Oregon Health & Science University
School of Medicine

Scholarly Projects Final Report

Title *(Must match poster title; include key words in the title to improve electronic search capabilities.)*

Evaluation of the Standardization of Platelet-Rich Plasma Protocols and Composition in Treatment of Knee Osteoarthritis: A Systematic Review

Student Investigator's Name

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Date of Submission *(mm/dd/yyyy)*

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Graduation Year

2024

Project Course *(Indicate whether the project was conducted in the Scholarly Projects Curriculum; Physician Scientist Experience; Combined Degree Program [MD/MPH, MD/PhD]; or other course.)*

Scholarly Projects Curriculum

Co-Investigators *(Names, departments; institution if not OHSU)*

NA

Mentor's Name

Dr. Sean Robinson

Mentor's Department

Family Medicine

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Concentration Lead's Name

Dr. Alex Foster

Project/Research Question

Following a 2017 systematic review that evaluated the reporting of PRP preparation and composition, has there been an improvement in the frequency of studies reporting these metrics?

Type of Project *(Best description of your project; e.g., research study, quality improvement project, engineering project, etc.)*

Systematic Review

Key words *(4-10 words describing key aspects of your project)*

PRP, platelet-rich plasma, osteoarthritis, preparation, composition

Meeting Presentations

If your project was presented at a meeting besides the OHSU Capstone, please provide the meeting(s) name, location, date, and presentation format below (poster vs. podium presentation or other).

NA

Publications *(Abstract, article, other)*

If your project was published, please provide reference(s) below in JAMA style.

NA

Submission to Archive

Final reports will be archived in a central library to benefit other students and colleagues. Describe any restrictions below (e.g., hold until publication of article on a specific date).

NA

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Next Steps
What are possible next steps that would build upon the results of this project? Could any data or tools resulting from the project have the potential to be used to answer new research questions by future medical students?

The future area of study should involve analysis of PRP preparation and composition in all musculoskeletal conditions to further verify the results that were seen in this systematic review.

Please follow the link below and complete the archival process for your Project in addition to submitting your final report.

https://ohsu.ca1.qualtrics.com/jfe/form/SV_3ls2z8V0goKiHZP

Student's Signature/Date *(Electronic signatures on this form are acceptable.)*
This report describes work that I conducted in the Scholarly Projects Curriculum or alternative academic program at the OHSU School of Medicine. By typing my signature below, I attest to its authenticity and originality and agree to submit it to the Archive.

X

Student's full name

Mentor's Approval *(Signature/date)*

X

Mentor Name

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Report: *Information in the report should be consistent with the poster, but could include additional material. Insert text in the following sections targeting 1500-3000 words overall; include key figures and tables. Use Calibri 11-point font, single spaced and 1-inch margin; follow JAMA style conventions as detailed in the full instructions.*

Introduction *(≥250 words)*

Platelet-rich plasma (PRP) injections have shown promise in multiple fields, most commonly musculoskeletal injuries. The musculoskeletal conditions treated with PRP include rotator cuff tears, lateral epicondylitis, patellar tendinopathy, and osteoarthritis, the most common musculoskeletal condition treated with PRP. PRP is a product that is comprised of a patient's blood. After spending time in a centrifuge to spin off and eliminate non-essential products, such as white and red blood cells, the product consists of a large number of platelets in a relatively small amount of plasma. The platelets that remain contain multiple growth factors, which are thought to assist in the healing that has become associated with PRP in recent years. The growth factors all possess different abilities but are primarily thought to assist in cell growth, proliferation, differentiation, and potential bone and cartilage regeneration[1].

In regards to cartilage injuries in osteoarthritis, PRP is thought to decrease catabolism while additionally promoting chondral remodeling as well as increasing chondrocyte proliferation and decreasing apoptosis. Additionally, the counteraction of the inflammatory process by PRP is thought to reduce the pain experienced by patients with osteoarthritis[2]. With the increasing popularity in PRP therapy, it is thought that the market can grow as high $4.5 billion within the next ten years. Despite the increasing usage, PRP largely remains uncovered by insurance and has an average cost $707 per injection[3]. Despite some studies demonstrating that PRP provides an improvement in both pain and functional outcomes for knee osteoarthritis in comparison to hyaluronic acid and placebo, it still generally remains uncovered by insurance[4]. The lack of insurance coverage is primarily attributed to inconsistencies in patient outcomes and poor clinical replicability of these studies that may be due to differences in commercially available PRP collection kits that vary in collection volume and preparation protocols, therefore creating a unique PRP formulation.

A systematic review in 2017 titled "A Call for Standardization in Platelet-Rich Plasma Preparation Protocols and Composition Reporting: A Systematic Review of the Clinical Orthopedic Literature" evaluated the composition and preparation of PRP in all orthopedic literature published from 2006-2016. The systematic review discovered discrepancies in PRP protocols, primarily the reporting of centrifuge parameters and anticoagulation use. Since the article was published in 2017, no repeat systematic review has been performed[5]. This project will aim to repeat the initial publication using the same PubMed search terms, but this time evaluating only PRP injections performed on patients with knee osteoarthritis. The aim of this study will be to determine the efficacy of the initial call for standardization in PRP literature to help determine if clinical trials are becoming more replicable and therefore more reliable.

Methods *(≥250 words)*

A systematic review of the literature regarding the preparation of PRP in knee osteoarthritis clinical trials conducted from 2017 to 2023 was performed using PubMed and MEDLINE. After discussion with the OHSU clinical research team, the following search was performed on PubMed and MEDLINE in September through December 2023: (("platelet-rich plasma"[MeSH Terms] OR ("platelet-rich"[All

Fields] AND "plasma"[All Fields]) OR "platelet-rich plasma"[All Fields] OR ("platelet"[All Fields] AND "rich"[All Fields] AND "plasma"[All Fields]) OR "platelet rich plasma"[All Fields]) AND (Clinical Trial[ptyp]) AND (2017:2024[pdat])) AND (knee osteoarthritis).

Human clinical trials, both prospective and retrospective, that were written in the English language and reported on the use of PRP in knee osteoarthritis were included. Basic science articles, commentary, and redacted articles were excluded from the systematic review.

Data were recorded using an encrypted information extraction table. The data points that were collected were identical to the previously mentioned 2017 study. This study collected data on the protocol used for PRP preparation, including the initial whole blood volume, anticoagulant used, type of centrifuge used, number of spins (including RPM and time), platelet activation method, final platelet count, total increase in platelet count, growth factor analysis, and final volume.

Results *(≥500 words)*

Applying Selection Criteria for Eligible Articles

The detailed selection of eligible articles used in this systematic review is outlined in Figure 1. Using the search terms as detailed above in the methods section, 81 articles were identified. Of those initial 81 articles, 25 did not meet the inclusion criteria primarily due to not being written in English, having been retracted since the initial publication, or the article pertained to PRP injections being performed for reasons other than knee osteoarthritis. Of the remaining 56 articles, it was determined that 51 met all inclusion criteria and were therefore used to calculate all percentages that this systematic review sought to analyze.

PRP Processing Characteristics

PRP processing characteristics are seen in Table I. The initial whole blood volume drawn for PRP preparation was reported in 48 (94%) of the studies, an 8% increase from the 86% of studies reporting in the 2017 study. Regarding the details of the centrifugation process, all studies reported performing at least one spin using a centrifuge machine. Of the 51 articles, 41 (80%) reported the exact rotations per minute (RPM) used while 46 (90%) included the time for how long centrifugation took place. There were 10 articles that did not perform a second round of centrifugation, but of the remaining 41 articles there were 27 (66%) that reported the RPM and time spent in the centrifuge machine. In comparison to the analysis of the first spin in the centrifuge noted in the 2017 review, there was a 24% increase in reporting the RPM and a 33% increase in time spent in the centrifuge. Additionally, there was a 46% increase in studies reporting the RPM and time of the second spin in comparison to 2017. Finally, only 1 (2%) study reported a third spin in comparison to the 0 that reported a third spin in the previous systematic review.

There were 36 (71%) studies that reported the use of an anticoagulant used in PRP preparation. The anticoagulants used were acid citrate dextrose (n=15), sodium citrate (n=11), citrate phosphate dextrose (n=8), citrate dextrose (n=2). While there was an overall 19% increase in studies reporting the exact anticoagulant in comparison to the 2017 review, acid citrate dextrose and sodium citrate were the most commonly used anticoagulants in both reviews. There were a total of 22 (43%) studies reporting the specific centrifuge machine used, a decline of 33% from the 76% reported in the 2017 review.

The activation method used to cause degranulation of platelets and induce growth factor release was reported in 15 (29%) studies, a decline of 12% from the 41% reported in the previous review. The activation methods included calcium chloride (n=10), calcium gluconate (n=4), and thrombin (n=1). Calcium chloride was also the most commonly used activation agent used in the previous review. Only 2 (4%) recent studies reported the use of a buffering agent, a 7% decline from the 11% reported in the 2017 review.

PRP Composition Characteristics

PRP composition characteristics are seen in Table II. Post-preparation analysis that involved evaluation of the PRP product that was injected was performed in 29 (57%) recent studies, a 29% increase from the 28% reported in 2017. The platelet concentration of the initial blood sample was reported in 20 (39%) of the studies and 29 (57%) reported the platelet concentration of the final PRP product, a 22% and 26% increase in those reported in the 2017 review, respectively. The fold increase in platelet count above that of the initial blood samples was reported in 24 (47%) studies, a decline of 7% from those reported in the 2017 review. Other specific details of post-preparation analysis showed an increase from the 2017 review, including 12 (24%) studies that reported growth factor analysis and 46 (90%) studies that reported the final volume of the PRP product also increased from the previous review.

Figure I. PRISMA flow diagram presenting the systematic review process used in this study.

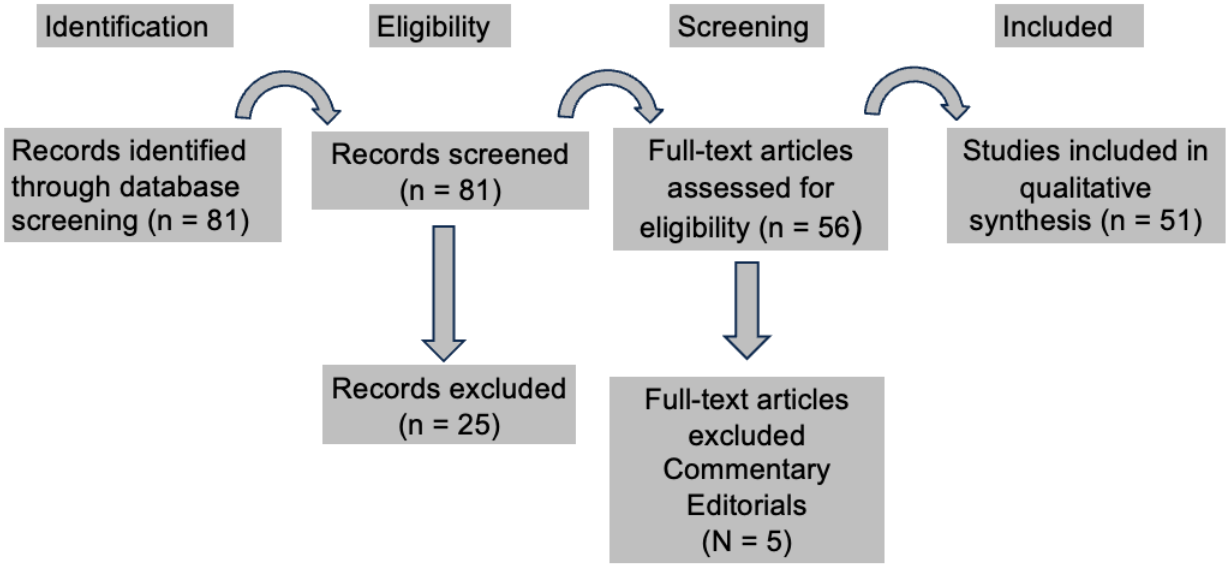

Table I. Harvest Protocols and Spin Parameters Reported in the Included Studies

				Spin 1		Spin 2	
	Initial Whole Blood Volume	Anticoagulant	Processing Machine	Speed (rpm)	Time (min)	Speed (rpm)	Time (min)
No. (%) of studies reporting	48 (94%)	36 (71%)	22 (43%)	41 (80%)	46 (90%)	27 (66%)	27 (66%)
Percentage of studies reporting in 2017	86%	52%	76%	56%	57%	20%	20%
Percentage Change	8%	19%	-33%	24%	33%	46%	46%
Mean and std. dev.	49.1 ± 56.4	NA	NA	2274 ± 916.4	9.3 ± 4.2	3126 ± 846.4	9.4 ± 3.9
Mode	10	Acid Citrate Dextrose	Angel Centrifuge	1800	15	3500	10
Median	40	NA	NA	1800	8	3400	10
Minimum	4.65	NA	NA	900	1.5	250	3
Maximum	300	NA	NA	3800	20	4000	15

Table II. Key Properties Reported in the Included Studies

	Initial Platelet Concentration ($10^3/\mu L$)	Final Platelet Count ($10^3/\mu L$)	Platelet Increase Factor	Growth Factors	Final Volume (mL)
No. (%) of studies reporting	20 (39%)	29 (57%)	24 (47%)	12 (24%)	46 (90%)
Percentage of studies reporting in 2017	22%	26%	54%	13%	56%
Percentage Change	17%	31%	-7%	9%	34%
Mean and std. dev.	227.5 ± 37.7	813.74 ± 453.2	3.3 ± 1.6	NA	5.6 ± 2.2
Mode	194	694	3	NA	5
Median	232.5	794.5	2.9	NA	5
Minimum	140	9.8	1.7	NA	2
Maximum	320	2179	7.2	NA	10

Table II (Continued)

	Activation	Buffer	Time from Preparation (min)	Post-Preparation Analysis
No. (%) of studies reporting	15 (29%)	2 (4%)	13 (25%)	29 (57%)
Percentage of studies reporting in 2017	41%	11%	26%	28%
Percentage Change	-12%	-7%	-1%	29%
Mean and std. dev.	NA	NA	35 ± 31.9	NA
Mode	Calcium chloride	NA	30	NA
Median	NA	NA	25	NA
Minimum	NA	NA	15	NA
Maximum	NA	NA	120	NA

Discussion *(≥500 words)*

Similar to what was noted in the 2017 systematic review, this updated systematic review shows a large variability in the reporting of PRP preparation protocols as well as post-preparation analysis. Despite the increasing popularity of PRP, there continues to be a lack of consensus on the most beneficial formulation of the product. However, although the efficacy of PRP is still being evaluated, this systematic review determined a positive shift in the reporting of how the product is created.

Following the "Call for Standardization" as requested by the 2017 systematic review, there has been improvement in multiple aspects of PRP preparation, most notably in the reporting of the initial whole blood volume, anticoagulation use, and centrifugation parameters. The previous review stated "at a minimum, reported metrics should include the starting volume, anticoagulant, preparation technique (including spin rate [with rotor length] and/or g-forces and times), make and model of the centrifuge, use of activating agents, and the final concentration of platelets, nucleated cells, and erythrocytes"[5]. Although the number of studies listing all these qualities was not mentioned in the previous review, the current review demonstrates that 3 (6%) studies met all the above details of both PRP preparation and post-preparation analysis.

There were 7 (14%) studies that outlined all the above details of PRP preparation, a 4% increase from the 10% of studies satisfying these same requirements from the previous review. Although this improvement may seem rather minor, it should be noted that the most common missing metric within the PRP preparation analysis was the type of centrifuge machine used, a metric that was more commonly reported in the studies analyzed during the 2017 review. When taking into account studies that had mentioned all other details of PRP preparation besides the model of the centrifuge, there was 18 (35%) studies that satisfied the mentioned requirements suggested by the previous review. Previous studies have suggested that although different centrifuge machines can result in various platelet concentrations, there is not a singular centrifuge machine that is officially recommended for PRP preparation[6]. Although not explicitly stated, the decline of studies reporting the centrifuge machine used may be due to the lack of official recommendations. The reason for the increase in the other PRP preparation metrics is unclear. While it may be due to the call for standardization in PRP

protocols, it is also reasonable to assume that it may be a result of improving data published after the original review that highlights the necessity of certain components. For example, the use of an anticoagulant (primarily acid citrate dextrose) has been found to preserve platelet morphology and functionality in comparison to placebo[7]. While data for the most beneficial parameters of the centrifuge are still unclear, previous studies suggest a significant increase in platelet yield in samples that undergo a second spin[8], which may suggest why there has been an increase in the number of studies reporting the use of a second spin.

The primary limitation of this study is the difference in the indications for PRP injection in the 2017 review versus this systematic review. The 2017 review analyzed the use of PRP in multiple musculoskeletal conditions, as opposed to our review which reviewed only the use of PRP in knee osteoarthritis. Unfortunately, the previous review did not further subcategorize their data based on the specific indications, therefore making it difficult to determine if the improvement seen in our results is significant. However, given that knee osteoarthritis is the most common indication for PRP injection, it is our belief that the results would be similar if all musculoskeletal indications had been analyzed. Ultimately, the future area of study should involve analysis of PRP preparation and composition in all musculoskeletal conditions to further verify the results that were seen in this systematic review.

As initially established by the original 2017 review, this systematic review emphasizes the importance of reporting various PRP preparation parameters. With improved reporting and communication, the development of PRP and the study of its efficacy on various conditions can be further investigated. While reporting of certain parameters could be more consistent, this systematic review has demonstrated that "A Call for Standardization" has pointed the field in the right direction and will hopefully continue to improve with further research.

Conclusions *(2-3 summary sentences)*

This systematic review discovered improvements in multiple PRP preparation and post-analysis metrics following the initial "Call for Standardization" that was published in 2017. Although it is unclear at this time whether the improvement in certain categories is due to changing literature or the effectiveness of the previous review, it is evident that there has been an improvement in the reporting of PRP preparation in clinical studies.

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