VAS scores of both groups at baseline and at 3- and 6-month follow-ups (p<0.05; *Independent sample test; **Mann-Whitney test).*

Khoshbin., *et al*. [20] conducted an SR with quantitative synthesis in order to identify all RCTs and prospective cohort studies that evaluated clinical efficacy of PRP against control injections (HA or normal saline (NS)), for treatment of knee OA. Six studies were included (four RCTs, two prospective cohorts), with 577 patients included in the analysis (PRP, n = 264; Controls, n = 313). Utilizing a random-effects model to evaluate therapeutic outcomes of PRP at 24 weeks, outcome measures such as WOMAC, VAS, IKDC, and overall patient satisfaction were considered. WOMAC (mean difference = -18.0, 95% CI (-28.8 to -8.3); $p < 0.001$) and IKDC (mean difference = 7.9, 95% CI (3.7 to 12.1); $p < 0.001$) scores were significantly superior for PRP injections than those of controls. No difference was identified for VAS or overall patient satisfaction; however, the PRP group did demonstrate more adverse effects (mild pain, swelling) than controls.

Anitua., *et al*. [1] conducted an SR of use of plasma rich in growth factors (PRGF) in treating knee OA. Following PRISMA guidelines, all studies included a PRGF group and control group. Five eligible citations were selected (two RCTs, two prospective studies, and one retrospective study). Evaluated measures included pre- and post-treatment clinical measures (joint pain, stiffness, function), WOMAC, KOOS, and IKDC. A follow-up period of at least four weeks was required. RCTs demonstrated PRGF treatment achieving greater than 50% reduction in pain, significantly higher than controls. The retrospective study found WOMAC pain scores decreased by more than 40% in the PRGF group, significantly higher than in controls. All other measured variables demonstrated statistically significant superiority for PRGF-treated patients.

Chang., *et al.* [7] and Dold., *et al.* [12] each conducted literature-based MAs to elucidate the effectiveness of PRP in treating chondral and osteochondral degeneration of the knee. Chang., *et al.* [7] conducted an SR and MA, identifying eight single-arm studies, three quasi-experimental studies, and five RCTs (n=1,543 patients). After identifying changes in functional scales following interventions, they compared pooled values from PRP treatment groups with those prior to treatment as well as with groups receiving HA or placebo. PRP intervention demonstrated better outcomes than other interventions with a higher summed effect size in the PRP group, while showing no overlap of the 95% CI of the HA group at two- and six-month follow-ups (Table 9).

Intervention Group	2 Months	6 Months	12 Months
PRP	1.84 (95% CI, 1.53 to 3.09)	2.19 (95% CI, 1.73 to 2.66)	2.35 (95% CI, 0.51 to 4.20)
HA	1.15 (95% CI, 0.78 to 1.52)	0.75 (95% CI, 0.62 to 0.88)	0.85 (95% CI, 0.46 to 1.24)

Table 9: *Effect size and confidence interval at 2, 6, and 12 months following PRP or HA injection (Statistically significant).*

Dold., *et al*. [12] conducted a systematic literature search and selected ten studies (n = 570 joints) with degenerative hip or knee OA treated with PRP. Clinical outcome scores and PRP preparation and delivery methods were among the data extracted. The majority of the studies demonstrated significant improvements in joint-specific clinical scores, general health scores, and pain scores at six-month follow-up compared to baseline. In three of the four studies where HA injections were used for comparison, PRP demonstrated significantly better pain and/or clinical scores.

Bernasek., *et al*. [3] conducted a retrospective review of various perioperative treatment modalities following TKA, including PRP, fibrin sealant injections, or periarticular pain cocktail (control). Four hundred patients were included, and outcome measures included per-case hospital injection cost, post-operative blood loss, among others. PRP and fibrin sealants resulted in significantly reduced blood loss ($p < 0.05$) compared to controls; no other measure showed significant differences among the groups, including cost.

Raeissadat., *et al.* [27] conducted an observational study without controls to evaluate the effects of LR-PRP injections on patient QOL (assessed by physical/PCS and mental/MCS) and function (WOMAC and SF-36). Sixty-five patients were enrolled, but only 60 patients were included in the results, presumably due to loss at follow-up. All patients filled out WOMAC and SF-36 questionnaires at baseline and then received two courses of LR-PRP injections four weeks apart. Questionnaires were repeated at six months following intervention. WOMAC as well as SF-36 physical and mental domains demonstrated significant changes, and QOL enhancements were significant following injections (although moreso in physical QOL aspects).

Tendinopathy and Ligament Pathology

Several RCTs were evaluated in order to determine a relation between outcomes and efficacy of PRP application to tendinopathy and ligament pathology. None considered cost.

Kesikburun., *et al.* [19] conducted an RCT to evaluate efficacy of PRP injections against that of saline (placebo) in improving pain and shoulder function in patients with chronic RC tendinopathy. Following careful selection of eligible patients (at least 3-month history of shoulder pain with overhead throwing, MRI findings of RC tendinopathy, and at least 50% improvement in shoulder pain with anesthesia), 40 patients were randomized into two groups (n = 20). All patients underwent ultrasound-guided injection and six weeks of a standard exercise program. The PRP group received 5 mL of autologous PRP (from venous blood). The placebo group received 5 mL of saline solution. Outcome measures included WORC, SPADI, VAS, Neer Test, and shoulder range-of-motion (ROM). Measurements were collected at baseline, 3, 6, 12, 24, and 52 weeks following injection. Within each group for all assessment points, WORC, SPADI, and VAS scores demonstrated significant enhancement from baseline. However, for all time points through the one-year follow-up, no significant difference was found between the groups for WORC ($p = 0.174$), SPADI ($p = 0.314$), and VAS ($p = 0.904$) scores.

de Jonge., *et al.* [11] evaluated the use of PRP injections in chronic Achilles tendinopathy of the mid-portion of the tendon. This RCT included 54 patients with tendinopathy required to be within 2-7 cm proximal to the Achilles tendon. Patients were divided up (n = 27 each) into two groups (PRP, Saline/Placebo). They received blinded injections followed by an eccentric training program. Measured outcomes included Victorian Institute of Sports Assessment (VISA) -Achilles score, patient satisfaction, and ultrasonic evaluation at baseline and one-year following intervention. No significant differences were found between both groups (adjusted between-group difference = 5.5; 95% CI = -4.9 to 15.8; $p = 0.292$), although both groups showed ultrasonographic improvements at one-year follow-up.

Krogh., *et al.* [22] compared efficacy of single injections of PRP, saline (placebo), and glucocorticoids in decreasing pain in adults with LE. Sixty patients with chronic LE were enrolled and randomized 1:1:1 (n = 20) to receive blinded injections of PRP, saline, or glucocorticoids. Measured outcomes included change in pain (Patient-Related Tennis Elbow Evaluation (PRTEE)) at three months following intervention. All groups demonstrated reduction in pain at follow-up; no significant difference was found between the groups (Table 10).

Comparison of Groups	Mean Difference	95% Confidence Interval
Glucocorticoid vs. Saline	-3.8	-9.9 to 2.4
PRP vs. Saline	-2.7	-8.8 to 3.5
Glucocorticoid vs. PRP	-1.1	-7.2 to 5.0

Table 10: *Mean differences between treatment groups at three months (PRP, Saline, and Glucocorticoids).*

Gosens., *et al.* [16] conducted a prospective study of treatment of patellar tendinopathy, comparing PRP treatment given prior intervention (cortisone, surgery, and/or ethoxysclerol) to PRP with no prior treatment. Thirty-six patients were enrolled and allocated to two treatment groups: prior treatment (n = 14) or no prior treatment (n = 22). Measurements included VISA-Patellar questionnaire (VISA-P) and VAS scores to help determine pain in ADL, during work and sports, as well as before and after PRP treatment. Both groups demonstrated significant improvements in all VAS scores, while only those not treated previously showed significant improvements in VISA-P (Table 11).

Group	Baseline	Follow-up	p-value
Prior Treatment			
VAS ADL	6.5 ± 2.3	2.8 ± 2.2	0.005
VAS Work	6.9 ± 2.5	3.1 ± 2.5	0.005
VAS Sport	8.6 ± 0.9	3.8 ± 2.9	0.003
VIAS-P	41.8 ± 14.3	56.3 ± 26.2	0.093
No Prior Treatment			
VAS ADL	5.6 ± 2.9	2.6 ± 2.7	0.001
VAS Work	6.0 ± 3.0	3.2 ± 2.9	0.001
VAS Sport	8.5 ± 1.1	5.1 ± 3.2	≤ 0.0001
VIAS-P	39.1 ± 16.6	58.6 ± 25.4	0.003

Table 11: *Means and Standard Deviations of VAS and VISA-P at baseline and follow-up ($p < 0.05$).*

Krogh., *et al*. [21] identified 17 trials (n = 1,381 patients) in an SR and MA analysis of RCTs to evaluate and compare efficacy and safety of eight different injection treatments for LE: botulinum toxin, autologous blood, PRP, glucocorticoids, polidocanol, prolotherapy, HA, and glycosaminoglycan. Utilizing the Cochrane risk of bias tool, trials including data regarding pain intensity changes were evaluated. Network/random-effects MAs were performed to pool all evidence; these were reported as standardized mean differences (SMDs; 95% CI). PRP and autologous blood were statistically greater than placebo (-1.13, 95% CI (-1.77 to -0.49)). However, only one trial included was at low risk for bias. Prolotherapy, HA, and botulinum toxin were also beneficial compared to placebo. Glucocorticoids, polidocanol, and glycosaminoglycan showed insignificant differences from placebo.

Coombes., *et al.* [10] and Sadoghi., *et al*. [31] both conducted SRs related to management of different tendon injuries. Coombes., *et al.* [10] selected 41 RCTs, including 2,672 patients, in order to evaluate effectiveness of one or more peritendinous injections with placebo or non-operative methods for tendinopathy. MAs were then conducted to generate a random-effects model with estimated relative risk and SMDs. Sadoghi., *et al.* [31] focused on evaluating the efficacy of in-vivo PRP use for Achilles tendinopathy and tendon-rupture treatment. After utilizing multiple databases, 14 manuscripts were included and evidence of outcomes pooled. Coombes., *et al.* [10] found PRP injections did not differ in efficacy from placebo for Achilles tendinopathy. Sadoghi., *et al.* [31] found a similar absence of benefit of platelets for Achilles tendinopathy ($p = 0.929$; weighted mean difference = 0.56; 95% CI (-1.05 to 2.16)). However, platelet concentrates demonstrated a significant benefit in treating Achilles tendon ruptures in-vivo in humans ($p = 0.001$).

Tendon and Ligament Rupture/Tear, Repair, and Reconstruction

Four RCTs were identified that evaluated the application of PRP for treatment of tendon or ligament rupture. No considerations were made to cost.

Jo., *et al*. [18] evaluated PRP application to enhance arthroscopic repair of large RC tears. Forty-eight patients underwent arthroscopic repair for large RC tears and then were randomly allocated into two groups. Each patient in the PRP group received three PRP gels (3x3 mL) between the greater tuberosity and torn RC end. The control group (control) received conventional repair without biologics. Re-tear rate was assessed by MRI or CT arthrography at a minimum of nine months post-op. Other measures included functional scores, ROM, and pain, among others. The PRP group demonstrated significantly reduced re-tear rates in comparison to the conventional group (20% vs. 55.6%; $p = 0.023$). There was no appreciable difference between the two groups with respect to clinical outcomes, except for overall function ($p = 0.43$).

Ruiz-Moneo., *et al*. [30] evaluated the potential of PRGF application in enhancing structural and functional outcomes following arthroscopic repair of full-thickness RC tears. Sixty-three patients were enrolled in this RCT and were randomly allocated to two different

groups following repair. One group received a PRGF injection, which was then spread onto the sutures. The other group underwent standard surgical repair only. Patients were evaluated for function (UCLA score) and structure (Arthro-MRI) at one-year post-op. No significant difference was observed between both groups, despite both demonstrating improvements from their baseline scores.

Cervellin., *et al*. [4] assessed the efficacy of PRP in reducing donor-site morbidity as well as kneeling and anterior knee pain in patients undergoing bone-patellar tendon-bone (BPTB) graft ACL reconstruction. Forty patients meeting criteria for BPTB graft ACL reconstruction were included in this RCT and randomly divided into groups (n = 20): control or PRP. The PRP group received autologous PRP gel application at both tendon and patellar plug harvest sites with peritenon suture stabilization. Patients were evaluated at one-year post-op with VAS and VISA questionnaires. Additionally, average daily knee pain and pain experienced with specific activities were measured. The PRP group yielded higher VISA scores (84 ± 11.8 vs. Control: 97.8 ± 2.5; p = 0.041), whereas the VAS scores showed no significant difference between the two groups.

Randelli., *et al*. [28] conducted a prospective RCT to evaluate the ability of autologous PRP to enhance tendon healing for arthroscopic RC repair. Fifty-three patients scheduled to undergo shoulder arthroscopy were randomized into two groups. The treatment group (n = 26) patients received PRP and autologous thrombin intraoperatively. The control group (n = 27) did not receive anything beyond repair. Outcome scores utilized included UCLA, Simple Shoulder Test (SST), and Constant scores. These were evaluated at 3, 7, 14, and 30 days post-op. MRI was performed at least one year following intervention. The treatment group yielded significantly higher SST (8,92,2 vs. 7,12,7), UCLA (26,93 vs. 24,24,9), and Constant (659 vs. 57,912) scores at every time point than the control group did ($p < 0.05$). Both groups showed no difference at later follow-up time points (6, 12, and 24 months), and the MRI demonstrated no significant difference in healing rate.

Chahal., *et al.* [6] conducted an SR and quantitative synthesis in order to synthesize all available evidence to compare and evaluate the efficacy of PRP application in patients undergoing arthroscopic repair of full-thickness RC tears. Five studies were selected (n=261 patients) and extracted data was pooled for analysis utilizing a random effects model. Estimates of treatment effect were determined. Between both treatment groups, no significant difference was identified in RC re-tear rate (risk ratio, 0.77; 95% CI (0.48 to 1.23)).

Podesta., *et al.* [26] published a case series in order to evaluate the ability of PRP to enhance healing of partial ulnar collateral ligament tears and accelerate return to play for athletes. Thirty-four patients meeting inclusion criteria were enrolled and received a single 1A PRP injection under ultrasound-guidance. Before athletes returned to sports-related activities, physical therapy was completed. KJOC and DASH measures were obtained at baseline and following return to play (mean = 12 weeks). Patients were followed-up with at 70 weeks. PRP treatment yielded significantly improved mean DASH (21 vs. 1; $p < 0.0001$) and KJOC (93 vs. 46; $p < 0.0001$) scores.

Discussion

With respect to clinical outcomes alone, it is not currently possible to make an overarching recommendation for the use of PRP for various orthopaedic conditions, given the mixed results that many studies have produced.

Knee OA and TKA

With respect to knee OA and TKA, authors of various studies make a number of different recommendations. PRP has been outright recommended for no consideration as first-line treatment by several studies [3,14]. The basis of these recommendations stem from lack of significant differences between PRP and alternative interventions, including HA or pain cocktails [3,14]. Additionally, Bernasek., *et al.* [3] were unable to identify significant cost-effectiveness for PRP or fibrin sealants.

Other studies report that PRP use does produce functional and clinical outcomes superior to those of alternative interventions [1,5,7,12,20,27,29,32]. However, these findings often required further clarification. Cerza., *et al.* [5] suggested that PRP treatment may lead to improved overall clinical outcomes compared to treatment with HA. They also found that HA was relatively ineffective for patients with more severe OA. This may influence whether PRP is truly superior to HA for patients with advanced OA.

Say., *et al.* [32] found the cost of PRP application to be lower than that of HA application in their patient population, while yielding better KOOS scores and VAS results at both follow-up time points. Another study qualified their findings by suggesting that multiple sequential PRP injections intra-articularly may achieve positive results within six months in adult patients afflicted with mild/moderate OA, with no comment on the effect in patients with advanced OA [20]. Chang., *et al.* [7] identified lasting efficacy for one year in patients treated with PRP injections compared to their baseline, also finding PRP as likely superior and to result in longer-lasting effects than HA or placebos. They went a step further than Say et al. did by suggesting that patients with milder OA received greater benefit and outcomes than did patients with advanced OA.

Dold., *et al*. [12] found significant improvements with the use of PRP in the majority of their evaluated outcomes; however, they made clear that the majority of these were poor quality studies at high risk for bias. They recommended higher quality trials be performed with longer-term follow-up to be conducted.

Tendinopathy and Ligament Pathology

A similar theme as above is identified with respect treatment of ligament and tendon pathology with PRP. However, the majority of studies included found the PRP outcomes to be insignificantly different from placebo or alternative interventions.

Kesikburun., *et al*. [19] found no significant differences between PRP or placebo (saline) application for treatment of chronic RC tendinopathy, concluding that PRP may be no more effective than standard treatment and exercise for chronic RC tendinopathy. Measures evaluated included pain, quality of life, disability, and shoulder ROM. A number of other studies evaluating PRP against other interventions made similar findings [10,11,16,22].

Studies that did identify significant differences also further qualified their results, muddling the true potential benefit of PRP application. Krogh., *et al*. [21] found PRP and autologous blood to be statistically better than placebo; however, only one trial included in their meta-analysis had a low risk for bias. They concluded that evidence-based recommendations for treating LE with PRP injections lack strength and insufficient evidence is available from unbiased studies.

Sadoghi., *et al.* [31] also identified in-vivo benefits of treating Achilles tendon rupture in humans with PRP; however, they attributed this to quicker and enhanced scar tissue maturation resulting from treatment with platelet concentrates. They believe no evidence supports PRP treatment for Achilles tendinopathy.

Tendon and Ligament Tear/Rupture, Repair, and Reconstruction

Relatively consistent promise was seen in PRP application to tendon and ligament injuries and in augmentation of their repair/reconstruction. PRP showed beneficial effects in improving outcome scores and was suggested to be an effective treatment option for concurrent use in treating partial UCL tears, reducing subjective pain following ACL reconstruction, and reducing re-tear rate in arthroscopic repair of massive RC tears [4,18,26]. Jo., *et al.* [18] found improved structural outcomes, suggesting that clinical outcomes may also improve with PRP at longer-term follow-ups. Cervellin., *et al*. [4] added that despite the potential utility of PRP in ACL reconstruction with BPTB graft, the mechanism of action should be elucidated to confirm the efficacy of PRP; thus, further investigation is required.

Randelli., *et al.* [28] found significantly improved outcome measures and scores at three-months post-op but no difference at later follow-up points up to two years. It is likely that adjuvant use of autologous PRP along with arthroscopic RC repair may assist in reducing pain in the first few months following surgery.

The other studies included did not find significantly better outcomes using PRP in comparison with standard methods of repair [6,30]. Ruiz-Moneo., *et al.* [30] did not find any disparity in functional improvements or healing of PRP compared to conventional arthroscopic RC repair. Chahal., *et al*. [6] found no difference in RC re-tear rate between PRP-treated and non-PRP-treated groups, but called for more well designed RCTs with low bias risk to confirm their findings.

Limitations of Recommending PRP in Orthopaedic Management

It is difficult to take an overall stance on the efficacy, or lack thereof, of PRP when current evidence has produced an assortment of clinical outcomes and recommendations. In addition to the conflicting outcomes reported by the available evidence, this study encountered a number of limitations.

One of the biggest hurdles in achieving a consensus on the efficacy of PRP application is the lack of high quality studies with low bias risk [12,21]. Of the ten RCTs evaluated, only two studies exceeded 63 patients. While the several SRs and MAs pooled data of over 1,000 patients, they often aggregated this data from lower quality studies with high bias risk. Until additional larger, multi-center RCTs can be conducted with double-blinding, consistent inclusion criteria, longer-term follow-up and consistent PRP delivery methods (at least consistent with respect to each condition), it is difficult to make strong, evidence-based recommendations regarding PRP utility.

Moreover, a recent editorial noted that of the 109 articles on PubMed related to orthopaedic research on PRP or platelet-derived products in humans, less than half were clinical trials. Fifty-eight of these were simply literature analyses that reviewed available evidence. Given the high variability in PRP collection, delivery, and application methods based on condition, SRs and MAs will have limited use. Without further high quality preclinical and clinical studies, PRP's true potential cannot yet be clarified [15].

With respect to the intervention itself, there are many inconsistencies that hinder the ability to collect reliable data and formulate strong evidence-based recommendations. There are a lack of standardization of study protocols, platelet-separation techniques, and outcome measures, as well as PRP delivery methods [33]. These protocols significantly affect both cost and quality of PRP delivered to patients. A standardized dosage or concentration also must be determined for various types and degrees of injuries, as well as for each targeted tissue. These should be the focus of future studies, in order to optimize PRP delivery for different injuries and determine if, at optimal dosage, PRP can yield improved clinical, structural, and functional outcomes when compared to alternatives.

Another limitation is the lack of standardized outcome measures for different conditions and injuries. The studies included in this investigation utilized a number of measures of outcome, including a variety of questionnaires and scales, functional and clinical outcome measures, and physical exam findings. WOMAC scores were a common outcome measure utilized by a number of studies, especially in those supporting the use of PRP for knee OA [5,20,27,29]. However, the studies included chose different outcome measures without providing justification for their use. Future investigations should aim at identifying which measures best evaluate the PRP efficacy for each musculoskeletal condition. This would strengthen future studies performed in identifying the true utility of PRP in the orthopaedic setting. Additionally, these scores and questionnaires may also have been subject to bias. Reliance on patient self-evaluation introduces a possibility of subjective bias; thus, it may be more beneficial to shift towards more objective composite summary measures, such as QALYs [35].

Another limitation in recommending PRP use is the lack of cost consideration with respect to outcomes achieved. This study's goal was to quantify and compare cost-effectiveness of PRP use against alternative interventions with respect to various musculoskeletal problems. We were unable to accomplish this, given the lack of publicly available information regarding cost, as well as the lack of PRP delivery standardization and absence of such costs being reported by available studies. Cost was not considered in most of these studies. In order to strongly recommend one treatment modality over the standard of care, especially given the necessity of more fiscally-conscious healthcare spending, it is important give major consideration to cost and relate it to outcomes.

Cost Analysis

Our goal was to conduct a CEA; however, it is not the most prudent method of analyzing current data. CEAs are heavily rely the validity of data. There are various publications that believe between 3 - 6% of orthopaedic studies are RCTs, thus increasing the room for bias and unreliability. Conducting stronger RCTs with low bias risk may enable a future CEA, which could potentially bolster evidence-based clinical recommendations. CEAs also rely on clinical outcomes; thus, without standardizing outcome evaluation and availability of cost data, it

is not possible to evaluate PRP utility with a CEA [35]. Two CEAs comparing PRP application to alternatives for non-healing diabetic foot ulcers were identified, both concluding that there is a cost-effective and clinical advantage to using PRP [13,24]. Such an analysis could significantly impact orthopaedists decision-making.

After evaluating the currently available evidence, a CMA may be more appropriate to evaluate PRP against alternatives. Given two treatment options with overall similar effectiveness or outcomes, a CMA dictates that preferred treatment is the less costly one [35]. Since a significant portion of available evidence suggests a lack of significant difference between PRP and alternatives, a carefully-conducted CMA could potentially identify a preferred intervention. CMAs, however, are outdated and have limited utility, due to the limitations described above. CEAs and CUAs were more recently developed and are preferred over the older CMA [35].

Such an approach poses additional limitations, as it is not possible to be certain about the efficacy of an intervention as well as the costs associated. However, with a larger collection of stronger RCT and standardized PRP production protocols and experimental protocols, a CMA may have a more meaningful impact in clinical decision-making related to the utility of PRP in the orthopaedic setting. If studies start to utilize composite summary outcomes, such as QALYs, or until investigators can standardize which composite measures to use for each orthopaedic conditions (ex: WOMAC for knee OA), it may eventually be possible to conduct a CUA or CEA.

Future Directions

Given the potential benefits of PRP and demand for use, there is a strong urgency to conduct more multicenter, double-blinded RCTs with long-term follow-up and minimize bias risks. Also necessary is the standardization of study protocols, PRP collection and delivery methods, and outcome measures. Associated costs should also be reported in future investigations. These are the most important elements that are currently preventing performance of a reliable cost analysis, which could guide clinical decision-making and account for costs incurred by patients, physicians, and the health system. Such considerations are vital to aiding reduction and re-allocation of healthcare dollars in the United States.

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Conflict of Interest

Both authors have no financial relationships or any conflicts of interest to disclose.

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