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OPTIMAL INJECTION VOLUME IN TREATMENT OF TENDINOPATHY: A SYSTEMATIC REVIEW OF PLATELET RICH PLASMA INJECTATE VOLUMES

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Abstract

Background: Tendinopathy, a pathology of tendons characterized by inflammation and or degeneration, is a prevalent cause of disease and disability in active and working patients. Within the past decade, orthobiologic injections such as Platelet Rich Plasma (PRP) have become increasingly popular within the musculoskeletal physician's practice for treatment of chronic tendinopathies. However, there is a lack of standardization of PRP preparation and injection protocols, leading to gaps in our knowledge regarding the optimal administration dosages to maximize treatment efficacy.

Purpose: This review aims to compile and evaluate the existing data for PRP injection volumes for various tendinopathies in hopes of contributing to standardization of PRP protocols, with a further goal of minimizing waste of a costly therapeutic.

Study Design: Systematic Review

Methods: In June 2020, comprehensive electronic database searches were conducted by a medical librarian in Medline via PubMed, EMBASE (embase.com), CINAHL (EbscoHost), CENTRAL and Scopus according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Data was extracted from studies meeting inclusion criteria on injection volumes and outcomes and grouped based on anatomic injection location.

Results: Twenty-eight studies were identified for inclusion in which ultrasound-guided intra-tendinous PRP injections were administered to patients to treat various tendinopathies. For all tendon locations, the minimum volume of injectate reported achieved positive clinical outcomes in patients compared to baseline.

Conclusions: Despite its many benefits—tendon healing, pain relief, increased function—PRP can pose a significant financial burden to patients, with patients often having to pay for the full cost out-of-pocket due to lack of insurance coverage. This study provides evidence that PRP can be effective at smaller volumes, minimizing waste and the out-of-pocket cost to the patient. In addition, this study further stresses the importance of protocol standardization.

Clinical Relevance: Though more data is needed, it is apparent that the minimum amount of injectate used clinically for various anatomic locations is enough for overall positive outcomes, and therefore can be the recommended dose given. As such, the authors have incorporated the minimum injection volume into their practice using the following volumes: Rotator Cuff-1 mL, Lateral or Medial Epicondyle-1.5 mL, Gluteal or

Hamstring-3 mL, Patella-2 mL, Achilles-3 mL. Unfortunately, without more data available in the literature, the authors cannot make stronger recommendations at this time.

What is known about the subject: Among intralesional injections for the treatment of tendinopathy, PRP has shown positive results in multiple trials and has made its way into many musculoskeletal physicians' practice. However, there is a significant lack of standardization in PRP protocols.

What this study adds to existing knowledge: While other reviews have highlighted the discrepancies amongst PRP protocols, our review is the first to examine injection volume and its effect on outcomes. We were able to suggest a minimum injectate amount for positive outcomes, either pain relief or improvement in the tendon appearance on imaging.

Keywords: *Biologic Healing Enhancement; Platelet Rich Plasma; Tendinopathy; Systematic Review*

INTRODUCTION

Tendon pathologies are extremely prevalent in the general population, accounting for over 30% of musculoskeletal consultations.[1,2] Tendinopathy, the chronic degeneration or inflammation of a tendon, is most typically caused by mechanical stress and overuse, with vascular and metabolic risk factors playing an additional role in its development.[3–5] While tendinopathy is frequently acquired through sport, it also poses a significant problem to the workforce, with a prevalence of 3% among working adults.[6,7] Altogether, the high prevalence of tendinopathy leads to significant productivity loss and disease compensation.[8,9] Because of this disease burden, treatment methods are constantly developing to optimize pain reduction and return to activity level. Currently, treatment options include oral anti-inflammatory medications, intralesional injections, dry needling, extracorporeal shock wave therapy, and physical therapy.[7] Surgical repair may be applicable for larger lesions or recalcitrant disease; however, the clinical preference, as well as standard of practice, is to proceed with surgery only as a last resort once more conservative measures have been exhausted.

Among intralesional injections, Platelet Rich Plasma (PRP) has shown positive results in multiple trials and has made its way into many musculoskeletal physicians' practice. PRP injections consist of autologous plasma containing platelet concentrations above that found in peripheral blood, having been centrifuged and extracted from other plasma components.[9,10] Histologically, chronic tendinopathies are characterized by collagen disorganization, increased overall cellularity, and chondroid-like cells incapable of accommodating the tendon's tensional demands.[3,11,12] Intralesional PRP can increase healing in these areas by stimulating the growth and differentiation of local progenitor cells and by modifying local inflammatory responses.[9,10,13–17] Unfortunately, PRP preparations, their growth factor profiles, and their injection protocols are highly variable.[18] As a result, there is a lack of data on the optimal treatment techniques using PRP.[10] Furthermore, PRP is currently only approved by the Food and Drug Administration (FDA) in the operative setting to mix with bone graft materials and use outside this setting is considered off-label.[19] Since PRP is not approved by the FDA for the many musculoskeletal ailments it targets, treatment in the outpatient setting is not covered by insurance companies.[19,20] The preparation kits used to procure PRP may vary in yield, and larger injection volumes possibly require more than one kit. Therefore, the out-of-pocket treatment costs can be a significant financial barrier.[20]

The lack of standardization amongst PRP therapy and its reporting has substantially limited its effective translation into everyday clinical practice.[9,10] Due to the heterogeneity in reported PRP treatment techniques, the optimal volume of PRP is not clear to maximize positive outcomes. Furthermore, the volume of injectate delivered within the lesion is not often recorded.[10] It is possible that larger

volumes of treatment are not contributing to more improved tendon healing, especially in smaller tendons. Therefore, our objective was to systematically review the available literature on PRP injections for the treatment of tendinopathy to assess the volume of PRP necessary to achieve positive outcomes in various anatomic locations, with the hopes of initiating further discussions on the standardization of injectate volumes.

METHODS

Search Strategy and Selection Criteria

In June 2020, comprehensive electronic databases searches were conducted by a medical librarian in Medline via PubMed, EMBASE (embase.com), CINAHL (EbscoHost), CENTRAL and Scopus according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A total of 352 articles were uploaded into systematic review software (http://www.Covidence.org). Strategies were developed for each database using pre-defined search terms, incorporating concepts specific to tendinopathy, platelet-rich plasma, and intralesional injection. Terms were modified for each database, and strategies incorporated both keywords and subject headings. No date restriction or other limits were applied (see attached document).

Authors [redacted] independently assessed all titles and abstracts to determine whether articles met our inclusion criteria. Inclusion criteria were as follows: (1) specification of ultrasound-guided intra-tendinous PRP injection, (2) patients 18 years and older, (3) randomized control trials, case-control studies, cohort studies, or case series, (4) patients with clinical tendinopathy or low grade (<50%) partial tear, (5) injection volume and pain or function outcome reported. Conversely, our exclusion criteria were (1) non-US-guided injections, (2) non-intratendinous injections, (3) patients under 18 years of age, (4) high-grade tendon tears, and (5) intraoperative injections. Additionally, systematic reviews, commentary, case reports, studies with a number of participants <10, non-English language studies, and studies that did not specify injection methodology or outcomes were excluded. Disagreements for inclusion were resolved by discussion author [redacted].

Data Extraction

Authors [redacted] extracted data on injection volume and methods independently. Disagreements on data extraction were resolved by consensus between the two authors. The following data were extracted for the included studies: author, title, inclusion and exclusion criteria, anatomic location of tendinopathy, group differences, injection technique, injection volume, PRP preparation technique, platelet concentration, follow-up time, and outcomes. Once all the data were extracted, studies were divided into groups based on the anatomic location of tendinopathy for interpretation.

Primary and Secondary Outcomes

The primary outcome was to catalogue intratendinous biologic injection volumes that were shown to yield positive outcomes. These interventions were categorized by the anatomic location of tendinopathy. The secondary outcome was determining the minimum volume of injectate reported by tendon location that yielded positive outcomes.

RESULTS

The search yielded 419 articles, with 352 remaining after duplicates were removed. After screening titles and abstracts, 75 articles were selected for full-text review. 47 of these studies were excluded in full-text review based on the study criteria (Figure 1).

A total of 28 studies were included in this review. All studies specified intratendinous injection of PRP confirmed under ultrasound guidance. Six studies evaluated the rotator cuff tendons,[21–26] six studies evaluated the common extensor tendon,[27–32] three studies evaluated the gluteal tendons,[33–35] one study evaluated the hamstring tendons,[12] six studies evaluated the patellar tendon.[36–42] and five studies evaluated the Achilles tendon[43–47] (Table 1). One study, Dallaudiere et al 2014,[48] evaluated outcomes in multiple tendon locations (common extensor tendon, common flexor tendon, hamstring, and adductor tendons, patellar tendon, peroneal tendons, and Achilles tendon) (Table 2).

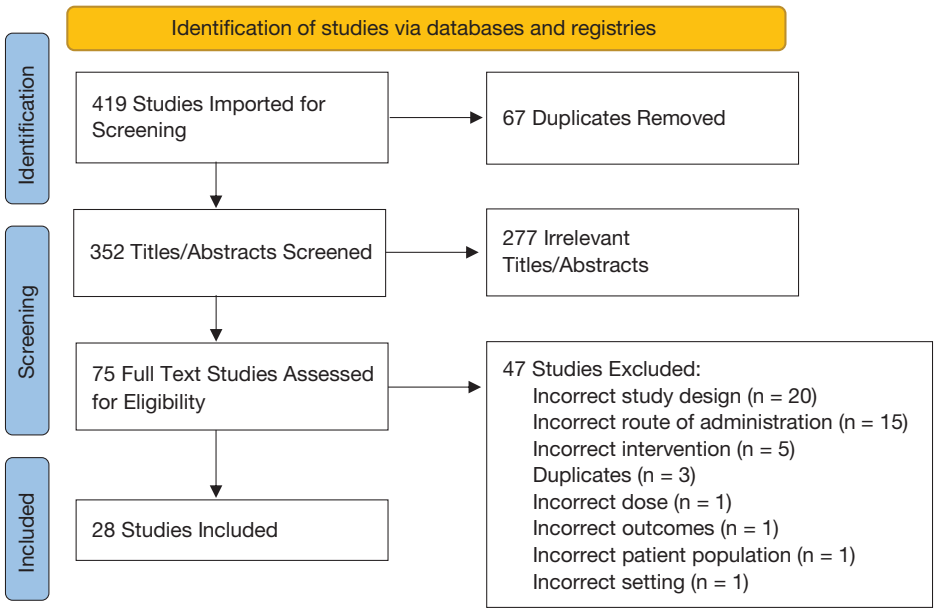

Figure 1. PRISMA flow diagram of systematic review progression.

Table 3 describes the range and average PRP volumes based on the body regions. Of the rotator cuff group, injection volumes ranged from 1–5 mL of PRP, with a mean of 2.58 mL. Of the common extensor group, injection volumes ranged from 1.5–4.5 mL of PRP, with a mean of 2.79 mL. In the gluteal tendon group, injection volumes ranged from 3–7 mL of PRP, with a mean of 5.5 mL. The hamstring tendon injection was reported as 3mL of PRP. The patellar group's injection volume ranged from 2–6 mL of PRP, with a mean of 4.75 mL. In the Achilles group, injection volume ranged from 4–6 mL of PRP, with a mean of 4.6 mL. For all the groups, the minimum injection volume was able to achieve significant improvements in reported outcome measures.

DISCUSSION

Although the clinical effectiveness of PRP has been demonstrated, there remains poor consistency amongst preparation and injection techniques. Multiple variable areas within protocols must be studied to establish the optimal therapeutic scheme. The volume of injectate is one of these areas that requires elucidation. The main findings of this study suggest that for any given tendinopathy, a minimal injection volume of PRP is adequate to achieve clinical improvement. Injection protocols were consistently heterogenous, unless studies were performed by the same investigators. All anatomic regions with more than one study reported a range of injections. Injection volumes ranged by as much as 4 mL between studies for the rotator cuff, gluteal, patellar, and Achilles tendons. There appeared a trend toward greater volumes of injectate given in the larger size tendons; for example, up to 7 mL of PRP was reported for gluteal tendons. Even so, injecting only 3 mL of PRP for gluteal tendinopathy was also able to produce positive clinical outcomes.

Conversely, average injection volume in the smaller, upper extremity tendons was less than 3 mL. Given that the minimum injection volumes at each anatomic site could also improve outcomes, there does not seem to be a clear dose-dependent response to PRP in tendinopathy. Though more data is needed, it is apparent that the minimum amount of injectate used clinically for various anatomic locations is enough for overall positive outcomes, and therefore can be the recommended dose. As such, the authors have incorporated the minimum injection volume into their practice using the following volumes: Rotator Cuff-1 mL, Lateral or Medial

Table 1. Characteristics of Included Studies

Author, year	Group Differences	Injectate Volume	PRP Preparation Technique	[Platelets]	F/u Time	Outcomes
Rotator Cuff Tendons						
Kesikburun 2013[21]	20 PRP v. 20 NS	5mL	GPS III Platelet Concentration System (Zimmer Biomet)	4-fold increase	3w, 6w, 12w, 24w, 1y	WORC*, SPADI*, Pain with Neer Impingement*, PROM
Kim 2018[22]	12 BMAC + PRP v. 12 PT control	3mL (2mL of BMAC + 1mL of PRP)	GPS III Platelet Concentration System (Zimmer Biomet)	-	3w, 3m	VAS†, MMT, ASES†, US Tear Size
Ladermann 2016[23]	28 PRP	1mL	GPS II Platelet Concentration System (Biomet)	1,603,000/ microLiter	6m	Tear Volume*, Constant Score*, SANE*, EVA*
Rha 2013[24]	20 PRP v. 19 DN	3mL	Prosys PRP Platelet Concentration System (Tozaiholdings Inc)	-	2w, 4w, 6w, 3m, 6m	SPADI*†, ROM*†
Scarpone 2013[25]	18 PRP	3.5mL	SmartPreP (Harvest Technologies)	-	2w, 8w, 12w, 52w	VAS*, Functional Shoulder Testing*, MRI appearance, Satisfaction
Schwitzguebel 2019[26]	41 PRP vs. 39 NS	2mL	RegenKit BCT (Regen Lab)	-	7m, 12m	MRA Lesion Volume, VAS, SANE, ASES, Constant
Lateral Epicondyle Tendons						
Behera 2015[27]	15 PRP v. 10 Bupivacaine	3.5mL	Terumo BCT	6-8 x 10^5microL	1m, 3m, 6m, 12m	VAS†, MMCPIE†, Nirschl Score†
Creaney 2011[28]	70 PRP v. 60 AWB	1.5mL	-	between 542-849 x 10^9	1m, 3m, 6m	PRTEE*
Krogh 2013[29]	20 PRP v. 20 CSI v. 20 NS	3-3.5mL	Recover GPS II system (Biomet)	8-fold increase	3m	PRTEE, tendon thickness
Lim 2018[30]	61 PRP v. 59 PT control	2mL	sPRP Kit (HUONS)	-	12w, 24w	VAS, MMCPIE, MRI Grade
Martin 2019[31]	41 PRP v. 39 lidocaine	4.5mL	-	2.3-fold increase	6m, 12m	spanish DASHE*, VAS*

Montalvan 2016[32]	25 PRP v. 25 NS	2mL	Arthrex ACP Double Syringe System (Arthrex)	1.6-fold increase	1m, 3m, 6m, 12m	GPS, Roles-Maudsley, functional testing
Gluteal Tendons						
Fitzpatrick 2018[33]	39 PRP v. 39 CSI	6-7mL	GPS III kit (Zimmer Biomet)	-	2w, 6w, 12w	mHHS†, PASS
Fitzpatrick 2019[34]	39 PRP v. 39 CSI	6-7mL	GPS III kit (Zimmer Biomet)	964 x 10^9/L	2y	mHHS*†
Lee 2016[35]	21 PRP	3-4mL	Magellan Autologous Platelet Separator System (Isto Biologics)	-	20m	mHHS*, HOS-ADL*, HOS-Sport*, iHOt33*
Hamstring Tendons						
Davenport 2015[36]	12 PRP v. 7 AWB	3mL PRP v. 5mL AWB	SmartPreP (Harvest Technologies)	-	2w, 6w, 12w, 6m	mHHS, HOS-ADL*, HOS-Sport*, iHOT33†, functional testing, US imaging
Patellar Tendons						
Abdelbary 2018[37]	10 PRP v. 10 HVIGI	6mL PRP vs. 40ml HVIGI	Arthrex ACP Double Syringe System (Arthrex)	-	2m, 6m, 12m	VAS
Dragoo 2014[38]	10 PRP v. 13 DN	6mL	GPS II kit (Biomet)	-	3w, 6w, 9w, 12w, 6m	VISA*†, Tegner, VAS*, SF-12
Filardo 2013[39]	43 PRP	5mL	-	-	2m, 6m, 48m	VISA-P*, EQ-VAS*, Blanzina Score*, Tegner*
Kaux 2016[40]	10 PRP x1 v. 10 PRP x2	6mL	-	8.5-9 x 10^5/microL	12w	VAS*, VISA-P*, functional testing*, IKCD*, US imaging
Scott 2019[41]	19 LR-PRP v. 19 LP-PRP v. 19 NS	3.5mL	Cytomedix Angel Concentrated PRP System (Arthrex)	3.8 x increase in LR-PRP; and 3.0 x increase in LP-PRP	12w, 1y	VISA-P, NPS

(Continues)

Table 1. (Continued)

Author, year	Group Differences	Injectate Volume	PRP Preparation Technique	[Platelets]	F/u Time	Outcomes
Vetrano 2013[42]	23 PRP x2 v. 23 ESWT x3	2mL	MyCells Autologous Platelet Preparation System (MyCells), Recover Platelet Separation Kit (Zimmer Biomet)	0.89-1.1 x 10^9/mL	2m, 6m, 12m	VISA-P*†, VAS*†, Modified Blanzina*†, Satisfaction†
Achilles Tendons						
Albano 2017[43]	28 PRP v. 30 SVF	4mL	GPS III (Zimmer Biomet)	-	6m	VAS*, MR/US imaging*
deJonge 2011[44]	27 PRP v. 27 NS	4mL	Recover Platelet Separation kit GPS III (Zimmer Biomet)	-	1y	VISA-A*, satisfaction, return to sport, US imaging
deVos 2010[45]	27 PRP v. 27 NS	4mL	-	-	6w, 12w, 24w	VISA-A*, satisfaction, return to sport, exercise adherence
Filardo 2014[46]	34 PRP	5mL	-	5-fold increase	2m, 6m, 30m	Blanzina*, VISA-A*, EQ-VAS*, Tegner*
Krogh 2016[47]	12 PRP v. 12 NS	6mL	GPS II system (Biomet)	8-fold increase	3m	VISA-A, functional testing, US imaging*
Miscellaneous: Lateral Epicondyle, Medial Epicondyle, Hamstring and Adductor Longus, Patellar, Achilles, and Peroneal Tendons						
Dallaudiere 2014[48]	408 PRP	3mL	-	3-fold increase	6w, 32m	QuickDASH*, WOMAC*, VAS*, US imaging*

PRP: Platelet Rich Plasma, NS: Normal Saline, BMAC: Bone Marrow Aspirate Concentrate, PT: Physical Therapy, DN: Dry Needling, AWB: Autologous Whole Blood, CSI: Corticosteroid Injection, HVIGI: High Volume Image Guided Injection, LR-PRP: Leukocyte Rich PRP, LP-PRP: Leukocyte Poor PRP, ESWT: Extracorporeal Shockwave Therapy, SVF: Adipose Derived Stromal Vascular Fraction, WORC: Western Ontario Rotator Cuff Index, SPADI: Shoulder Pain and Disability Index, PROM: Passive Range of Motion, VAS: Visual Analog Scale, MMT: Manual Muscle Test, ASES: American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form, SANE: Single Assessment Numeric Evaluation, ROM: Range of Motion, MR: Magnetic Resonance Imaging, MMCPIE: Modified Mayo Clinic Performance Index for the Elbow, GPS: Global Pain Score, mHHS: modified Harris Hip Score, PASS: Patient Acceptable Symptom State Questionnaire, HOS-ADL: Hip Outcome Score- Activities of Daily Living, HOS-Sport: Hip Outcome Score- Sports subscale, iHOT33: International Hip Outcome Tool-33, SF-12: 12-Item Short Form Survey, EQ-VAS: EuroQol Visual Analogue Scale, IKDC:InternationalKneeDocumentationCommitteeSubjectiveKneeForm, VISA-P:VictorianInstituteofSportAssessment-Patella, VISA-A:VictorianInstituteofSportAssessment-Achilles, QuickDASH: Abbreviated Disabilities of Arm Should and Hand Questionnaire, WOMAC: Western Ontario and McMaster University Index

**Significant Improvement from Baseline, †Significant Difference between Groups*

Table 2. Characteristics of Dallaudiere 2014[48]

Region	Body Part	N	PRP Volume	PRP Composition	F/u Time	Primary Outcome	Secondary Outcome	Secondary Outcome
Upper Limb	Lateral Epicondyle	220	3mL	~ 3 fold increase; a controlled platelet number (900,000 per mm^3 +/– 25,000) and controlled leukocyte number (200 per mm^3 +/–35)	6w, 20m	Quick-DASH*	VAS* for all groups	US Lesion size*
	Medial Epicondyle	30				Quick-DASH*		US Lesion size*
Lower Limb	Achilles	54				WOMAC*		US Lesion size*
	Patellar	41				WOMAC*		US Lesion size*
	Ham-strings and Adductor Longus	40				WOMAC*		US Lesion size*
	Peroneal	23				WOMAC*		US Lesion size*

*Key: *Significant Improvements from Baseline*

Table 3. PRP Injection Volume by Body Region

Anatomic Region	N (Studies)	Mean Volume per Study	Range mL
Rotator Cuff	6[26,28,31,45–47]	2.58 mL‡	1–5
Lateral Epicondyle	6[6,9,30,35,38,43]	2.79 mL	1.5–4.5
Gluteal	3[22,23,33]	5.5 mL	3–7
Hamstring	1[12]	3 mL	–
Patellar	6[1,18,20,25,48,51]	4.75 mL	2–6
Achilles	5[2,13,15,19,29]	4.6 mL	4–6
Miscella-neous	1[10]	3 mL	–

‡Volume for Kim 2018[28] analyzed as 1 mL PRP, though 2 mL of additional Bone Marrow Aspirate Concentrate were present in injectate as well.

Epicondyle-1.5 mL, Gluteal or Hamstring-3 mL, Patella-2 mL, Achilles-3 mL. Unfortunately, without more data available in the literature, the authors cannot make stronger recommendations at this time.

It remains unknown how much of the injectate a tendon can receive and keep localized to the target region. In one study, ultrasound evaluation of PRP injections in the common extensor tendons of the elbow revealed injectate spread to surrounding soft tissue in 51% of patients. However, the volume of these injections was only 1.5 mL.[49] Similarly, in patients who received injections to the elbow with 3.5 mL of PRP, the majority exhibited PRP diffusion into adjacent soft tissue.[50] Though PRP therapy remains localized at the lesion site, a proportion of the injectate is lost to off-target soft tissues, even with smaller injection volumes. Wilson et al. evaluated PRP distribution in an ex vivo animal extensor tendon model and found volume retention of PRP within the tendon was less than two-thirds of total injectant.[51] It is difficult to assess the amount of platelets and growth factors reaching the target area. As opposed to increasing the volume of injectate, the effective dose may be increased by increasing the concentration of therapeutic factors within the injectate, or by increasing their viscosity to prevent diffusion via binding agents such as calcium chloride or thrombin.[49] Maintaining on-target treatment has the potential to minimize costly therapeutic waste. In addition, extravasation of injectate to surrounding tissues should be avoided as it may cause increased short-term pain and discomfort.

The rationale behind PRP is that a supraphysiologic concentration of growth factors and cytokines may augment the healing response by enhancing stem cell and macrophage migration.[10,13,15,17]

However, in our review, there were mixed results when comparing the efficacy of PRP to control saline injection or needle tenotomy.[21,32,47] Though outcomes were improved from baseline, there were no differences between treatment and control. There are many explanations for these inconsistent results, possibly stemming from inconsistencies in methodology. Aside from varying injection volumes, these studies varied in PRP preparation techniques, PRP and control delivery method, and rehabilitation protocols. Our aim was to assess volume discrepancies, but variance elsewhere in PRP protocols further emphasizes the need for standardization in reporting and administration of PRP.

This study focused solely on ultrasound-guided injections to ensure that treatment was being delivered within the tendon. A review of available literature by Daniels et al. concluded that ultrasound-guided injections are more accurate than landmark-guided injections (LMGI) and are also more efficacious than LMGI in the lower extremities.[52] Moreover, the American Medical Society for Sports Medicine has concluded that there is strong evidence that ultrasound guidance is more accurate for tendon sheath and peritendinous injection than landmark guidance alone.[53] Ultrasound guidance allows for real-time visualization of therapeutics delivery within the tendon lesion. And, given the potential cost burden of PRP extraction and preparation, it is important to guarantee that such expensive treatment is being delivered accurately.

Our study is limited by the paucity of data on PRP outcomes in tendinopathy. There was not enough comparable data to perform advanced statistical analysis; thus, our findings are only observational. As with other studies on the emerging use of PRP, our study is limited by the heterogeneity of methods by which PRP is administered. Aside from differences in injection volumes, PRP protocols varied by preparation technique, concentration of platelets and leukocytes, number of doses, and post-injection physical therapy protocols. More standardization is needed within treatment protocols to better assess and optimize the clinical effects of PRP. The authors agree with the 2015 recommendations published by the American Academy of Physical Medicine and Rehabilitation that minimal PRP reporting and classification standards would greatly improve the study and analysis of PRP efficacy on a population scale.[39]

CONCLUSION

Though PRP injection protocols remain heterogenous in clinical practice, protocols with lesser volumes of injectate can still produce positive patient outcomes. However, more standardization of protocols is necessary to thoroughly analyze the optimal volume of injectate necessary to produce desired therapeutic effects.

DISCLOSURES

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