Systematic Review

Does the Use of Platelet-Rich Plasma at the Time of Surgery Improve Clinical Outcomes in Arthroscopic Rotator Cuff Repair When Compared With Control Cohorts? A Systematic Review of Meta-analyses

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Purpose: The aims of the study were as follows: (1) to perform a systematic review of meta-analyses evaluating platelet-rich plasma (PRP) use at the time of arthroscopic rotator cuff repair surgery and to determine its effect on retear rates and clinical outcomes; (2) to provide a framework for the analysis and interpretation of the best currently available evidence; and (3) to identify gaps within the literature where suggestions for continued investigational efforts would be valid. **Methods:** Literature searches were performed to identify meta-analyses examining arthroscopic rotator cuff repairs augmented with PRP versus control (no PRP). Clinical data were extracted and meta-analysis quality was assessed using the Quality of Reporting of Meta-analyses and Oxman-Guyatt scales. **Results:** Seven meta-analyses met inclusion and exclusion criteria. All were considered as being of similar quality with Quality of Reporting of Meta-analyses scores >15 and Oxman scores of 7. A total of 3,193 overlapping patients treated were included with mean follow-up from 12 to 31 months. When compared with control patients, use of PRP at the time of rotator cuff repair did not result in significantly lower overall retear rates or improved clinical outcome scores. The following postoperative functional scores comparing PRP versus control were reported: Constant (no significant difference demonstrated with PRP use in 5 of 6 reporting meta-analyses), University of California − Los Angeles (no difference, 6 of 6), American Shoulder and Elbow Society (no difference, 4 of 4), and Simple Shoulder Test (no difference, 3 of 5). Subgroup analysis performed by 3 meta-analyses showed evidence of improved outcomes with solid PRP matrix versus liquid, small- and/or medium-sized versus large and/or massive tears, PRP application at the tendon-bone interface versus over tendon, and in the setting of double-row versus single-row rotator cuff. **Conclusions:** The current highest level of evidence suggests that PRP use at the time of arthroscopic rotator cuff repair does not universally improve retear rates or affect clinical outcome scores. However, the effects of PRP use on retear rates trend toward beneficial outcomes if evaluated in the context of the following specific variables: use of a solid PRP matrix; application of PRP at the tendon-bone interface; in double-row repairs; and with small- and/or medium-sized rotator cuff tears. **Level of Evidence:** Level III, systematic review of Level II and III studies.

The incidence of arthroscopic rotator cuff tear repair continues to increase with overall satisfactory results, but retear of the rotator cuff tendon has been reported with appreciable frequency.[1,2] Technical strides have been made with varying fixation devices and techniques in an attempt to improve on prior reported clinical outcomes and complications from a biomechanical standpoint. However, there is still room for improvement given the need to lower retear rates and improve patient subjective and objective outcomes with the knowledge that recurrent or persistent defects in the rotator cuff after repair are common, and important differences in strength and clinical outcomes exist

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between patients with healed and nonhealed rotator cuff repairs.[3]

Some patient-related factors have been identified as reasons for poor results or tendon failure after rotator cuff repair including increased patient age, larger preoperative size of the cuff tear, impaired patient soft tissue quality, smoking, and systemic disease including diabetes.[4] Other extrinsic factors have additionally been attributed as the reason for tendon retear, including overaggressive postoperative rehabilitation.[5] Another proposed cause for the high rate of observed retears is the fibrovascular scar tissue that forms at the tendon-bone interface of repair, which has inferior biomechanical properties in comparison to the native tissue.[6,7] Biologic augmentation has been suggested in an effort to improve on the strength and quality of this repair tissue, but again studies are limited showing significant improvement with routine use.

Platelet-rich plasma (PRP) or platelet-rich fibrin matrix (PRFM) has recently gained popularity in multiple areas of orthopedic sports medicine either as an isolated nonoperative management option or for concurrent use at the time of surgery for biologic augmentation.[8-10] There is growing evidence from animal studies that these platelet-derived autologous growth factors may specifically aid in the regeneration of tendon tissue through collagen synthesis, vascularization, and tendon cell proliferation if incorporated at the site of rotator cuff pathology in the setting of operative repair.[11,12] However, there has been discordance in the results of recent meta-analyses that have explored the efficacy of using PRP at the time of rotator cuff repair because they have been unable to show any overall clinical superiority of its use versus controls.[13-19]

The overall objective of this review was to conduct a systematic review of these overlapping meta-analyses evaluating the efficacy of PRP use at the time of arthroscopic rotator cuff repair. More specifically, the aims of the study were as follows: (1) to perform a systematic review of meta-analyses evaluating PRP use at the time of arthroscopic rotator cuff repair surgery and to determine its effect on retear rates and clinical outcomes; (2) to provide a framework for the analysis and interpretation of the best currently available evidence; and (3) to identify gaps within the literature where suggestions for continued investigational efforts would be valid. Clinical outcomes include clinical indices (Constant, Simple Shoulder Test [SST], American Shoulder and Elbow Society [ASES], University of California − Los Angeles [UCLA], Single Assessment Numeric Evaluation [SANE], and Overall Function Scores), subjective measures (patient Visual Analog Scale [VAS] score, Constant Pain score), and complications (revision surgery, overall complications) including the retear rates.

Our hypothesis was that PRP would not significantly improve patient outcomes or retear rates in arthroscopic rotator cuff repair when compared with controls.

Methods

A comprehensive systematic review of the literature was performed using the PubMed, Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL Complete), Excerpta Medica Database (EMBASE), and Cochrane Database of Systematic Reviews databases. The following search terms were used: [meta-analysis OR systematic review] AND [platelet-rich plasma OR PRP] AND (rotator cuff repair). The search was performed on May 25, 2015, and was limited to articles written in English. To identify all studies with potential relevancy, broad search query terms were used. To ensure that all potential studies were included, all reviewed articles were manually cross-referenced.

All resulting abstracts from the aforementioned search terms were reviewed by 2 of the authors, who applied the study inclusion and exclusion criteria. Inclusion criteria comprised the following: meta-analyses evaluating the utility of PRP treatment at the time of arthroscopic rotator cuff repair in comparison with patients who did not receive PRP. Exclusion criteria included the following: animal, cadaveric, or biomechanical studies; narrative reviews; reviews without an organized or reported search algorithm; studies that did not report clinical outcomes; non-English language studies; and systematic reviews that did not pool data or perform a comprehensive meta-analysis. Full texts of articles meeting the aforementioned criteria were evaluated, and their reference lists were manually screened to determine if any studies appropriate for inclusion were missed. In addition, the tables of contents from the past 2 years of publications in the following journals were searched manually to identify any additional studies appropriate for inclusion: *Arthroscopy*, *Journal of Bone and Joint Surgery*, *Clinical Orthopaedics and Related Research*, and *American Journal of Sports Medicine*. Figure 1 depicts the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram of this study's selection algorithm.

Tables 1-6 highlight the methodological and study data extracted from the included studies with regard to the meta-analysis characteristics and standardized outcome scores. Pooled effect sizes and mean differences of these data points were extracted. Subgroup analyses were recorded and included the following variables: initial tear size, repair technique, study evidence level, PRP preparation, PRP consistency. One study[19] performed a cost-effective analysis that was additionally evaluated.

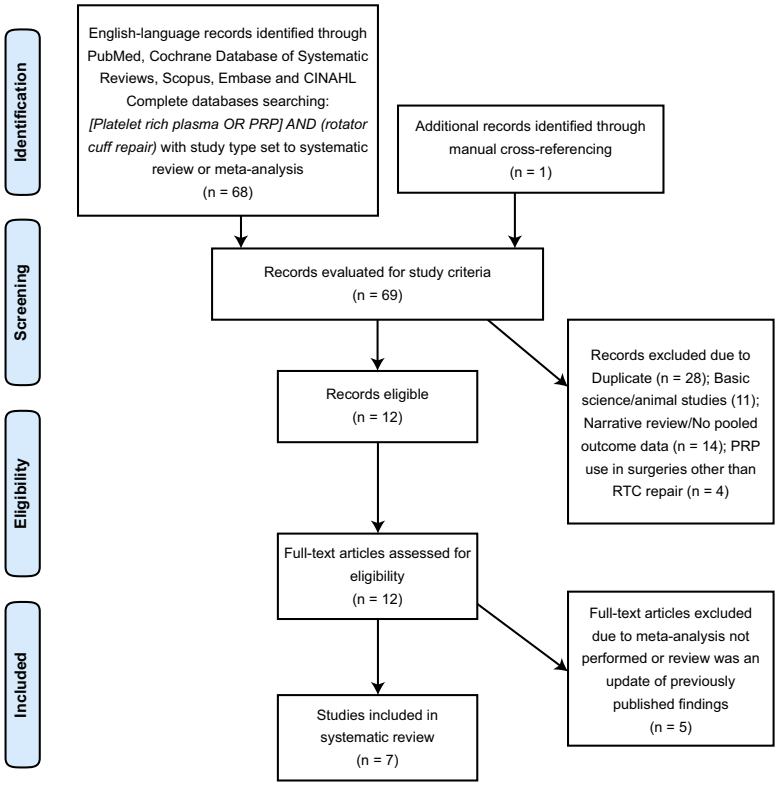

Fig 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram showing the results of application of the study algorithm to the number of studies included, with the number of studies removed after application of each exclusion criterion. (PRP, platelet-rich plasma; RTC, rotator cuff.)

The Quality of Reporting of Meta-analyses (QUOROM) system was used to score meta-analysis quality. This system provides a method for evaluation of meta-analyses by evaluating the quality of their reporting and methodology in total 18 categories.[33] Each meta-analysis is awarded 1 point in each category of this evaluation should more than half of the category's criteria be met; the total possible number of points is thus 18 points. The meta-analyses were additionally graded by the Oxman-Guyatt quality appraisal tool.[34] Biases within the literature that were reported were also noted. Finally, the Jadad decision algorithm[35] was used to guide the interpretation of discordant reviews, including differences in the clinical question, inclusion/exclusion criteria, data pooling, data extraction, quality assessment, and statistical analysis. Scoring was performed based on the assessment of randomization, randomization methodology, double blinding, withdrawals or dropouts from the study, and allocation concealment. This algorithm was independently applied by 2 of the authors, and their results were compared to determine which of the included studies provided the best current evidence to make recommendations.

Results

Eighty abstracts were initially identified by the search terms with the application of the entire selection algorithm providing 7 total studies for inclusion in this review (Fig 1).[13-19] All studies were performed recently, with publication dates after 2012, and no individual studies included within these meta-analyses were performed before 2010. All 7 performed a pooled meta-analysis.

The mean follow-up of the individual studies referenced in each included review ranged from 12[14,18] to 31 months.[13] Two studies reported mean overall clinical follow-up periods of 14.9[17] and 16.1 months,[14] whereas 2 studies additionally reported a separate mean overall imaging follow-up of 11[17] and 15.5 months.[16] The number of patients in each study ranged from 261[13] to 778.[19]

Authors' Assessment of Prior Systematic Review Literature

All 6 studies published after the initial systematic review by Chahal et al.[13] had the opportunity to cite this study. Two of the final studies published[16,17] additionally had the opportunity to cite the Zhang et al.[14] study, and the last published study[19] had the opportunity to cite Moraes et al.[15] In all studies but 2,[17,19] the papers cited all preexisting meta-analyses or systematic reviews, and provided their rationale for repeating the systematic review, highlighting in each that the study or studies before it included study types that were not isolated to randomized controlled trials or had a search strategy that did not capture a particular study appropriate for inclusion (Table 1).

Table 1. Number of Prior Systematic Reviews or Meta-analyses Actually Cited Compared With the Maximum Number That Could Possibly Have Been Cited, in Addition to the Authors' Rationale for Repeating the Systematic Review

First Author	Date of Publication, mo/d/yr	Date of Last Literature Search, mo/d/yr	Level of Evidence	Number of Systematic Reviews or Meta-analyses Possible to Cite	Number of Systematic Reviews or Meta-analyses Cited	Rationale for Repeating Meta-analysis as Abstracted From Manuscript
Chahal[13]	11/–/2012	12/–/2011	III	0	0	N/A
Zhang[14]	7/–/2013	4/20/2013	II	1	1	"A previous meta-analysis is a low level of evidence, but it included all types of studies, including retrospective studies. The present study aims to conduct a meta-analysis of level I and II evidence studies to investigate the clinical and imaging outcomes of PRP application during the arthroscopic repair of full-thickness rotator cuff tears"
Moraes[15]	4/–/2014	3/25/2013	II	1	1	"We found some narrative reviews that… overlapped with our analysis. All of these reviews focused on functional outcomes, such as pain and functional scores, but included studies other than randomized trials"
Li[18]	11/–/2014	5/1/2013	II	1	1	"To our knowledge, the latest systematic review addressing the role of platelet concentrate in rotator cuff repair concluded that platelet-rich plasma/ platelet concentrates did not have an effect on the overall retear rate or shoulder-specific outcomes, but its statistical power was limited because of the weakness of evidence levels of the studies it had included"
Zhao[16]	1/–/2015	9/–/2013	II	2	2	"Although 2 meta-analyses on this topic have been reported, neither was a meta-analysis of specifically only randomized controlled trials. Chahal et al. reported a meta-analysis including various study types — such as randomized controlled trials, cohort studies, and case-control trials — and only 2 randomized controlled trials were included. The other meta-analysis performed by Zhang et al. omitted a high-quality randomized controlled trial with their search strategy, and a nonrandomized controlled trial was also included in their data. Therefore, their results should be treated with caution. The present analysis included more randomized controlled trials through a more extensive and updated search. The enlarged sample size provided more accurate estimates of the effects. Furthermore, the GRADE system, adopted by more than 70 international organizations, was used to assess the quality of a body of evidence for each individual outcome in this meta-analysis, which made the conclusions more reliable"

(continued)

Table 1. Continued

First Author	Date of Publication, mo/d/yr	Date of Last Literature Search, mo/d/yr	Level of Evidence	Number of Systematic Reviews or Meta-analyses Possible to Cite	Number of Systematic Reviews or Meta-analyses Cited	Rationale for Repeating Meta-analysis as Abstracted From Manuscript
Warth[17]	2/–/2015	9/–/2013	II	2	0	N/A
Vavken[19]	3/12/2015	8/1/2014	II	3	1	"First, we wanted to know if the addition of platelet-rich plasma (PRP) to arthroscopic rotator cuff repair would lead to a statistically relevant as well as clinically meaningful reduction in retear rates, expressed as the number needed to treat (NNT). Second, we were interested if the addition of PRP to arthroscopic rotator cuff repair was not only effective but also safe. This was expressed as the relative difference in complication rates. Third, we wanted to assess if any potentially beneficial effect of PRP on retear rates would be cost-effective. This was estimated with the use of the incremental cost-effectiveness ratio (ICER), or the amount of additional clinical effect afforded per additional dollar spent. Last, but not least, since this was a meta-analysis of prior data, we also wanted to assess the quality of the included primary data that this analysis was built upon."

GRADE, Grading of Recommendations Assessment, Development, and Evaluation; N/A, not available; PRP, platelet-rich plasma.

Outcome Measures

There was variability among the 7 included reviews with regard to the standardized and nonstandardized patient clinical and functional outcome measures that were reported (Table 2). There was variability among the referenced studies within these reviews in terms of the surgical fixation technique (single- or double-row repair),[14,16,17,19] performance of acromioplasty concurrently at the time of surgery,[17] size of rotator cuff tear preoperatively (designated by size in centimeters, qualitative gradations of sizing, or complete/incomplete),[13-19] and means of imaging to assess for postoperative retear occurrence (MRI or ultrasound).[13-19] The characteristics of the PRP used within these studies additionally varied in terms of the use of an initiating agent (calcium *v* calcium/batroxobin *v* autologous thrombin *v* none),[16] the preparation of PRP (self-prepared *v* commercially available)[17] and system used

Table 2. Outcomes That Were Assessed for and Reported by Each of the Included Studies

	Chahal[13]	Zhang[14]	Moraes[15]	Li[18]	Zhao[16]	Warth[17]	Vavken[19]
Clinical indices							
Constant score	+	+	+	+	+	+	–
SST score	+	+	+	+	–	+	–
ASES score	+	+	–	+	–	+	–
UCLA Shoulder score	+	+	+	+	–	+	–
SANE score	+	–	–	–	–	–	–
Overall Function	–	–	+	–	–	–	–
Subjective measures							
Patient VAS Pain	–	–	+	–	–	+	–
Constant Pain score	–	–	–	+	–	–	–
Complications							
Retear rate	+	+	+	+	+	+	+
Revision surgery	–	–	–	–	+	–	+
Overall complications	–	–	–	–	–	–	+

ASES, American Shoulder and Elbow Society; SANE, Single Assessment Numeric Evaluation; SST, Simple Shoulder Test; UCLA, University of California — Los Angeles; VAS, Visual Analog Scale.

Table 3. Search Methodology Used by Each of the Included Studies

First Author	PubMed/ MEDLINE	EMBASE	Cochrane Library of Databases	CINAHL	LILACS	BIOSIS	Ovid	Number of Primary Studies	Primary Studies Included Only RCTs or Quasi-RCTs
Chahal[13]	+	+	+	−	−	−	−	5	−
Zhang[14]	+	+	+	−	−	−	−	7	−
Moraes[15]	+	+	+	−	+	−	−	6	+
Li[18]	+	+	+	−	−	+	+	7	+
Zhao[16]	+	+	+	−	−	−	−	8	+
Warth[17]	+	+	−	−	−	−	−	11	−
Vavken[19]	+	+	+	+	−	−	−	13	−

BIOSIS, BioSciences Information Service of Biological Abstracts; CINAHL, Cumulative Index to Nursing and Allied Health Literature; EMBASE, Excerpta Medica Database; LILACS, Latin-American and Caribbean Center on Health Sciences Information; MEDLINE, Medical Literature Analysis and Retrieval System Online; RCT, randomized-controlled trial.

(Cascade *v* COBE Spectra LRS Turbo *v* GPSII *v* other),[13,17] PRP consistency (fibrin matrix *v* liquid *v* pellet),[17-19] and the means of administration of PRP at the time of surgery (injection over repair site or at the bone-tendon interface).[15,18]

Table 7 shows the number of meta-analyses reporting each of the following clinical outcome indices and the results of these studies, including significance in comparison of patients with PRP use and control cohort patients: Constant score, SST score, UCLA score, SANE score, Constant Pain score, ASES score, Functional Outcomes, VAS Pain score; Overall Complications, and Retear Rate. All seven[13-19] meta-analyses pooled the overall retear rate to compare those patients with PRP use at the time of rotator cuff repair and those control patients without its use. In all but 1 individual study from 1 of the 7 included meta-analyses, the individual studies identified retear through either magnetic resonance imaging or ultrasound, and tears were quantified by anteroposterior size (in centimeters) or amount of retraction. The retear rate in those patients with PRP use ranged from 25.6% to 28.7%, in comparison with those without PRP use who had retear rates ranging between 28% and 36.7%. All 7 meta-analyses reported an absence of significant difference in the retear rate for patients with PRP use compared with those without (risk ratio [RR] range, 0.55 to 0.94; one odds ratio [OR] 1.11). However, 1 of these meta-analyses[17] determined that there was a significantly lower risk of retear when PRP was used after a single outlying study[27] was removed from the pooled analysis (RR = 0.83) during their "leave-one-out" analysis. This technique assesses the final outcomes with each of the included studies removed individually as a technique to try and identify and remove data that are substantially different from the remaining cohort of information.

Four of the studies[13,14,17,19] performed pertinent subgroup analyses to address whether PRP use in certain circumstances or preparations provided any significant results in comparison with control patients. Interestingly, PRP use showed significantly lower retear rates in rotator cuff tears that were categorized

Table 4. Primary Studies Included in Meta-analysis

Primary Study	Chahal[13]	Zhang[14]	Moraes[15]	Li[18]	Zhao[16]	Warth[17]	Vavken[19]
Castricini 2010[20]	+	+	+	+	+	+	+
Randelli 2011[21]	+	+	+	+	+	+	+
Barber 2011[22]	+	−	−	−	−	−	+
Buford 2011[N/A]*	−	−	−	−	−	−	+
Longo 2011[N/A]*	−	−	−	−	−	−	+
Bergeson 2012[23]	+	−	−	−	−	−	+
Jo 2011[24]	+	+	−	−	−	+	+
Gumina 2012[25]	−	+	+	+	+	+	N/A
Weber 2013[26]	−	+	−	+	+	+	+
Antuna 2013[27]	−	+	+	+	−	+	N/A
Jo 2013[28]	−	−	−	−	+	+	N/A
Ruiz-Moneo 2013[29]	−	−	−	+	+	+	N/A
Malavolta 2014[30]	−	−	+	−	−	+	N/A
Sanchez Marquez 2011[31]	−	−	−	−	+	+	N/A
Rodeo 2012[32]	−	+	+	+	+	+	N/A

N/A, data not available.

*The study by Vavken et al.[19] did not cite all the sources of their 13 included primary studies; as such, the information is not entirely available to note here.

Table 5. Comparisons Performed by Each Meta-analysis and the Quality Scores for Each Meta-analysis

First Author	PRP+ *v* PRP− Retear Rate (RR/OR*)	PRP+ *v* PRP− Constant Score (MD/SMD*)	PRP+ *v* PRP− Constant Pain Score (SMD)	PRP+ *v* PRP− SST Score (MD/SMD*)	PRP+ *v* PRP− ASES Score (MD/SMD*)	PRP+ *v* PRP− UCLA Score (MD/SMD*)	PRP+ *v* PRP− SANE Score (MD)	PRP+ *v* PRP− VAS Score (MD)	PRP+ *v* PRP− Complications (RR)	PRP+ *v* PRP− All Scores/ Instrumentation (MD)	QUOROM Score	Oxman-Guyatt Score
Chahal[13]	+	+	−	+	+	+	+	−	−	−	16	7
Zhang[14]	+	+	−	+	+	+	−	−	−	−	16	7
Moraes[15]	+	+	−	+	−	+	−	+	−	+	16	7
Li[18]	+*	+*	+	+*	+*	+*	−	−	−	−	16	7
Zhao[16]	+	+	−	−	−	+	−	−	−	−	17	7
Warth[17]	+	+	−	+	+	+	−	+	−	−	17	7
Vavken[19]	+	−	−	−	−	−	−	−	+	−	15	7

NOTE. All 5 studies performed data pooling. Asterisks indicate that the corresponding measurement with an asterisk in the column heading was presented in this study.
ASES, American Shoulder and Elbow Society; MD, mean difference; OR, odds ratio; PRP, platelet-rich plasma; PRP+, patients *with* PRP use; PRP−, patients *without* PRP use; QUOROM, Quality of Reporting of Meta-analyses; RR, risk ratio; SANE, Single Assessment Numeric Evaluation; SMD, standard mean difference; SST, Simple Shoulder Test; UCLA, University of California – Los Angeles; VAS, Visual Analog Scale.

preoperatively as "small/medium"—the retear rate was reported as 7.9% versus 26.8% in 1 of the studies and the RR ranged from 0.32 to 0.60.[13,19] The definitions for tear size were derived from those definitions used in the individually included studies; "small/medium" was thus defined as those measuring less than 3 cm in the anteroposterior dimension or qualitatively if the tear exposed the humeral head but did not retract all the way to the glenoid surface.[13,19] This provided a calculated "number needed to be treated to benefit with PRP to prevent one episode of retear" ranging from 6 to 14 patients.[13,19] The same was not true of PRP use in "large/massive" tears in any study's subgroup analysis.[13,14,19] Chahal et al.[13] evaluated the risk of retear in patients who underwent a "double-row" rotator cuff repair technique and found no difference with the use of PRP compared with control patients (retear rate, 9.1% *v* 20.0%; RR = 0.54; $P = .19$). They additionally demonstrated that when they pooled level I studies alone and nonrandomized studies alone, there was no significant difference in the overall retear rate for either in isolation (RR 0.65 and 0.81, respectively). However, similar analysis for small- and/or medium-sized tears showed a significantly lower retear rate among patients treated with PRP in the pooled nonrandomized studies (RR 0.31; $P = .04$).

Warth et al.[17] performed subgroup meta-analyses for Constant scores across their analyzed studies; this clinical outcome score was not affected by the level of study analyzed (level I only or level II only), size of initial rotator cuff tear (< 3 cm or > 3 cm sagittal length), repair technique (single- or double-row fixation), PRP preparation (manual or commercial system), or PRP consistency (fibrin matrix or liquid), but did show a significantly decreased gain in score value when PRP was treated by injection over the surface of the repaired tendon as opposed to PRP treatment through application at the tendon-bone interface (−6.88 points *v* +0.78 points; $P = .046$). Warth et al.[17] similarly performed subgroup meta-analyses for retear rate across their analyzed studies and determined that PRP use exhibited a larger retear reduction effect after double-row repair in patients with initial tear sizes > 3 cm in anterior-posterior length when compared with patients without PRP use (25.9% *v* 57.1%; $P = .046$). In addition, PRP use exhibited a larger retear reduction effect with PRFM when compared with liquid-based PRP use (14.8% *v* 46.8%; $P = .054$).

Vavken et al.[19] performed a unique cost-effectiveness analysis on patients with small- and medium-sized tears because these patients had shown a significant improvement in results when PRP was used (similar to other studies).[13,14] They reported a difference in effectiveness between repair with and without PRP of 0.0059 quality-adjusted life years, and ultimately through their decision analytic tree model reported that

Table 6. Heterogeneity or Subgroup Analyses of Primary Studies

	Chahal[13]	Zhang[14]	Moraes[15]	Li[18]	Zhao[16]	Warth[17]	Vavken[19]
Statistical heterogeneity analysis	+	+	+	+	+	+	+
Subgroup or statistical analysis							
Risk ratio retear rate: PRP+ *v* PRP− (small- and/or medium-sized rotator cuff Tears)	+	+	−	−	−	−	+
Risk ratio retear rate: PRP+ *v* PRP− (large- and/or massive-sized rotator cuff tears)	+	+	−	−	−	−	+
Risk ratio retear rate: PRP+ *v* PRP− (double-row fixation)	+	−	−	−	−	−	−
Risk ratio retear rate: PRP+ *v* PRP− (level I studies only)	+	−	−	−	−	−	−
Risk ratio retear rate: PRP+ *v* PRP− (nonrandomized studies only)	+	−	−	−	−	−	−
Risk ratio retear rate: PRP+ *v* PRP− (small- and/or medium-sized tears from level I studies only)	+	−	−	−	−	−	−
Risk ratio retear rate: PRP+ *v* PRP− (small- and/or medium-sized tears from nonrandomized studies only)	+	−	−	−	−	−	−
Cost-effectiveness analysis: PRP+ *v* PRP− (small- and/or medium-sized tears only)	−	−	−	−	−	−	+
Mean difference constant score: PRP+ *v* PRP− (level I only)	−	−	−	−	−	+	−
Mean difference constant score: PRP+ *v* PRP− (level II only)	−	−	−	−	−	+	−
Mean difference constant score: PRP+ *v* PRP− (initial tear size < 3 cm sagittal length only)	−	−	−	−	−	+	−
Mean difference constant score: PRP+ *v* PRP− (initial tear size > 3 cm sagittal length only)	−	−	−	−	−	+	−
Mean difference constant score: PRP+ *v* PRP− (single-row technique fixation only)	−	−	−	−	−	+	−
Mean difference constant score: PRP+ *v* PRP− (double-row technique fixation only)	−	−	−	−	−	+	−
Mean difference constant score: PRP+ *v* PRP− (manual preparation PRP only)	−	−	−	−	−	+	−
Mean difference constant score: PRP+ *v* PRP− (commercial system preparation PRP only)	−	−	−	−	−	+	−
Mean difference constant score: PRP+ *v* PRP (PRP application via injection over tendon only)	−	−	−	−	−	+	−
Mean difference constant score: PRP+ *v* PRP− (PRP application via injection at the bone-tendon interface only)	−	−	−	−	−	+	−
Mean difference constant score: PRP+ *v* PRP− (PRP consistency as fibrin matrix only)	−	−	−	−	−	+	−
Mean difference constant score: PRP+ *v* PRP− (PRP consistency as liquid only)	−	−	−	−	−	+	−
Risk ratio retear rate: PRP+ *v* PRP− (level I only)	−	−	−	−	−	+	−
Risk ratio retear rate: PRP+ *v* PRP− (level II only)	−	−	−	−	−	+	−
Risk ratio retear rate: PRP+ *v* PRP− (initial tear size < 3 cm sagittal length only)	−	−	−	−	−	+	−
Risk ratio retear rate: PRP+ *v* PRP− (initial tear size > 3 cm sagittal length only)	−	−	−	−	−	+	−
Risk ratio retear rate: PRP+ *v* PRP− (single-row technique fixation only)	−	−	−	−	−	+	−
Risk ratio retear rate: PRP+ *v* PRP− (double-row technique fixation only)	−	−	−	−	−	+	−
Risk ratio retear rate: PRP+ *v* PRP− (manual preparation PRP only)	−	−	−	−	−	+	−
Risk ratio retear rate: PRP+ *v* PRP− (commercial system preparation PRP only)	−	−	−	−	−	+	−
Risk ratio retear rate: PRP+ *v* PRP− (PRP application via injection over tendon only)	−	−	−	−	−	+	−
Risk ratio retear rate: PRP+ *v* PRP− (PRP application via injection at the bone-tendon interface only)	−	−	−	−	−	+	−
Risk ratio retear rate: PRP+ *v* PRP− (PRP consistency as fibrin matrix only)	−	−	−	−	−	+	−
Risk ratio retear rate: PRP+ *v* PRP− (PRP consistency as liquid only)	−	−	−	−	−	+	−

PRP, platelet-rich plasma; PRP+, patients *with* PRP use; PRP−, patients *without* PRP use.

Table 7. Number of Meta-analyses Evaluating Overall Pooled Outcome Variables and Their Results

Pooled Outcome Variable	Number of Meta-analyses Evaluating the Outcome	Meta-analyses Reporting Significant Superiority With PRP Use		Meta-analyses Reporting No Significant Superiority With PRP Use	
		Number of Meta-analyses	Results of These Meta-analyses	Number of Meta-analyses	Results of These Meta-analyses
Constant score	6	1	• MD = 2.47, CI = 0.68-4.26 at 1 yr postoperative[15]	5	• MD varied between 0.48 and 1.83[13,14,16,17,19] • One study reporting SMD = 2.47
SST score	5	2	• MD ranging from 0.38 to 0.42[15,17]	3	• MD ranging from 0.12 to 0.34 • One study reporting SMD = 0.28
UCLA score	6	0	—	6	• MD ranged from −0.79 to 1.56[13-18] • One study with SMD 0.16
SANE score	1	0	—	1	• MD = 1.56[13]
Constant Pain score	1	0	—	1	• SMD = 0.99[18]
ASES score	4	0	—	4	• MD ranged from 1.15 to 2.89[13,14,17,18] • One study reporting SMD = 2.99
Functional Outcomes	1	0	—	1	• MD = 0.13[15]
VAS Pain score	2	1*	• MD = −1.40 at 7 d after surgery[15]	2*	• One study reporting MD = −0.22[17] • One study reporting MD = −0.69 at 30 d and MD = −0.30 at 1 yr postoperatively[15]
Overall Complications	1	0	—	1	• RR 1.04[19]
Retear Rate	7	0	—	7	• RR ranged from 0.55 to 0.94[13-19] • One study reported OR = 1.11 • Retear rate in patients with PRP use ranged from 25.6% to 28.7%, in comparison with those without PRP use where it ranged from 28.0% to 36.7%
Retear Rate—using "leave-one-out" analysis	1	1	• RR = 0.83 (this technique assesses the final outcomes with each of the included studies removed individually as a technique to try and identify and remove data that is substantially different from the remaining cohort of information)	0	—

ASES, American Shoulder and Elbow Society; CI, confidence interval; MD, mean difference; OR, odds ratio; PRP, platelet-rich plasma; RR, relative risk; SANE, Single Assessment Numeric Evaluation; SMD, standardized mean difference; SST, Simple Shoulder Test; UCLA, University of California — Los Angeles; VAS, Visual Analog Scale.

*Note that 1 study reported significant differences at one time period and nonsignificant results at another time period.

a total cost of PRP use of greater than $652.11 (including operating room time and venipuncture) would lose cost-effectiveness—this is in the context of PRP costs that typically vary widely between $450 and $2500 in many preparations and companies.[19]

Search Methodology

Although all 7 of the included studies searched PubMed/Medline, there was heterogeneity in the other databases that were used. These included Cochrane, EMBASE, Latin-American and Caribbean Center on Health Sciences Information (LILACS), BioSciences Information Service of Biological Abstracts (BIOSIS), Ovid, CINAHL, trial registers, and conference abstracts. Each of the included studies used between 2 and 6 databases to gather information (Table 3). The total number of unique primary studies cited by the included reviews was 17 (from the information available, because 5 of the individual studies in the Vavken et al.[19] meta-analysis were not cited in their references), and the number of these studies cited in each study ranged from five[13] to 13,[19] with the median being 7 primary citations (Tables 3 and 4).

Study Results

The mean age of the patients who underwent treatment ranged from 58.9 to 60.7 years[13,16,17,19] with a range from the individual studies reported between 29 and 77 years.[18] In comparison to control (no PRP) patients, PRP use at the time of rotator cuff repair surgery does not provide significantly lower overall retear rates or significantly better UCLA scores postoperatively.[13-19] In addition, there appears to be no superiority with PRP use in terms of Constant score,[13,14,16-18] Constant Pain score,[18] SANE score,[13] ASES score,[13,17,18] SST score,[13,14,17,18] or VAS score more than 1 week postoperatively,[15,17] although these findings were not universal among reporting meta-analyses. Isolated discordant results from the above include that Moraes et al.[15] reported significantly superior Constant score, SST score, and VAS score at 7 days after surgery with PRP use compared with patients without PRP at the time of surgery. In no outcome measures was the absence of PRP use at the time of surgery significantly superior to patients who received PRP at the time of surgery.

Through subgroup analyses, the commonly reported results were that small- and/or medium-sized rotator cuff tears had significantly lower rates of retear when PRP was used in comparison with patients without PRP use, although these findings were not present when evaluating in isolation those patients with large and/or massive tears.[13,14,19] PRP injection at the tendon-bone interface may provide a higher gain of Constant score postoperatively when PRP is used.[17] There is additionally an apparent cost-effectiveness of PRP use at the time of surgery, although this is dependent on the cost that can be achieved for the PRP itself and its preparation and added operating room time.[19] Overall, none of the included meta-analyses supported the routine use of PRP at the time of arthroscopic rotator cuff repair given the currently available evidence.

Study Quality and Validity

The QUOROM scores were determined for each of the included meta-analyses and ranged from 15[19] to 17,[16,17] with a median of 16 (maximum possible score = 18). All 7 studies were scored with the maximum Oxman-Guyatt score of 7, indicating that each meta-analysis is of high quality (Table 5). Of note, the fact that these included studies were high quality does not obviate the need to critically note that there was bias noted in numerous individual studies included in each of the meta-analyses. For example, Warth et al.[17] reported a high risk of bias in 5 of 11 included studies (45.5%) regarding randomization procedures (selection bias) and for 7 of 11 studies (63.6%) regarding performance bias. Vavken et al.[19] reported an average modified Jadad score of 3.1 of 4 in assessment of their included studies' risk of bias.

Heterogeneity Assessment and Subgroup Analyses

All 7 studies performed a statistical heterogeneity analysis, including I^2, Cochrane X^2, τ^2, and Q-test statistics. Two studies[13,18] performed sensitivity analyses to assess such parameters as the overall retear rate from level I studies pooled alone or from nonrandomized studies pooled alone, retear rates in small- and/or medium-sized tears from level I studies pooled alone or from nonrandomized studies pooled alone, and overall retear rates (Table 6). Subgroup analyses evaluating PRP versus control cohorts in terms of retear rates were performed based on tear size,[13,14,17,19] fixation technique,[13,17] PRP preparation and application,[17] and study level of evidence.[13,17] Subgroup analyses evaluating PRP versus control cohorts in terms of Constant score were performed based on the study level of evidence,[17] tear size,[17] fixation technique,[17] PRP preparation, and application.[17]

Application of the Jadad Decision Algorithm

The Jadad decision algorithm was applied by 3 authors independently to determine which of the 7 included meta-analyses provided the best currently available evidence to develop recommendations for the use of PRP at the time of arthroscopic rotator cuff repair. This led to the determination that all 7 included studies provided a high level of currently available evidence.[13-19] Thus, the current highest level of evidence suggests that nondiscriminatory, routine PRP use at the time of arthroscopic rotator cuff repair surgery does not universally improve retear rates or affect clinical outcome scores. However, the effects of PRP use on

retear rate may be beneficial in a specific combination of circumstances as follows: (1) a composition of PRFM; (2) application at the tendon-bone interface; (3) in double-row technique repair; and (4) with small- and/or medium-sized rotator cuff tears.

Discussion

Our literature search yielded 6 level II[14-19] and 1 level III[13] meta-analyses for critical examination. All 7 meta-analyses were scored with high QUOROM and Oxman-Guyatt quality assessments, which add a certain degree of validity to the conclusions and recommendations for practice that are made. Based on the currently available evidence in the highlighted literature, our hypothesis that PRP does not substantially improve overall outcomes or retear rates in arthroscopic rotator cuff repair is confirmed. In addition, it was confirmed that PRP may have a potential use in smaller- and/or medium-sized tears given that all of the meta-analyses evaluating this subgroup of patients found significant superiority with the use of PRP compared with control in terms of retear rate.[13,14,19] Further investigation into the use of PRP that focuses on variables such as leukocyte-rich versus leukocyte-poor formulations, repair technique stratifications, and application location has the potential to offer insights into the potential role that biological augmentation with PRP may play in rotator cuff repair.

Based on the findings of this systematic review of overlapping meta-analyses, the routine use of PRP at the time of arthroscopic rotator cuff repair is not warranted. However, the combined results of subgroup analyses in 4 of the included studies[13,14,17,19] suggests that in the setting of a small- and/or medium-sized tear being fixed with a double-row technique, application of a solid PRP matrix at the bone-tendon interface could be an appropriate concomitant treatment option for close evaluation going forward. However, these specific variables in combination were not all evaluated within a single study but rather as a summative result of each of them. Although this may not provide any significant improvements in the patient clinical outcome scores, it appears possible that this could be an avenue for decreasing the retear rate, which could over time potentially be a source of pain, lower patient satisfaction and outcome scores, and potentially lead to a reoperation. Future studies should evaluate these variables in combination to assess for a support of the use of PRP for small- and/or medium-sized tears; this could have implications on the potential to provide a potential benefit in terms of reducing the potential decrease in work productivity and increased health care costs that could result from a retear and possible revision surgery.

With an increasing number of arthroscopic rotator cuff repair surgeries being performed, it is crucial for optimization of techniques to allow for a high degree of clinical and functional success. Single-row and double-row transosseous-equivalent suture-bridge techniques have been developed and refined in recent years to improve on postoperative retear rates and clinical outcomes, but the results are still far from perfect.[36] As such, the application of growth factor mixtures in the form of PRP is hypothesized to decrease overall structural failure rate, and to facilitate the regeneration of a more biomechanically sound tendon-bone interface. However, the promising results of PRP use in rotator cuff repair in animal models have not been necessarily translated as well in clinical practice, where its use in patients has not provided the same anticipated outcomes.[13-18,37]

It is important to note that data exist, which suggests that PRFM may have an inhibitory effect on tendon healing, potentially due to an altered biological milieu (with increased inflammatory cytokines that may produce scar tissue rather than healthy tendon microstructure), or because the clot may have a space-occupying effect at the tendon-bone interface that leaves a gap once the material dissolves.[32] However, most of analyzed data in these included meta-analyses do not show this inhibitory effect, and thus it may be an effect of small sample size that should prevent first causation conclusions. It is possible that the small- and/or medium-sized tears may have a better opportunity to incorporate the platelet-derived autologous growth factor effects through collagen synthesis, vascularization, and tendon cell proliferation because they are more biomechanically sound in their repair. That is, because the anchor points of the rotator cuff experience load transmission across the joint, small- and/or medium-sized tears are more stable than the large and/or massive tears that have less points of fixation to dissipate force generation.[19]

In addition, there are some variables that were not assessed in the 7 included meta-analyses and their referenced individual studies. That is, there still remain multiple unanswered questions about the best formulation and volume of PRP for this given clinical scenario. For example, in light of the recent data on the clinical differences between the application of leukocyte-rich and leukocyte-poor PRP,[38] it remains to be determined if one preparation would lead to better results in the setting of rotator cuff repair. In addition, the role of single- or double-spinning cycles to isolate the PRP and the utility of subacromial PRP injection in the weeks after surgery need further evaluation. Finally, the timing of PRP use (at the time of repair or injected postoperatively) and the frequency as single or multiple doses should be considered. These questions in the context of PRP use in rotator cuff repair offer an interesting area of future study, for which more high-quality randomized double-blinded trials will be needed to provide further insights. Given the findings

from the cost-effectiveness analysis of Vavken et al.,[19] the question of whether a consistently cheaper opportunity for PRP preparation and administration exists, as the cost-efficacy held true at a cost less than $652.11, although most standard preparations and administration techniques cost between $450 and $2,500.[19]

Of note, a recent randomized controlled trial using PRP in the arthroscopic repair of medium to large rotator cuff tears showed efficacy of PRP in the retear rate (3.0% *v* 20.0%) and cross-sectional area of the supraspinatus muscle. The authors suggest that, in part, this efficacy is attributed to their PRP formulation, namely that it is a leukocyte-poor PRP preparation—although there was no comparison with a leukocyte-rich PRP preparation group. The authors suggest that leukocytes play a role in the inflammatory stage of the regeneration process in tendon injuries, but that this inflammation should be avoided in the rotator cuff repair in lieu of a greater proliferation stage where matrix synthesis is of greater importance.[39] This would suggest a potential future avenue for study in what is a cohort of patients with the inherently highest risk of retear because of large size.

Limitations

As with all systematic reviews, the limitations present in this study are reflected by those limitations inherent to the 7 meta-analyses that are included in this analysis. Selection, reporting, and publication biases were inherent to some of the primary studies identified by the individual meta-analyses.[16,17] Many of the primary studies additionally did not provide details of follow-up or specific outcome measurement results. There was additionally a substantial amount of heterogeneity in terms of a surgical fixation technique, performance of acromioplasty concurrently at the time of surgery, size of rotator cuff tear preoperatively, and type of imaging used to assess for postoperative retear occurrence. There was also significant heterogeneity between studies in terms of the PRP initiating agent, preparation, system, consistency, and means of administration. Although subgroup analyses in 3 of the 7 included meta-analyses attempted to account for these variables in their analysis, these factors may lead to potentially differing postoperative results and biological activity of the PRP used.

Conclusions

The current highest level of evidence suggests that PRP use at the time of arthroscopic rotator cuff repair does not universally improve retear rates or affect clinical outcome scores. However, the effects of PRP use on retear rate trend toward beneficial outcomes if evaluated in the context of the following specific variables that have shown some significance with its use: use of a solid PRFM; application at the tendon-bone interface; in double-row repairs; and with small- and/or medium-sized rotator cuff tears.

References

1. Jost B, Pfirrmann CW, Gerber C, Switzerland Z. Clinical outcome after structural failure of rotator cuff repairs. *J Bone Joint Surg Am* 2000;82:304-314.
2. Walton JR, Murrell GA. A two-year clinical outcomes study of 400 patients, comparing open surgery and arthroscopy for rotator cuff repair. *Bone Joint Res* 2012;1:210-217.
3. Slabaugh MA, Nho SJ, Grumet RC, et al. Does the literature confirm superior clinical results in radiographically healed rotator cuffs after rotator cuff repair? *Arthroscopy* 2010;26:393-403.
4. Edwards SL, Lynch TS, Saltzman MD, Terry MA, Nuber GW. Biologic and pharmacologic augmentation of rotator cuff repairs. *J Am Acad Orthop Surg* 2011;19:583-589.
5. Denard PJ, Burkhart SS. Arthroscopic revision rotator cuff repair. *J Am Acad Orthop Surg* 2011;19:657-666.
6. Carpenter JE, Thomopoulos S, Flanagan CL, DeBano CM, Soslowsky LJ. Rotator cuff defect healing: A biomechanical and histologic analysis in an animal model. *J Shoulder Elbow Surg* 1998;7:599-605.
7. Thomopoulos S, Williams GR, Soslowsky LJ. Tendon to bone healing: Differences in biomechanical, structural, and compositional properties due to a range of activity levels. *J Biomech Eng* 2003;125:106-113.
8. Franchini M, Dupplicato P, Ferro I, De Gironcoli M, Aldegheri R. Efficacy of platelet gel in reconstructive bone surgery. *Orthopedics* 2005;28:161-163.
9. Hee HT, Majd ME, Holt RT, Myers L. Do autologous growth factors enhance transforaminal lumbar interbody fusion? *Eur Spine J* 2003;12:400-407.
10. Sanchez M, Azofra J, Anitua E, et al. Plasma rich in growth factors to treat an articular cartilage avulsion: A case report. *Med Sci Sports Exerc* 2003;35:1648-1652.
11. Mei-Dan O, Carmont MR. The role of platelet-rich plasma in rotator cuff repair. *Sports Med Arthrosc* 2011;19:244-250.
12. McCarrel T, Fortier L. Temporal growth factor release from platelet-rich plasma, trehalose lyophilized platelets, and bone marrow aspirate and their effect on tendon and ligament gene expression. *J Orthop Res* 2009;27:1033-1042.
13. Chahal J, Van Thiel GS, Mall N, et al. The role of platelet-rich plasma in arthroscopic rotator cuff repair: A systematic review with quantitative synthesis. *Arthroscopy* 2012;28:1718-1727.
14. Zhang Q, Ge H, Zhou J, Cheng B. Are platelet-rich products necessary during the arthroscopic repair of full-thickness rotator cuff tears: A meta-analysis. *PLOS One* 2013;8:e69730-e69736.
15. Moraes VY, Lenza M, Tamaoki MJ, Faloppa F, Belloti JC. Platelet-rich therapies for musculoskeletal soft tissue injuries. *Cochrane Database Syst Rev* 2014;4:CD010071.
16. Zhao JG, Zhao L, Jiang YX, Wang ZL, Wang J, Zhang P. Platelet-rich plasma in arthroscopic rotator cuff repair: A meta-analysis of randomized controlled trials. *Arthroscopy* 2015;31:125-135.

17. Warth R, Dornan GJ, James EW, Horan MP, Millett PJ. Clinical and structural outcomes after arthroscopic repair of full-thickness rotator cuff tears with and without platelet-rich product supplementation: A meta-analysis and meta-regression. *Arthroscopy* 2015;31:306-320.
18. Li X, Xu C, Hou Y, Song J, Cui Z, Yu B. Are platelet concentrates an ideal biomaterial for arthroscopic rotator cuff repair? A meta-analysis of randomized controlled trials. *Arthroscopy* 2014;30:1483-1490.
19. Vavken P, Sadoghi P, Palmar M, et al. Platelet-rich plasma reduces retear rates after arthroscopic repair of small- and medium-sized rotator cuff tears but is not cost-effective. *Am J Sports Med* 2015;43:3071-3076.
20. Castricini R, Longo UG, De Benedetto M, et al. Platelet-rich plasma augmentation for arthroscopic rotator cuff repair: A randomized controlled trial. *Am J Sports Med* 2011;39:258-265.
21. Randelli P, Arrigoni P, Ragone V, Aliprandi A, Cabitza P. Platelet rich plasma in arthroscopic rotator cuff repair: A prospective RCT study, 2-year follow-up. *J Shoulder Elbow Surg* 2011;20:518-528.
22. Barber FA, Hrnack SA, Snyder SJ, Hapa O. Rotator cuff repair healing influenced by platelet-rich plasma construct augmentation. *Arthroscopy* 2011;27:1029-1035.
23. Bergeson AG, Tashjian RZ, Greis PE, Crim J, Stoddard GJ, Burks RT. Effects of platelet-rich fibrin matrix on repair integrity of at-risk rotator cuff tears. *Am J Sports Med* 2012;40:286-293.
24. Jo CH, Kim JE, Yoon KS, et al. Does platelet-rich plasma accelerate recovery after rotator cuff repair? A prospective cohort study. *Am J Sports Med* 2011;39:2082-2090.
25. Gumina S, Campagna V, Ferrazzag, et al. Use of a platelet-leukocyte membrane in arthroscopic repair of large rotator cuff tears: A prospective randomized study. *J Bone Joint Surg Am* 2012;94:1345-1352.
26. Weber SC, Kauffman JI, Parise C, Weber SJ, Katz SD. Platelet-rich fibrin matrix in the management of arthroscopic repair of the rotator cuff: A prospective, randomized, double-blinded study. *Am J Sports Med* 2013;41:263-270.
27. Antuna S, Barco R, Martinez Diez JM, Sanchez Marquez JM. Platelet-rich fibrin in arthroscopic repair of massive rotator cuff tears: A prospective randomized pilot clinical trial. *Acta Orthop Belg* 2013;79:25-30.
28. Jo CH, Shin JS, Lee YG, et al. Platelet-rich plasma for arthroscopic repair of large to massive rotator cuff tears: A randomized, single-blind, parallel-group trial. *Am J Sports Med* 2013;41:2240-2248.
29. Ruiz-Moneo P, Molano-Munoz J, Prieto E, Algorta J. Plasma rich in growth factors in arthroscopic rotator cuff repair: A randomized, double-blind, controlled clinical trial. *Arthroscopy* 2013;29:2-9.
30. Malavolta EA, Gracitelli ME, Ferreira Neto AA, Assuncao JH, Bordalo-Rodrigues M, de Camargo OP. Platelet-rich plasma in rotator cuff repair: A prospective randomized study. *Am J Sports Med* 2014;42:2446-2454.
31. Sanchez Marquez JM, Martinez Diez JM, Barco R, Antuna S. Functional results after arthroscopic repair of massive rotator cuff tears: Influence of the application of platelet-rich plasma combined with fibrin. *Rev Esp Cir Ortop Traumatol* 2011;55:282-287.
32. Rodeo SA, Delos D, Williams RJ, Adler RS, Pearle A, Warren RF. The effect of platelet-rich fibrin matrix on rotator cuff tendon healing: A prospective, randomized clinical study. *Am J Sports Med* 2012;40:1234-1241.
33. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: The QUOROM statement. Quality of reporting of meta-analyses. *Lancet* 1999;354:1896-1900.
34. Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. *J Clin Epidemiol* 1991;44:1271-1278.
35. Jadad AR, Cook DJ, Browman GP. A guide to interpreting discordant systematic reviews. *Canadian Med Assoc J* 1997;156:1411-1416.
36. Boileau P, Brassart N, Watkinson DJ, et al. Arthroscopic repair of full-thickness tears of the supraspinatus: Does the tendon really heal? *J Bone Joint Surg Am* 2005;87:1229-1240.
37. Bosch G, van Schie HT, de Groot MW, et al. Effects of platelet-rich plasma on the quality of repair of mechanically induced core lesions in equine superficial digital flexor tendons: A placebo-controlled experimental study. *J Orthop Res* 2010;28:211-217.
38. Riboh JC, Saltzman BM, Yanke AB, Fortier L, Cole BJ. Effect of leukocyte concentration on the efficacy of platelet-rich plasma in the treatment of knee osteoarthritis. *Am J Sports Med* in press, available online 29 April, 2015. doi:10.1177/0363546515580787.
39. Jo CH, Shin JS, Shin WH, Lee SY, Yoon KS, Shin S. Platelet-rich plasma for arthroscopic repair of medium to large rotator cuff tears: A randomized controlled trial. *Am J Sports Med* 2015;43:2102-2110.