A Call for Standardization in Platelet-Rich Plasma Preparation Protocols and Composition Reporting

A Systematic Review of the Clinical Orthopaedic Literature

Jorge Chahla, MD, PhD, Mark E. Cinque, MS, Nicolas S. Piuzzi, MD, Sandeep Mannava, MD, PhD, Andrew G. Geeslin, MD, Iain R. Murray, MD, PhD, Grant J. Dornan, MSc, George F. Muschler, MD, and Robert F. LaPrade, MD, PhD

Investigation performed at the Steadman Philippon Research Institute, Vail, Colorado, and The Cleveland Clinic Foundation, Cleveland, Ohio

Background: Platelet-rich plasma (PRP) is a blood-derived preparation whose use has grown exponentially in orthopaedic practice. However, there remains an unclear understanding of the biological properties and effects of PRP on musculoskeletal healing. Heterogeneous processing methods, unstandardized nomenclature, and ambiguous classifications make comparison among studies challenging. A comprehensive assessment of orthopaedic clinical PRP trials is key to unraveling the biological complexity of PRP, while improving standardized communication. Toward this goal, we performed a systematic review of the PRP preparation protocols and PRP composition utilized in clinical trials for the treatment of musculoskeletal diseases.

Methods: A systematic review of the literature was performed from 2006 to 2016. Inclusion criteria were human clinical trials, English-language literature, and manuscripts that reported on the use of PRP in musculoskeletal/orthopaedic conditions. Basic-science articles, editorials, surveys, special topics, letters to the editor, personal correspondence, and nonorthopaedic applications (including cosmetic use or dental application studies) were excluded.

Results: A total of 105 studies (in 104 articles) met the inclusion criteria for analysis. Of these studies, only 11 (10%) provided comprehensive reporting that included a clear description of the preparation protocol that could be used by subsequent investigators to repeat the method. Only 17 studies (16%) provided quantitative metrics on the composition of the final PRP product.

Conclusions: Reporting of PRP preparation protocols in clinical studies is highly inconsistent, and the majority of studies did not provide sufficient information to allow the protocol to be reproduced. Furthermore, the current reporting of PRP preparation and composition does not enable comparison of the PRP products being delivered to patients. A detailed, precise, and stepwise description of the PRP preparation protocol is required to allow comparison among studies and provide reproducibility.

Platelet-rich plasma (PRP) offers promise for the treatment of various musculoskeletal conditions, as indicated by basic-science and emerging clinical studies[1-4]. The biological rationale for the clinical use of PRP includes the local delivery of growth factors, modification of the inflammatory response, and positive effects of PRP on cell proliferation and differentiation[3]. From a practical U.S. Food and Drug Administration (FDA) regulatory standpoint, PRP falls into the category of minimally manipulated tissue and, as an autologous blood product, it is easier to utilize clinically without extensive testing in preclinical and clinical trials. The lack of regulatory hurdles prior to clinical implementation has resulted in the recent explosion of PRP use in musculoskeletal medicine. However, the specific characteristics of the optimal PRP formulations for use in treating different musculoskeletal pathologies remain unknown.

The current literature, including many published clinical trials evaluating PRP, fails to either include sufficient experimental detail or report the basic attributes of PRP formulations[5]. The clinical characterization of PRP faces 2 interrelated challenges. First, peripheral blood from individual patients is characterized by a large inherent variability in the concentrations of platelets and growth factors[6]. Second, preparation protocols themselves have multiple stages that each provide

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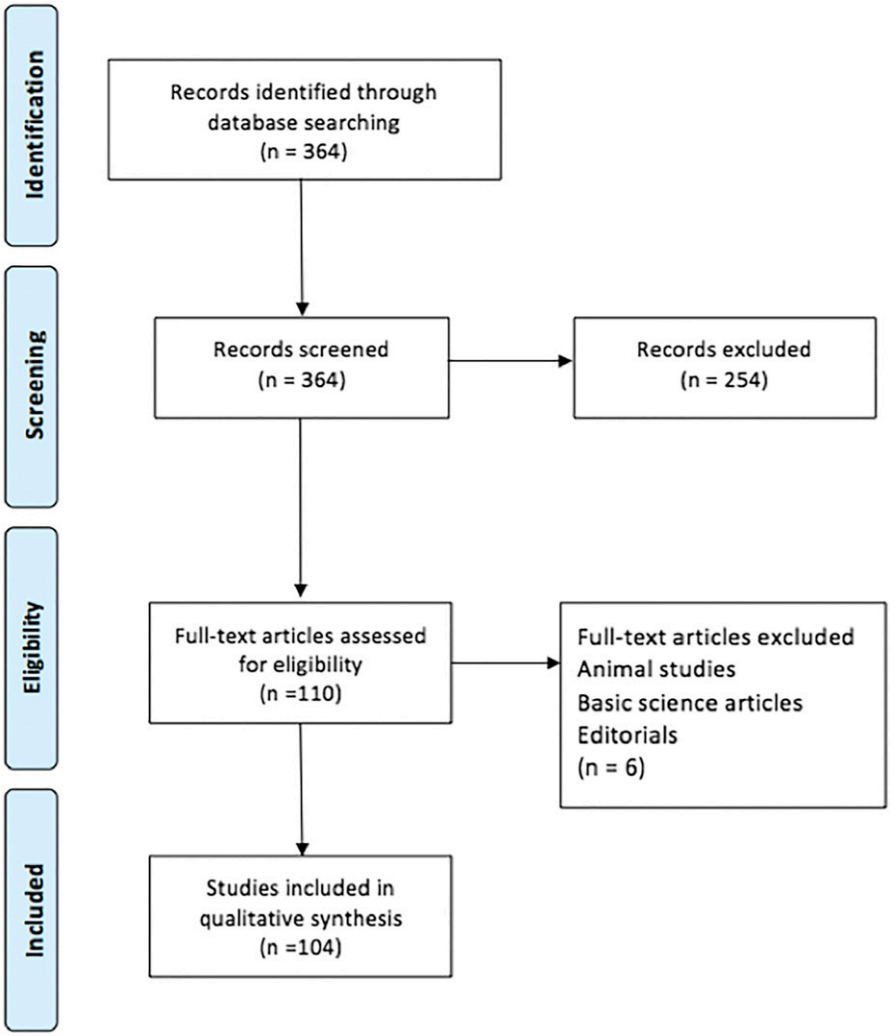

Fig. 1
PRISMA flow diagram presenting the systematic review process used in this study.

sources of additional variation (sample volume; anticoagulation methods; centrifuge device characteristics; the g-forces [forces expressed as the number of times Earth's gravity] applied to the samples during centrifugation; the duration of spin cycles; the number of spin cycles; and the method of separation between serum, cell, and platelet fractions). Taken together, these factors make it challenging to compare the effectiveness of PRP in individual studies or between studies unless the comprehensive

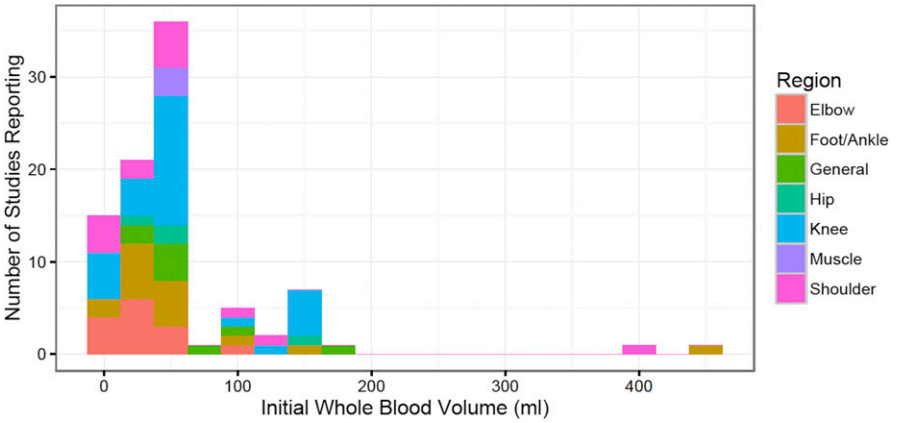

Fig. 2
Histogram of initial whole blood volume stratified by anatomic region among 90 reporting studies.

TABLE I PRP Processing System Used in the Studies That Reported That Information (N = 54)*

Make and Model	Method	No.
GPS (Biomet)	Centrifugation	25
Magellan Autologous Platelet Separator System (Medtronic Perfusion Systems [now Arteriocyte])	Centrifugation	9
Arthrex ACP Double Syringe System (Arthrex)	Centrifugation	7
Centrifugation (not specified)	Centrifugation	7
PRGF technique (BTI Systems)	Centrifugation	5
Smart-PReP 2 system (Harvest Autologous Hemobiologics)	Centrifugation	4
Platelet-pheresis system with a leukoreduction set, COBE Spectra LRS Turbo (Rontis Medical)	Platelet-pheresis	3
Cascade autologous platelet system (Musculoskeletal Transplant Foundation)	Centrifugation	2
Haemonetics MCS1 9000 cell separator with a specific kit for platelet apheresis, 995-E (Haemonetics)	Platelet-pheresis	2
Huons HC-1000 system (Huons)	Centrifugation	1
Harvest system (Harvest)	Centrifugation	1
PRP fast biotech kit PPT-Platelet Preparation Tube (MyCells)	Centrifugation	1
Centra CL2 (IEC)	Centrifugation	1
Kubota refrigerated centrifuge 9800 (Kubota)	Centrifugation	1
Jouan B4i centrifuge (Jouan)	Centrifugation	1
RegenKit (Regen Laboratory)	Centrifugation	1
Tabletop centrifuge 2420 (Kubota)	Centrifugation	1
Centrifuge (Beckman)	Centrifugation	1
Accelerate Sport platelet concentration system (Exactech)	Centrifugation	1
Prosys PRP platelet concentration system (Tozai Holdings)	Centrifugation	1
Clinispin Horizon 755VES centrifuge (Woodley Laboratory Diagnostics)	Centrifugation	1
LC6 Centrifuge (Sarstedt)	Centrifugation	1
Labofuge 400R (Heraeus)	Centrifugation	1
Standard centrifuge, J-6B (Beckman)	Centrifugation	1
PRF (Vivostat)	Centrifugation	1
Total		80

*PRGF = plasma rich in growth factors.

reporting of PRP preparation protocols and the composition of PRP are provided. Therefore, to understand the current level of reporting and the variation in current methods for PRP preparation and composition, we performed a systematic review of clinical trials using PRP formulations for the treatment of musculoskeletal diseases. We hypothesized that the orthopaedic clinical literature regarding the use of PRP for the treatment of musculoskeletal conditions would be characterized by heterogeneous reporting of PRP preparation methodology and composition.

Materials and Methods

Article Identification and Selection

This study was conducted in accordance with the 2009 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[7]. A systematic review of the literature regarding the preparation of PRP in musculoskeletal clinical trials was performed using PubMed and MEDLINE (2006 to 2016). The query was performed in August 2016. Registration of the systematic review was performed using the PROSPERO International prospective register of systematic reviews (registration number CRD42016047610).

The following search was performed on MEDLINE/PubMed on August 2016: ("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]).

Human clinical trials (with prospective or retrospective characteristics), presented in the English language, that reported on the use of PRP in musculoskeletal/orthopaedic conditions were included. Basic-science articles, editorials, surveys, special topics, letters to the editor, personal correspondence, and nonorthopaedic studies (including cosmetic use or dental applications) were excluded from the present study.

Three investigators (J.C., M.E.C., and N.S.P.) independently reviewed the abstracts from all articles identified in these searches. Full-text articles were reviewed when necessary to confirm eligibility according to the inclusion and exclusion criteria. Reference lists were also reviewed to minimize the risk of missing relevant articles.

Data Collection

Data were recorded into an information extraction table. We collected data on the protocol used for PRP preparation, including the initial whole blood volume, anticoagulant used, processing machine, disposable equipment, method of separation (centrifugation or platelet-pheresis), number of spins (with rate

TABLE II Harvest Protocols and Spin Parameters Reported in the Included Studies*

	Initial WB Volume *(mL)*	Anticoagulant	Processing Machine	Spin 1		Spin 2	
				Speed *(rpm)*	Time *(min)*	Speed *(rpm)*	Time *(min)*
No. (%) of studies reporting	90 (86%)	54 (52%)	80 (76%)	59 (56%)	60 (57%)	21 (20%)	21 (20%)
Mean and std. dev.	60.8 ± 68.9	NA	NA	1,986 ± 1,098	11 ± 4	2,588 ± 1,208	12 ± 6
Mode	54	ACD-A, n = 24	GPS System, n = 25	3,200	15	No 2nd spin	No 2nd spin
Median	51	NA	NA	1,500	14	3,300	10
Minimum	8	NA	NA	120	3	200	2
Maximum	450	NA	NA	5,800	15	4,500	25
No. of unique entries	27	7	9	18	8	12	7

*WB = whole blood, and NA = not applicable.

or gravitational forces, when reported, and time), platelet activation method, nomenclature, final platelet count, fold increase in platelet count, growth factor analysis, final volume, and clinical use. These factors were selected on the basis of previously published reports on criteria that influence the composition or biological effect of PRP[8-11]. For the purpose of summarizing numerical descriptors across studies, ranges were reduced to 1 data point by using the

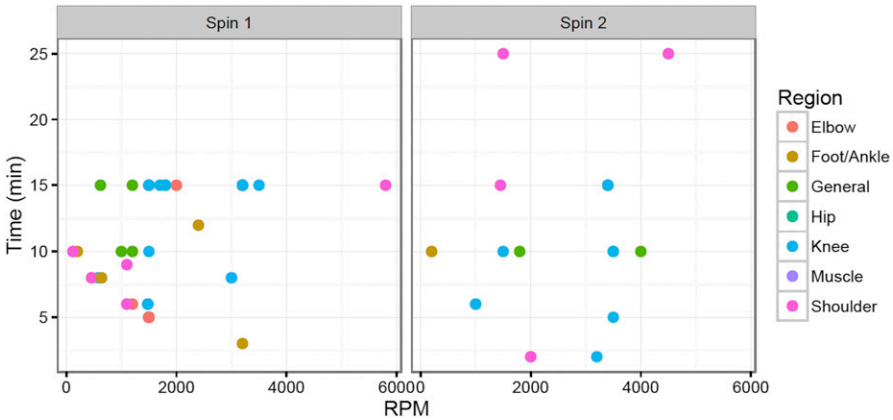

Fig. 3
Scatterplot demonstrating centrifugation characteristics stratified by body region.

TABLE III Key PRP Properties Reported in the Included Studies*

	Activation	Buffer	Time from Preparation *(hr)*	Post-Preparation Analysis
No. (%) of studies reporting	43 (41%) + 24 reporting none	11 (11%)	27 (26%)	29 (28%)
Mean and std. dev.	NA	NA	14 ± 33	NA
Mode	None	$NaHCO_3$	1	Complete blood-cell count
Median	NA	NA	1	NA
Minimum	NA	NA	NA	NA
Maximum	NA	NA	NA	NA
No. of unique entries	7	2	13	6

*NA = not applicable.

midpoint of the range. Articles were defined as providing *comprehensive reporting* when the study reported data on all of these metrics.

Results

Article Identification and Selection

The process for study selection is presented in Figure 1. The search strategy identified 364 individual reports. Application of inclusion and exclusion criteria to the title and abstract eliminated 254 studies, leaving 110 articles for full-text review. After a comprehensive review of these articles, a total of 104 articles met inclusion criteria for analysis[12-115]. One article[12] reported on and compared 2 preparation methods and was treated as 2 separate studies for the purpose of tabulating study characteristics. Therefore, percentage calculations were based on a total of 105 distinct data sets.

PRP Processing Characteristics

Heterogeneity was encountered among studies with respect to the PRP processing protocols. The initial whole blood volume was reported in 90 (86%) of the studies. The median whole blood volume extracted was 51 mL (range, 8 to 450 mL) (Fig. 2).

All studies used an anticoagulant; however, the specific anticoagulant that was used was reported in only 54 (52%) of the studies (acid citrate dextrose solution A [ACD-A, n = 24], calcium citrate [n = 2], citrate/citric acid [n = 6], citrate phosphate dextrose [CPD, n = 4], sodium citrate [n = 18]). The processing machine that was utilized for PRP preparation was reported in 80 (76%) of the studies. Twenty-four different processing machines were reported (Table I). Five studies used a platelet-pheresis system with a leukoreduction set[32,61,70,93,102], and the remainder used a centrifugation process. Processing machines utilized, with their respective platelet separation method, are shown in Table I.

Of the 100 studies that used a centrifugation process, 63 reported the spin time and/or rate of the first spin. Twenty-three studies reported performing a second spin, although only 21 of these reported the spin time and/or rate details of this process. The median rate for the first spin was 1,500 rpm (range, 120 to 5,800 rpm) and the median spin time was 14 minutes (range, 3 to 15 minutes). The most common first-spin combination of parameters was 3,200 rpm for 15 minutes. The median rate for spin 2 was 3,300 rpm (range, 200 to 4,500 rpm), and the median time was 10 minutes (range, 2 to 25 minutes) (Table II and Fig. 3).

The activation method used to induce platelet degranulation and release of platelet growth factors into solution after first concentrating the platelets was reported in 43 studies (41%). The activation agents included $CaCl_2$ (n = 24), thrombin (n = 6), dry needling (multiple tissue perforations before injections to release thrombin in the local environment) (n = 4), $CaCl_2$ and thrombin (n = 5), calcium gluconate (n = 3), and tissue factor (n = 1). Twenty-four studies (23%) specifically reported using no activation method, leaving 38 studies (36%) that did not report on the method of platelet activation. Whether a buffered solution was used during processing was reported in 11 studies; these included $NaHCO_3$ (n = 10) and no buffer (n = 1). The interval of time between processing and injection was reported for only 27 studies (mean and standard deviation = 14 ± 33 hours, median = 1 hour, and mode = 1 hour) (Table III).

PRP Composition Characteristics

Analysis of the composition of the PRP that was injected was reported in 29 of 105 studies (28%). Data from some form of cell counting was reported in 29 studies; these included the cell count (n = 10), platelet and leukocyte count (n = 14), and platelet count (n = 5).

Fourteen studies (13%) further reported on the following growth factors (Table III): epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-β), and insulin-like growth factor-1 (IGF-1) (n = 1)[16]; and interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) (n = 1)[17].

A specific nomenclature and terms used to classify or subclassify the PRP preparations that were used were reported in 51 studies. These included leukocyte-poor PRP (n = 3), leukocyte-rich PRP (n = 10), platelet-rich fibrin (PRF) (n = 2),

TABLE III (*continued*)

Initial Platelet Concentration *($10^3/\mu L$)*	Final Platelet Count *($10^3/\mu L$)*	Platelet Increase Factor	Growth Factors	Final Volume *(mL)*
23 (22%)	27 (26%)	57 (54%)	14 (13%)	59 (56%)
381 ± 391	1,473 ± 2,211	4.7 ± 1.96	NA	6.5 ± 5.5
NA	1,000	5	No growth factor	3
234	962	5	NA	5
38	250	1.2	NA	2
1,540	10,934	10	NA	30
23	25	24	2	15

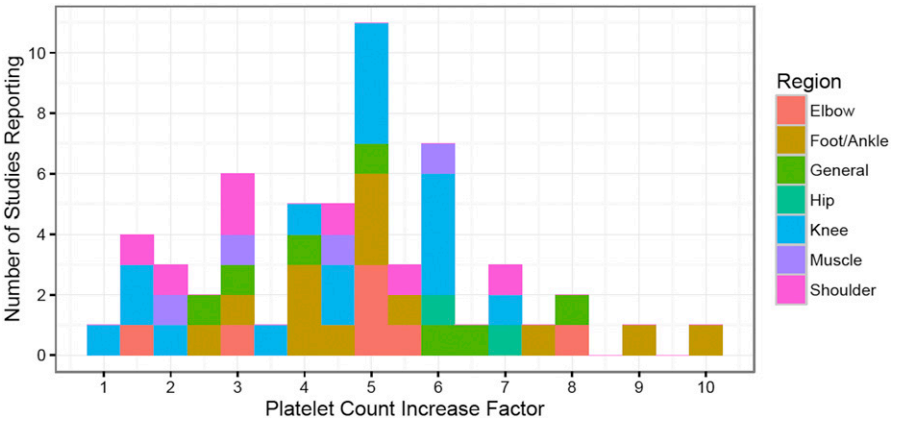

Fig. 4

Histogram of studies reporting the fold increase in platelet count stratified by body region (57 studies).

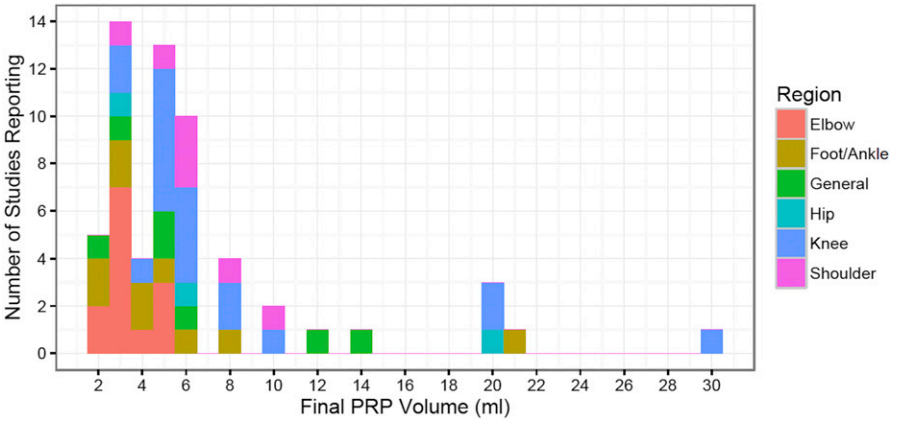

Fig. 5

Histogram of studies reporting final PRP volume stratified by body region (59 studies).

platelet rich in growth factors (PRGF) (n = 1), PRP (n = 20), PRP gel (n = 14), and PRP/leukocyte gel (n = 1).

The platelet concentration in the initial blood sample was reported in 23 studies, with a mean of 381 ± 391 × 10^3 platelets/μL and median of 234 × 10^3/μL. The final platelet count was reported in 27 studies, with a mean of 1,473 ± 2,211 × 10^3 platelets/μL, median of 962 × 10^3/μL, and mode of 1,000 × 10^3/μL. The fold increase in platelet count above that in the initial blood samples was reported in 57 studies, with a median of 5-fold (range, 1.2 to 10-fold) (Fig. 4).

The final volume of PRP was reported in 59 studies, with a median of 5 mL (range, 2 to 30 mL) (Fig. 5).

PRP Clinical Indications

The clinical indications for which PRP was used included hip and knee osteoarthritis (n = 17), rotator cuff pathology (n = 16), epicondylitis (n = 15), anterior cruciate ligament reconstruction (n = 10), Achilles tendinopathy (n = 6), patellar tendinitis (n = 6), muscle injury (n = 5), fracture-healing (n = 5), plantar fasciitis (n = 4), total knee and total hip arthroplasty (n = 3), talar osteochondritis dissecans (OCD) (n = 3), and other (n = 15). Studies were included in the "other" category if <3 articles reported on treating that pathology or body region (Fig. 6).

Discussion

The most important finding of this systematic review was that a wide spectrum of PRP preparation protocols and formulations were used, all grouped under the term "PRP." In the current orthopaedic PRP literature, PRP has been applied across a range of indications, without a consensus formulation or a standardized reporting methodology of preparation even for the same clinical indication. We identified 105 clinical studies (in 104 articles) evaluating the use of PRP in the treatment of musculoskeletal conditions. Of these studies, only 11 (10%) provided comprehensive reporting that included a clear description of the preparation protocol that could be used to repeat the method by subsequent investigators. Only 17 studies (16%) provided quantitative metrics on the composition of the PRP final product. From a scientific standpoint, we found limited information reported in the clinical literature regarding the actual growth factor or biologically active molecular composition of PRP. Therefore, heterogeneity in PRP composition may

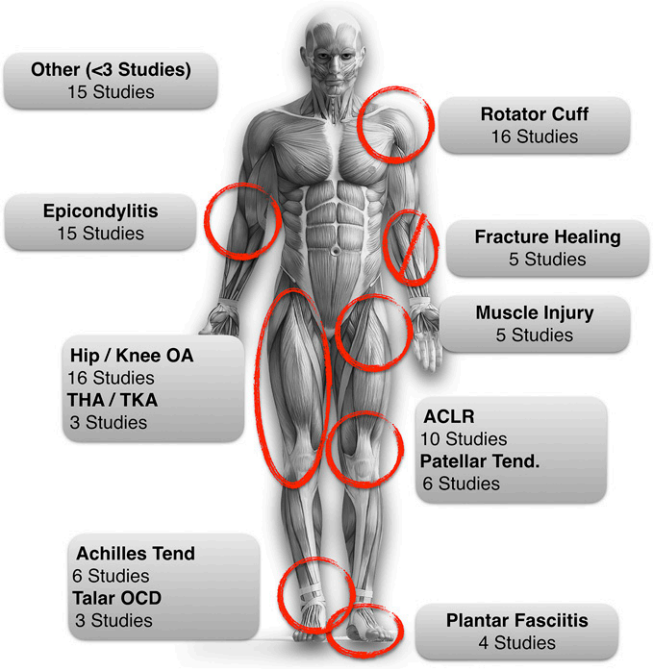

Fig. 6

Location and indication for PRP therapy among the articles included in the analysis. OA = osteoarthritis, THA = total hip arthroplasty, TKA = total knee arthroplasty, ACLR = anterior cruciate ligament reconstruction, and OCD = osteochondritis dissecans.

represent the main reason for the diverse effects that have been reported for PRP in the literature. This heterogeneity in approaches is not based on a definitive pathophysiological understanding of individual conditions, and thus precludes a meta-analysis-based analysis of clinical outcomes. This study highlights the importance of developing a culture of clinical analysis and communication that will be essential for the safe and rational development, as well as assessment, of the rapidly expanding array of local bioactive agents and cell therapy options that are becoming available in orthopaedic care.

Two salient omissions in a majority of studies included in this review make it challenging to develop a more broadly applicable PRP protocol: (1) details of the processing methods that convert whole blood to a PRP preparation, which could be used to repeat and reproduce the method; and (2) quantitative metrics on the composition of the starting blood sample and the final product. The lack of consistent reporting of the volume and the concentration of leukocytes, erythrocytes, and particularly platelets in the initial blood sample creates a challenge in identifying preferred injuries or pathological conditions for PRP therapy. The absence of such data also precludes a calculation of the yield and efficiency of any given processing method that is designed to concentrate platelets or other blood components. The lack of consistent reporting of the duration of the spin also poses a major issue in creating a generalized PRP protocol. The length of time of each spin cycle greatly affects the viability and concentration of the growth factors and cytokines contained in the end product[114]. Moreover, large variations were also found in the nomenclature and classification systems that were used in these studies to describe the PRP composition that was created. The absence of a clearly defined and internally consistent system of nomenclature, added to the absence of quantitative metrics, makes communication regarding comparison among studies challenging.

Reports of treatment for musculoskeletal conditions based on preparations described as "platelet-rich plasma," PRP, have increased almost exponentially in the past 10 years, despite a lack of robust clinical evidence supporting their efficacy[5]. PRP preparations are defined as containing blood-derived platelets and other blood components that are present in higher concentrations than in native whole blood. However, preparations that are referred to as PRP are highly heterogeneous both in the processing methods that are used and in composition (i.e., the concentrations of platelets, leukocytes, erythrocytes, cytokines, and growth factors that they provide)[19]. At present, there is no consensus on the optimal preparation method and composition of PRP for each clinical indication[4]. There is no definitive evidence of the mechanism of action of PRP preparations. Also lacking is a clear set of nomenclature and reporting conventions that can be used to accurately and precisely communicate the derivation and properties of a given PRP preparation. 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 final concentration of platelets, nucleated cells, and erythrocytes.

Data from this systematic review suggest that PRP is being utilized without clearly defined preparation protocols and the determination of its composition in most studies. We theorize that the reason for the wide adoption of PRP is its autologous composition and the "minimally manipulated" regulatory pathway to clinical application that is somewhat easier to navigate prior to clinical use in the United States and other countries. Furthermore, from a cost standpoint, many practitioners charge the patient directly for the use of PRP, because many insurance companies in the United States do not currently reimburse for its use. Unfortunately, as demonstrated in this systematic review, the effect of PRP is still not well understood, with inadequate consistency in reporting methodology leading to an imprecise understanding of the effect of PRP on the musculoskeletal system. It is our belief that PRP may be beneficial in treating musculoskeletal injuries and pathological conditions, but this will depend on a more robust understanding of its underlying mechanism(s)[3]. If such promise is to be realized, it is essential to focus early efforts on defining a system for communication that includes effective nomenclature and unambiguous quantitative metrics for PRP used in clinical applications. Without this commitment, there is an increasing danger that potentially effective PRP treatments will be reported to be ineffective or inconsistently effective, and thus dismissed prematurely, simply because (1) methods of preparation and resulting

compositions are inconsistent, (2) differentiation between effective and ineffective preparations is clouded by incomplete information, and (3) both effective and ineffective therapies are inappropriately lumped under a single name (currently "PRP")[3].

The present systematic review has some shortcomings. We did not attempt to correlate processing methods with the final patient-reported outcomes. Such an assessment is currently confounded by the variation in the clinical indications, outcome methods, and time points used in individual studies. Furthermore, there is such inconsistency in reported PRP processing and preparation that we are unable to suggest a consensus preparation protocol for PRP application to musculoskeletal medicine.

In conclusion, reporting of PRP preparation protocols in clinical studies is highly inconsistent, and the majority of studies did not provide sufficient information to allow the protocol to be reproduced. Furthermore, the current reporting of PRP preparation and composition does not enable comparison of the PRP products being delivered to patients. A detailed, precise, and stepwise description of the PRP preparation protocol is required to allow comparison among studies and enable reproducibility. Future investigations should include both the specifics of the preparation steps and the composition of the PRP delivered. The field demands a consensus regarding the recommended reporting guidelines for publication of studies using PRP. The combination of such accurate reporting of PRP preparation methodology with appropriately designed clinical studies, with clear inclusion and exclusion criteria and validated clinical outcomes measures, will be profoundly important in guiding the ongoing rational development of PRP formulations utilized in musculoskeletal care. ■

Jorge Chahla, MD, PhD[1]
Mark E. Cinque, MS[1]
Nicolas S. Piuzzi, MD[2,3]
Sandeep Mannava, MD, PhD[1,4]
Andrew G. Geeslin, MD[1,4]
Iain R. Murray, MD, PhD[5]
Grant J. Dornan, MSc[1]
George F. Muschler, MD[2]
Robert F. LaPrade, MD, PhD[1,4]

[1]Steadman Philippon Research Institute, Vail, Colorado

[2]Department of Orthopaedic Surgery and Bioengineering, The Cleveland Clinic Foundation, Cleveland, Ohio

[3]Instituto Universitario del Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

[4]The Steadman Clinic, Vail, Colorado

[5]Department of Orthopaedics, University of Edinburgh, Edinburgh, United Kingdom

E-mail address for R.F. LaPrade: drlaprade@sprivail.org

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