Regenerative Medicine for Osteoarthritis and Tendinopathy

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Goals

- What is "regenerative medicine?"
- What are current treatment options available for osteoarthritis and tendinopathy?
- What is the evidence behind these treatments?

"Regenerative Medicine"

• Field of medicine focused on "biologically repairing, replacing, or regenerating damaged or diseased tissues"

Osteoarthritis



Tendinopathy



Osteoarthritis Treatment



- Hyaluronic Acid
- Regenerative Medicine

Regenerative Medicine for Osteoarthritis

- 1. Platelet-rich plasma (PRP)
- 2. Bone marrow aspirate concentrate (BMAC)
- 3. Micro-fragmented adipose tissue (MFAT)
- 4. Umbilical cord products, amniotic tissue

Regenerative Medicine for Osteoarthritis

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The elements of blood



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Platelet count of 150 indicates 150 million platelets per mL of blood





9 billion platelets injected into joint

60mL whole blood → 6 mL of PRP = 10x platelet concentration 9 billion platelets

5 common questions

- 1. How do you explain the variability in the literature?
- 2. Will this cause my cartilage to grow back?
- 3. How long will it last?
- 4. How do I know if I am a good candidate?
- 5. I also have arthritis in my foot. Does PRP work for that?

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JAMA | Original Investigation

Effect of Intra-articular Platelet-Rich Plasma vs Placebo Injection on Pain and Medial Tibial Cartilage Volume in Patients With Knee Osteoarthritis The RESTORE Randomized Clinical Trial Buendía-López et al. J Orthop Traumatol (2019) 20:3 https://doi.org/10.1186/s10195-018-0501-3

Journal of Orthopaedics and Traumatology

ORIGINAL ARTICLE



Clinical and radiographic comparison of a single LP-PRP injection, a single hyaluronic acid injection and daily NSAID administration with a 52-week follow-up: a randomized controlled trial

David Buendía-López^{1*}, Manuel Medina-Quirós² and Miguel Ángel Fernández-Villacañas Marín³

288 participants, mild-moderate knee OA, PRP vs saline

12 month follow up: no difference in pain or cartilage volume

20mL blood draw Average **1.6 billion platelets injected** 106 participants, mild-moderate knee OA, PRP vs HA vs oral NSAID

12 month follow up: PRP group superior with pain, stiffness, and physical function

60mL blood draw Average **5.5 billion platelets injected**

PRP Dosing Matters



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A Greater Platelet Dose May Yield Better Clinical Outcomes for Platelet-Rich Plasma in the Treatment of Knee Osteoarthritis: A Systematic Review

William A. Berrigan, M.D., Zach Bailowitz, M.D., Anna Park, M.Phil., Aakash Reddy, Ryan Liu, and Drew Lansdown, M.D.

Purpose: To determine whether the platelet dose administered during a platelet-rich plasma (PRP) injection for knee osteoarthritis (OA) affects clinical outcomes. **Methods:** A systematic review was performed by searching PubMed, Cochrane Library, and Embase for randomized controlled trials with at least 1 study arm using PRP for knee OA. Only studies that provided a platelet count, concentration, or dose with a minimum of 6-month outcome scores were included. Studies in which the PRP group had statistically significant positive outcomes were separated from those without statistical significance. The average platelet doses for studies with positive outcomes in the PRP group were compared with those without positive outcomes. **Results:** After exclusion criteria were applied, 29 studies were analyzed. Of the 29, there were 31 arms that used PRP as a treatment method, of which 28 had statistically significant positive outcome was 5,500 \pm 474 \times 10⁶, whereas the 3 that had no positive difference had a mean platelet dose of 2,302 \pm 437 \times 10⁶ (*P* < .01). There were 18 studies with 12-month outcomes, with 16 of 18 having positive outcomes. The positive studies had an average platelet dose of 2,253 \pm 753 \times 10⁶ (*P* < .05). **Conclusions:** Improved clinical outcomes from PRP injections for knee OA may be related to a greater platelet dose. **Level of Evidence:** Level II, systematic review of Level I and II studies.

OPEN Platelet-rich plasma (PRP) in osteoarthritis (OA) knee: Correct dose critical for long term clinical efficacy

Himanshu Bansal¹¹², Jerry Leon², Jeremy L. Pont³, David A. Wilson³, Anupama Bansal¹, Diwaker Agarwal⁴ & Iustin Preoteasa⁵

Despite encouraging results reported with regards to Platelet-rich plasma (PRP) application in osteoarthritis (OA) knee, still critical issues like conclusive structural evidence of its efficacy, standard dose and good manual method of preparation to obtain high yield remains unanswered. Present study is an attempt to optimise the dose and concentration of therapeutic PRP and its correlation with structural, physiologic efficacy with a new manual method of PRP preparation. A total of one hundred and fifty patients were randomized to receive either PRP (10 billion platelets) or hyaluronic acid (HA; 4 ml; 75 patients in each group) and followed up till 1 year. An addition of filtration step with 1 μ m filter in manual PRP processing improved platelet recovery upto 90%. Significant improvements in WOMAC (51.94 ± 7.35 vs. 57.33 ± 8.92; *P* < 0.001), IKDC scores (62.8 ± 6.24 vs 52.7 ± 6.39; *P* < 0.001), 6-min pain free walking distance (+120 vs. +4; *P* < 0.001) persisted in PRP compared to HA group at 1 year. Significant decline IL-6 and TNF- α levels observed in PRP group (*P* < 0.05) compared to HA at 1 month. Study demonstrated that an absolute count of 10 billion platelets is crucial in a PRP formulation to have long sustained chondroprotective effect upto one year in moderate knee OA.

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- May decrease inflammatory biomarkers
- May halt degeneration

Frontiers | Frontiers in Medicine

Impact of autologous platelet-rich plasma therapy vs. hyaluronic acid on synovial fluid biomarkers in knee osteoarthritis: a randomized controlled clinical trial



TYPE Original Research ISHED 05 October 2023 10.3389/fmed.2023.1258727

> PRP injection can reduce the concentrations of inflammatory cytokines IL-6, IL-1β, TNF-α

Knee Surgery, Sports Traumatology, Arthroscopy (2022) 30:4063–4071 https://doi.org/10.1007/s00167-022-06887-7

KNEE



Intra-articular injections of platelet-rich plasma decrease pain and improve functional outcomes than sham saline in patients with knee osteoarthritis

Jiabao Chu^{1,7} · Weifeng Duan¹ · Ziqiang Yu^{2,3} · Tao Tao⁴ · Jie Xu⁵ · Qianli Ma⁶ · Lingying Zhao^{2,3} · Jiong Jiong Guo^{1,2}

Table 3 Change in til	biofemoral cartilage vol	ume between the PRP	and the NA group over	60 months		
PRP group		NS group		Absolute between-	P value	
	Baseline	Change at 60 mo ^a	At baseline	Change at 60 mo ^a	group difference	
Tibiofemoral car- tilage volume, mm ³	17,325 (15 558 to 18 429)	- 1171 (- 963 to - 793)	17,762 (14 637 to 17 441)	- 2311 (- 1004 to - 835)	1140 (- 79 to 1320)	< 0.001
Annual percentage change in tibi- ofemoral cartilage volume ^b , %	- 1.4 (- 3.0 to - 1.2)		- 2.6 (- 3.0 to - 2.4)		1.3 (-0.4 to 1.5)	< 0.001
P value	0.020		< 0.001	•		

^aThe within-group change and between-group difference were calculated in participants with baseline data of the outcome

 b Calculated as 100×[(follow-up cartilage volume – baseline cartilage volume)/baseline cartilage volume]/exact time between 2 scans in years. This formula requires complete data at both time points, therefore participants

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Duration

- Most studies include 1-2 years of follow up
- Longest study follow up 5 years

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Aging Affects the Efficacy of Platelet-Rich Plasma Treatment for Osteoarthritis

Kuntal Chowdhary, MD, Amrita Sahu, PhD, Hirotaka Iijima, PhD, PT, Sunita Shinde, MS, Joanne Borg-Stein, MD, and Fabrisia Ambrosio, PhD, MPT

- Osteoarthric human chondrocytes treated with PRP from younger (18-35) vs older (≥65) donors
- PRP from young donors induced more youthful chondrocyte phenotype



Platelets of younger individuals may be more potent

Platelet-Rich Plasma Injections for Advanced Knee Osteoarthritis

A Prospective, Randomized, Double-Blinded Clinical Trial

Nayana Joshi Jubert,*[†] MD, PhD, Luciano Rodríguez,[‡] PhD, Maria Mercedes Reverté-Vinaixa,[†] MD, PhD, and Aurora Navarro,[§] MD

Background: Intra-articular injections of platelet-rich plasma (PRP) to treat symptoms of knee osteoarthritis (OA) have been successfully used in young patients and in the early stages of disease. No previous studies have analyzed outcomes of PRP injections during the late stages.

Hypothesis: PRP reduces pain and leads to a more effective and lasting functional recovery than corticosteroid with local anesthetic.

Study Design: Randomized controlled trial; Level of evidence, 2.

Methods: A total of **75 patients with symptomatic knee OA (Kellgren-Lawrence grade 3 to 4)** were enrolled in this study between August 2013 and July 2014. Patients were randomized to treatment either with a single leukocyte-reduced PRP or corticosteroid intra-articular injection. The primary variable was visual analog scale assessment at 1 month. Secondary outcomes were the Knee injury and Osteoarthritis Outcome Score (KOOS) and Short Form–36 (SF-36) at 1, 3, and 6 months after treatment. Patient satisfaction at final follow-up was assessed. Both groups were homogeneous and comparable in baseline characteristics.

Results: All variables improved in both groups. Statistical differences between groups were not found for the majority of the outcome variables, although the magnitude of improvements tended to be greater in the PRP group. Quality-of-life differences between values at 3 and 6 months versus baseline increased significantly more in the study group (P = .05 and .03, respectively), and so did general health perception differences at 6 months (P = .018).

Conclusion: A single PRP intra-articular injection is effective for relieving pain and improving activities of daily living and quality of life in late-stage knee OA. For patients with late-stage knee OA who are 67 years or older, 1 intra-articular injection of PRP has similar results to 1 shot of corticosteroid.

Keywords: platelet-rich plasma; osteoarthritis; knee; intra-articular injections

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American Medical Society for Sports Medicine Position Statement: Principles for the Responsible Use of Regenerative Medicine in Sports Medicine

Jonathan T. Finnoff, DO,* Tariq M. Awan, DO,† Joanne Borg-Stein, MD,‡ Kimberly G. Harmon, MD,§ Daniel C. Herman, MD, PhD,¶ Gerard A. Malanga, MD,∥ Zubin Master, PhD,** Kenneth R. Mautner, MD,†‡‡ and Shane A. Shapiro, MD§§

TABLE 4. Summary of Meta-Analyses and Systematic Reviews Evaluating the Efficacy and Major Adverse Events of Platelet-Rich Plasma Injections for OA From 2019 to 2020

0A	Treatment Effective	Treatment Ineffective	Treatment Mixed Efficacy	Major Adverse Events
Unspecified location	1 study ³³	1 study ³⁴	0 studies	0 studies
Ankle	1 study ³⁵	0 studies	0 studies	0 studies
Foot	1 study ³⁶	0 studies	0 studies	0 studies
Hand	1 study ³⁶	0 studies	0 studies	0 studies
Нір	3 studies ^{11,37,38}	1 study ³⁹	0 studies	1 study ³⁹
Knee	14 studies ^{11,12,19,40–50}	0 studies	0 studies	1 study ⁴⁶
Temporo-mandibular	4 studies ^{51–54}	0 studies	0 studies	0 studies
OA, osteoarthritis.				

- Bone marrow aspirate concentrate (BMAC)
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100 0003-0293-05

KENALOG 40

Cell-based versus corticosteroid injections for knee pain in osteoarthritis: a randomized phase 3 trial

Various types of cellular injection have become a popular and costly treatment option for patients with knee osteoarthritis despite a paucity of literature establishing relative efficacy to each other or corticosteroid injections. Here we aimed to identify the safety and efficacy of cell injections from autologous bone marrow aspirate concentrate, autologous adipose stromal vascular fraction and allogeneic human umbilical cord tissue-derived mesenchymal stromal cells, in comparison to corticosteroid injection (CSI). The study was a phase 2/3, four-arm parallel, multicenter, single-blind, randomized, controlled clinical trial with 480 patients with a diagnosis of knee osteoarthritis (Kellgren-Lawrence II-IV). Participants were randomized to the three different arms with a 3:1 distribution. Arm 1: autologous bone marrow aspirate concentrate (n = 120), CSI (n = 40); arm 2: umbilical cord tissue-derived mesenchymal stromal cells (n = 120), CSI (n = 40); arm 3: stromal vascular fraction (n = 120), CSI (n = 40). The co-primary endpoints were the visual analog scale pain score and Knee injury and Osteoarthritis Outcome Score pain score at 12 months versus baseline. Analyses of our primary endpoints, with 440 patients, revealed that at 1 year post injection, none of the three orthobiologic injections was superior to another, or to the CSI control. In addition, none of the four groups showed a significant change in magnetic resonance imaging osteoarthritis score compared to baseline. No procedure-related serious adverse events were reported during the study period. In summary, this study shows that at 1 year post injection, there was no superior orthobiologic as compared to CSI for knee osteoarthritis. Clinical Trials.gov Identifier: NCT 03818737

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Summary: Regenerative Medicine for OA



Osteoarthritis Treatment



- Hyaluronic Acid
- Regenerative Medicine

Summary: Regenerative Medicine for OA

Platelet-rich plasma

- 1. Mostly studied in knee OA but also safe for other joints with OA
- 2. Has not been shown to "reverse" OA
 - May decrease inflammatory biomarkers and halt the progression of OA
- 3. Important factors in determining efficacy:
 - Platelet dose injected
 - Patient age
 - OA severity
- 4. Variable outcomes reported in the literature
 - May improve pain and function 1-2 years post-injection
- 5. Not covered by insurance
- 6. Does not work right away takes about 6 weeks to start having an effect

BMAC, MFAT, Umbilical cord products/amniotic tissue

• Less literature

Osteoarthritis



Tendinopathy





Tendonitis \rightarrow Tendon disrepair \rightarrow Tendinosis



Tendon has poor blood supply

Background



Background







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Treatment options

- Rest, ice, elevate, NSAIDs
- Inflammation is not the problem in tendinosis!



Figure 1. From an upright body position and standing with all body weight on the forefoot and the ankle joint in plantar flexion lifted by the noninjured leg (A), the calf muscle was loaded eccentrically by having the patient lower the heel with the knee straight (B) and with the knee bent (C).

Treatment options



- Anti-inflammatory
- Weakens tendon, reduces collagen strength

Regenerative Medicine



- Pro-inflammatory
- Controlled microtrauma to convert a chronic injury (i.e. tendinosis) into an acute injury with healing potential



Regenerative Procedures for Tendinosis

- 1. Extracorporeal shockwave therapy (ESWT)
- 2. Percutaneous Needle Tenotomy
- 3. PRP

Regenerative Procedures for Tendinosis

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Extracorporeal Shockwave Therapy (ESWT)



- Propagates sounds waves though tissue to the injured tendon
- Stimulates interstitial and extracellular responses
 - Increased collagen synthesis
 - Cellular proliferation
 - Neovascularization

Extracorporeal shockwave therapy (ESWT)

- Weekly sessions for 3-5 weeks
- Minimal side effects
- No time away from sport
- Clinical improvements ~6 weeks

Systematic review

Use of extracorporeal shockwave therapies for athletes and physically active individuals: a systematic review

Hye Chang Rhim (a), ^{1,2} Jaehyung Shin (b), ² Jane Kang, ³ Paige Dyrek, ¹ Zack Crockett, ¹ Pearl Galido, ⁴ Carrie Wade, ⁵ Karsten Hollander (b), ⁶ Joanne Borg-Stein, ¹ Steven Sampson, ⁷ Adam S Tenforde (b) ¹ ABSTRACT

Objective To determine the efficacy of extracorporeal shockwave therapy (ESWT) and investigate outcomes following the use of ESWT for athletes and physically active individuals.

Design Systematic review.

Data sources We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and searched four databases: PubMed (NLM), Embase (Elsevier), CINAHL Complete (EBSCO) and Web of Science (Clarivate).

Eligibility criteria for selecting studies Included studies were randomised controlled trials, cohort and case-control studies, cases series and reports that evaluated outcomes following ESWT for athletes, physically active individuals and occupational groups requiring regular physical activity such as military cadets. **Results** 56 studies with 1874 athletes or physically active individuals were included. Using the Oxford level of evidence rating, included studies were 18 level I (32.1%), 3 level II (5.4%), 10 level III (17.9%), 13 level IV (23.2%) and 12 level V (21.4%). Based on the level I studies, ESWT may be effective alone in plantar fasciitis, lateral epicondylitis and proximal hamstring tendinopathy and as an adjunct to exercise treatment in medial tibial stress syndrome and osteitis pubis in athletes or physically active individuals. In most studies, athletes were allowed to continue activities and training and tolerated ESWT with minimal side effects. Conclusion ESWT may offer an efficacious treatment alone or as an adjunct to concurrent exercise therapy in selected sports-related injuries and without major adverse events. Further high-level research is needed to better define the role and clinical outcomes of ESWT.

Regenerative Procedures for Tendinosis

- 1. Extracorporeal shockwave therapy (ESWT)
- 2. Percutaneous Needle Tenotomy
- 3. PRP

Percutaneous needle tenotomy

- 1. Microtrauma
- 2. Controlled acute inflammatory response
- 3. Release of angiogenic factors and neovascularization
- 4. Tendon healing and remodeling



Tenex: Percutaneous Ultrasonic Ablation





Utility of Percutaneous Ultrasonic Tenotomy for Tendinopathies: A Systematic Review

Sravya Vajapey, MD, MBA,[†] Sennay Ghenbot, BS,[‡] Michael R. Baria, MD,[§] Robert A. Magnussen, MD,[†] and W. Kelton Vasileff, MD*[†]

Context: Chronic tendinopathy is a challenging problem that can lead to significant disability and limitation in not only athletics but also activities of daily living. While there are many treatment techniques described for this overuse injury, no single modality has been proven superior to all others. With recent advances in medical technology, percutaneous ultrasonic tenotomy (PUT) for tendinosis has gained traction with promising results.

Objective: To examine the data published on PUT for treatment of tendinopathy, analyze the outcomes of the procedure, including duration of pain relief and patient-reported outcomes, and assess the rate of complications associated with the procedure.

Data Sources: PubMed, MEDLINE, EMBASE, and Google Scholar.

Study Selection: The following combination of keywords was entered into the electronic search engines: *ultrasonic tenotomy, ultrasound tenotomy, Tenex*, and *ultrasonic percutaneous tenotomy*. The search results were screened for studies relevant to the topic. Only English-language studies were considered for inclusion. Studies consisting of level 4 evidence or higher and those involving human participants were included for more detailed evaluation.

Level of Evidence: Level 4.

Data Extraction: Articles meeting the inclusion criteria were sorted and reviewed. Type of tendinopathy studied, outcome measures, and complications were recorded. Both quantitative and qualitative analyses were performed on the data collected.

Results: There were a total of 7 studies that met the inclusion criteria and quality measures—5 studies involving the treatment of elbow tendinopathy and 1 study each involving the management of Achilles tendinopathy and plantar fasciitis. PUT resulted in decreased pain/disability scores and improved functional outcome scores for chronic elbow tendinopathy and plantar fasciitis. Results for Achilles tendinopathy showed modest improvement in the short term, but long-term data are lacking.

Conclusion: PUT is a minimally invasive treatment technique that can be considered in patients with tendinopathy refractory to conservative treatment measures. Further higher quality studies are necessary to accurately assess the comparative effectiveness of this treatment modality.

Regenerative Procedures for Tendinosis

- 1. Extracorporeal shockwave therapy (ESWT)
- 2. Percutaneous Needle Tenotomy
- **3. PRP**

PRP





Does it cause tendon to grow back?

- Nothing definitive on MRI
- Animal studies show tendons post-PRP have increased biomechanical strength and improved histological appearance

PRP vs steroid: Tennis Elbow

- 100 patients with lateral epicondylitis
- Success: 25% reduction in pain score at 1 year
 - 49% steroid group
 - 73% PRP group
- Steroid better initially (at week 4), then declined by week 12

Positive Effect of an Autologous Platelet Concentrate in Lateral Epicondylitis in a Double-Blind Randomized Controlled Trial

Platelet-Rich Plasma Versus Corticosteroid Injection With a 1-Year Follow-up

Joost C. Peerbooms,^{*} MD, Jordi Sluimer,[†] MD, Daniël J. Bruijn,^{*} PhD, and Taco Gosens,^{†‡} PhD From the *Department of Orthopaedic Surgery, HAGA Hospital, The Hague, Netherlands, and [†]Department of Orthopaedic Surgery, St Elisabeth Hospital, Tilburg, Netherlands

	Time (wks)	CS	PRP
		Average ± SD	Average ± SD
VAS	0	65.8 ± 13.8	70.1 ± 15.1
	4	44.2 ± 26.4	55.4 ± 24.2
	8	42.9 ± 29.2	46.9 ± 24.9
	12	44.2 ± 27.1	38.7 ± 27.2
	26	56.6 ± 23.2	32.6 ± 31.5
	52	50.1 ± 28.1	25.3 ± 31.2

Efficacy of Platelet-Rich Plasma for Chronic Tennis Elbow

A Double-Blind, Prospective, Multicenter, Randomized Controlled Trial of 230 Patients



Figure 6. Clinically significant success rates, as measured by a $\geq 25\%$ reduction in pain score versus baseline, were found in platelet-rich plasma-treated patients at 24 weeks after treatment (P = .037).

- 230 patients: tenotomy vs (PRP + tenotomy)
- Successful outcome: 25% improvement in pain
- PRP group better pain relief at 24 months
 - 83% in PRP + tenotomy
 - 69% in tenotomy



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Adverse Events of Platelet-Rich Plasma Injections for Tendinopathy From 2019 to 2020					
Tendinonathy	Treatment Effective	Treatment Ineffective	Treatment Mixed Efficacy	Major Adverse Events	
Unspecified location	3 studies ^{10–12}	0 studies	0 studies	0 studies	
Achilles tendinopathy	1 study ¹³	2 studies ^{14,15}	2 studies ^{16,17}	0 studies	
Lateral epicondylopathy	5 studies ¹⁸⁻²²	1 study ²³	1 study ²⁴	1 study ²³	
Patellar tendinopathy	4 studies ^{25–28}	0 studies	0 studies	0 studies	
Rotator cuff tendinopathy	3 studies ^{29–31}	0 studies	1 studies ³²	0 studies	

Summary: Regenerative Medicine for Tendinopathy

- Tendinosis is a chronic condition resulting from tendon disrepair
- First line treatment is proper physical therapy!
- The goal of regenerative procedures is to cause a controlled acute inflammatory response to restart tendon healing process in refractory cases
- 3 main options
 - 1. Extracorporeal shockwave therapy
 - 2. Percutaneous needle tenotomy
 - 3. PRP
- Safety has been established
- Clinical outcomes are promising but precise role still needs to be established

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Thank you!