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Analytical-Systematic Review

Post-Procedure Protocols Following Platelet-Rich Plasma Injections for Tendinopathy: A Systematic Review

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Abstract

Objective: Platelet-rich plasma (PRP) has been increasingly studied as a treatment for tendinopathy. Many factors may influence outcomes after PRP, including different protocols following administration. It was hypothesized that there would be heterogeneity in post-PRP protocols.
Literature Survey: A systematized review of the literature on post-PRP protocols for tendinopathy was conducted using an electronic search of MEDLINE and Embase databases through September 2018.
Methodology: After duplicates were removed, English language articles involving adult patients who received PRP for tendinopathy were reviewed. Exclusion criteria included studies with fewer than 10 patients, PRP used to treat pathology other than tendinopathy, multiple protocols in one study, and surgical settings. Protocol specifics were extracted including nonsteroidal anti-inflammatory drugs (NSAID) restrictions before and after injection, postinjection restrictions on movement and weight bearing, use of orthoses, activity modifications, and postinjection rehabilitation protocols. Given limitations in the data, a meta-analysis was not performed.
Synthesis: Eighty-four studies met inclusion criteria. Following PRP injection, weight-bearing restrictions were mentioned rarely (12% of protocols). Orthosis use was uncommon overall (18%) but more common in Achilles tendinopathy protocols (53%). The majority of protocols instituted a period of stretching (51%) and strengthening (54%). Stretching programs generally began 2-7 days following injection, and strengthening programs began within 2-3 weeks. Preinjection NSAID restriction was reported rarely (20%), whereas postinjection NSAID restriction was more common (56%), with a typical restriction of greater than 2 weeks (38%). Return to play or full activity was reported in 42% of protocols, most commonly at 4-6 weeks following injection.
Conclusion: Although the clinical effectiveness of PRP remains controversial, even less is known about the effect of post-PRP protocols, which may affect the outcomes attributed to PRP itself. No studies directly compare post-PRP protocols, and the protocols studied demonstrate substantial heterogeneity. Some consensus regarding post-PRP protocols exists, although the rationale for these recommendations is limited.

Introduction

Platelet-rich plasma (PRP) has been increasingly studied as a treatment for tendinopathy over the past decade,[1] and though utilization trends are not well described, PRP use is fairly widespread for multiple musculoskeletal conditions. In a national sample based on billing data, the PRP utilization rate was 28 per 1000 patients per year; treatment of tendon disease was responsible for 12% of cases.[2]

PRP, an autologous mixture of concentrated platelets and growth factors produced from centrifugal separation of whole blood, is purported to trigger a regenerative response in poorly healing tissues. A recent increase in available Level 1 randomized controlled studies prompted a systematic review and meta-analysis of PRP use in tendinopathy, which concluded that PRP injection resulted in significantly less pain at long-term analysis compared with control.[1] Despite promising clinical results, the use of PRP as a treatment for tendinopathy has been controversial, due to heterogeneity in study designs and evidence of publication bias.[3] A number of factors may explain the differences in treatment effects seen in randomized trials of PRP injections, including

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differences in the length of follow-up (given the slow onset of action of PRP), PRP formulations such as leukocyte-rich or leukocyte-poor PRP[4] and post-PRP protocols.

Regarding post-PRP protocols, both nonsteroidal anti-inflammatory drug (NSAID) use and physical therapy, which are regarded as mainstays of conservative management in tendinopathy[5,6] are sometimes specifically included in rehabilitation protocols following PRP administration. Because these may be considered active treatments for tendinopathy on their own, separating the effect of the PRP injection itself from the effect of the post-PRP protocol may be challenging.

Multiple articles have proposed a standardized rehabilitation program following PRP injection[7-9] but substantial variability exists in the elements and timing of these recommendations. Furthermore, no studies have evaluated outcomes based on different post-PRP protocols. Our objective was to systematically review the described protocols utilized in the setting of PRP injection for tendinopathy and to categorize a number of important variables including weight-bearing restriction, activity modification, bracing, physical therapy, and the use or restriction of NSAIDs. In addition, we aimed to describe the timing of these interventions following PRP administration. We hypothesized there would be heterogeneity in post-PRP protocols, but that specific protocols would be presented in most studies.

Methods

Search Strategy and Selection Criteria

We conducted a review of the literature meeting the criteria of a systematized review as described by Grant and Booth.[10] An electronic search of PubMed and Embase databases through September 2018 was performed. We searched PubMed for the following terms: "PRP," "platelet rich plasma," "orthobiologics," "regenerative medicine," "autologous conditioned serum," or "autologous conditioned plasma" and "tendon," "tendinopathy," "tendinitis," "tendinosis," "rotator cuff," "supraspinatus," "infraspinatus," "hamstring," "semitendinosis," "semimembranosus," "conjoined tendon," "common extensor tendon," "patellar," "Achilles," "rectus femoris," "quadriceps," "tennis elbow," "golfer's elbow," "golf elbow," "gluteus maximus," "gluteus medius," "plantar fascia," "posterior tibialis," or "psoas." The same search terms were used for Embase database. Two authors (CT and KvR) independently assessed all titles and abstracts to determine whether articles met our inclusion criteria. Our inclusion criteria included (1) human patients ≥18 years old; (2) assessment of PRP injections for treatment of tendinopathy; (3) randomized controlled trials, case-control studies, or case series; and (4) articles published in English. Studies were excluded if they included patients <18 years of age or an N < 10 patients, assessed PRP for nontendinopathic purposes such as intra-articular injections, did not report a single PRP protocol used for the patients receiving PRP, used PRP in conjunction with a surgical intervention, and commentary, case reports, study proposals, or literature reviews. We had no inclusion criteria based on specific tendon injected, type of PRP utilized, number of PRP injections per site, peri- vs intratendinous injections or the efficacy of the injections. Disagreements for inclusion of full articles were resolved by discussion with an additional author (ZB and/or AG).

Data Extraction

The four authors (CT, KvR, ZB, AG) extracted data independently in pairs for predetermined data points. Disagreements on data extraction were resolved by consensus or discussion with an additional author. The following data were extracted for included studies: author, study design, sample size, participant characteristics, details of PRP intervention, study outcomes, NSAID restrictions both pre- and postinjection, immediate post-injection movement, weight-bearing, orthosis and activity restrictions, and postinjection rehabilitation protocols. If a study included a series of PRP injections delivered at different points in time, data were extracted for the protocol after the final PRP injection. Once all the data were extracted, studies were divided into three groups for interpretation: upper limb target tendon, lower limb target tendon, and studies that involved both upper and lower limb target tendons injections.

Primary and Secondary Outcomes

The primary outcome was to review the described post-PRP protocols for tendinopathy and categorize the protocols based on the use or restriction of NSAIDs, physical therapy, bracing, weight-bearing restriction, and activity modification. The secondary outcome was to determine the timing of these interventions and any differences between upper and lower limb protocols within the literature.

Results

The search yielded 1687 articles and 969 articles remained after duplicates were removed. After assessment of titles and abstracts, 113 articles were selected for full-text review and 29 were excluded according to the study criteria (Figure 1).

After all exclusion criteria were applied, a total of 84 studies were included in this review. Forty-three studies were randomized controlled trials, 8 were case-control studies, and 33 were case series. Thirty-seven articles studied PRP in upper limb tendons, 42 articles studied PRP in lower limb tendons, and five examined

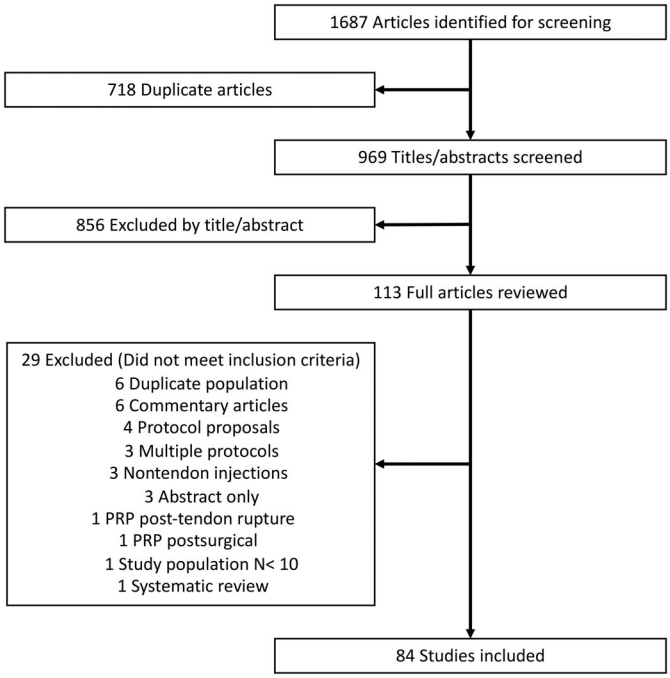

Figure 1. Flow diagram for study selection process.

more than one tendon in a combination of upper and lower extremities. Results are were divided into three tables by these aforementioned categories for ease of review (Tables 1–3). The most common tendons injected were the common extensor tendon (24 studies, 29%), followed by the plantar fascia (14 studies, 17%), rotator cuff (12 studies, 14%), and Achilles tendons (12 studies, 14%).

Postprocedure Rest, Weight-Bearing, Orthoses, and Activity Modification

Of the 84 protocols reviewed, most (80%) did not report any specific recommendations regarding postprocedure rest, weight-bearing, and orthosis use. However, 17 protocols (20%) recommended a period of immobility of the affected limb; 12 of these (71%) limited immobility to less than 30 minutes. The cited justification for immobility was often to allow time for PRP to bind to the target tendon.[5,6]

Similarly, most protocols (88%) did not report any weight-bearing restrictions. Only 10 of the 84 protocols studied (12%) mentioned any formal weight-bearing restriction, most commonly for lower limb tendons (Table 4). The most common duration of weight-bearing restriction was 2 to 7 days (70%). Notably, many protocols mentioned a period of activity modification and often used phrases such as "subjects were told to rest the extremity." However, we did not consider these to represent true weight-bearing restrictions as they were not deemed sufficiently specific.

Orthoses and crutches were also not commonly reported in the protocols. Sixty-nine protocols (82%) did not report the use of an orthosis following PRP injection. Of the 15 that did, four protocols pertained to upper limb tendinopathy and 11 to lower limb tendinopathy. All four upper limb tendinopathy protocols that used an orthosis were for common extensor tendon PRP injections; three of these described the use of a sling without specific weight-bearing status clarified, and one article described the use of a tennis elbow strap. The frequency of use of an orthosis in protocols involving the common extensor tendon was only 17%. Among the 11 lower limb tendinopathy protocols that specified orthosis use, seven pertained to the Achilles tendon, three to the plantar fascia, and one to the hamstring. A total of 53% of all protocols for Achilles tendinopathy required the use of crutch or walking boot following PRP injection, whereas 24% of all protocols for plantar fasciitis utilized a crutch or walking boot. Among the lower limb tendinopathy protocols in which orthoses or crutches were specified, the most commonly recommended duration of use was >7 days. Two protocols utilized a walking boot for either 4 or 6 weeks following PRP injection to the Achilles tendon.

Among the 84 protocols reviewed, activity limitation following PRP injection was reported in 42 (50%). Of these, 26% limited activity for <2 days, 57% for 2-7 days, and 17% for more than 7 days. Protocol descriptions of activity limitation were usually qualitative, such as encouraging patients to engage in "relative rest." In contrast to these protocols, eight protocols out of the 84 protocols studied specifically mentioned that *no* activity restrictions were instituted following injection.

Post-PRP Rehabilitation

Post-PRP rehabilitation was generally divided into two phases: phase one consisted of stretching and range of motion (ROM) exercises, and phase two focused on strengthening activities. Just over half of the 84 protocols mentioned specific details regarding phase one (51%) or phase two (54%) (Table 4). Most protocols initiated phase one prior to phase two, though four protocols mentioned both phases starting concurrently.[5,7-9]

Sixteen of the 43 protocols that specified formal rehabilitation activities (37%) initiated phase one within 2 to 7 days postinjection. Of these 43 protocols, 13 (30%) described phase one activities but did not mention a specific time frame in which they were initiated. Phase two was most commonly initiated 14 to 21 days following PRP injection, as noted in 25 of the 45 protocols (56%). Twelve of the 45 protocols (27%) mentioned phase two activities but did not indicate a specific time frame.

Removal of All Restrictions and Return to Play

Return to play was often described in the protocols as the removal of all restrictions, although not all patients completely returned to their sport or prior level of competition. Thirty-five protocols (42%) discussed return to

Table 1
Characteristics of post-PRP protocols involving upper limb tendinopathy

	NSAID Restriction		Immediate Post-PRP Restrictions			Post-PRP Rehabilitation		
Author, y	Pre-PRP	Post-PRP	Movement	Weight Bearing	Activity Limitation	Range of Motion/Stretching	Strengthening	Return to Play
Common extensor tendon								
Alessio-Mazzola et al, 2018[11]	-	>13 d	-	-	<2 d	-	-	Restricted
Behera et al, 2015[12]	-	-	<30 min	2-7 d	2-7 d	2-7 d	>13 d	>6 wk
Brkljac et al, 2015[13]	-	>13 d	30-59 min	-	<2 d	-	<7 d	-
Creaney et al, 2011[14]	-	Restricted	-	-	2-7 d	-	-	-
Gaspar et al, 2017[15]	-	-	-	-	-	2-7 d	>13 d	-
Gautam et al, 2015[16]	-	Restricted	30-59 min	-	-	-	-	-
Glanzmann et al, 2015[17]	-	Restricted	-	-	<2 d	<2 d	-	-
Hechtman et al, 2011[†18]	>13 d	-	-	-	-	<2 d	>13 d	4-6 wk
Karaduman et al, 2016[19]	-	>13 d	<30 min	-	-	2-7 d	<7 d	Restricted
Khattab et al, 2017[20]	>13 d	>13 d	-	-	-	>7 d	>13 d	4-6 wk
Krogh et al, 2013[21]	-	Restricted	-	-	2-7 d	Restricted	Restricted	-
Lebiedziński et al, 2015[22]	-	-	-	-	-	-	-	-
Lim et al, 2018[23]	-	-	-	-	-	-	-	-
Merolla et al, 2017[24]	-	>13 d	-	-	-	-	-	-
Mishra et al, 2006[25]	-	Restricted	<30 min	-	<2 d	<2 d	>13 d	4-6 wk
Mishra et al, 2014[26]	-	-	-	-	-	-	-	-
Montalvan et al, 2016[27]	-	-	-	-	-	-	-	-
Peerbooms et al, 2010[28]	-	Restricted	<30 min	-	<2 d	<2 d	>13 d	4-6 wk
Raeissadat et al, 2014[29]	-	Restricted	-	-	-	2-7 d	>13 d	4-6 wk
Stenhouse et al, 2013[30]	-	-	-	-	No restriction	-	-	-
Tetschke et al, 2015[31]	-	-	-	-	-	>7 d	>13 d	>6 wk
Thanasas et al, 2011[32]	-	Restricted	-	-	2-7 d	2-7 d	7-13 d	-
Yadav et al, 2015[33]	>13 d	7-13 d	-	-	-	-	-	-
Yerlıkaya et al, 2018[34]	7-13 d	7-13 d	-	-	-	2-7 d	<7 d	-
Rotator cuff tendons								
Damjanov et al, 2018[35]	-	-	-	-	-	-	-	-
Ibrahim et al, 2018[36]	-	Restricted	-	-	2-7 d	2-7 d	>13 d	-
Ilhanli et al, 2015[37]	-	-	-	-	<2 d	<2 d	>13 d	-
Kesikburun et al, 2013[38]	-	Restricted	<30 min	-	2-7 d	2-7 d	Restricted	-
Lädermann et al, 2016[39]	-	-	-	-	2-7 d	-	-	-
Nejati et al, 2017[40]	7-13 d	<7 d	-	-	2-7 d	-	-	-
Rha et al, 2013[41]	>13 d	Restricted	-	-	>7 d	<2 d	Restricted	-
Say et al, 2016[42]	-	Restricted	<30 min	-	-	Restricted	Restricted	-
Scarpone et al, 2013[43]	-	Restricted	-	-	2-7 d	-	-	-
Shams et al, 2016[44]	-	>13 d	-	-	-	-	-	4-6 wk
von Wehren et al, 2016[45]	-	>13 d	-	-	-	-	-	4-6 wk
Zafarani et al, 2017[46]	-	-	-	-	-	Restricted	-	-
Biceps tendon								
Sanli et al, 2016[47]	-	-	-	-	-	-	-	-

"Strengthening" indicates any activity beyond range of motion and stretching.
"Return to play" indicates completion of all physical restrictions.
"No restriction" indicates protocol specifically reported no restriction to mentioned medication or task.
"Restricted" indicates medication/task was restricted but no specifics were provided.
*Dash (-) indicates topic was not mentioned in the protocol.
[†]Also included common flexor tendons.
NSAID, nonsteroidal anti-inflammatory drug; PRP, platelet-rich plasma.

play recommendations, most commonly at 4-6 weeks after PRP injection (Table 4).

NSAID Restriction

Of 84 protocols, 67 (80%) did not report any restriction of NSAIDs prior to the procedure. Of the 17 that did, 10 protocols withheld NSAIDs for 7-13 days prior to PRP injection, whereas seven protocols restricted NSAID use for at least 2 weeks prior to injection. Postprocedure NSAID restrictions were reported in 47 protocols (56%). In those protocols reporting postprocedure NSAID restriction, 13% reported restriction for 13 days or less, 38% reported restriction for >13 days, and 49% did not specify the duration of restriction (Table 4). Notably, two protocols continued NSAID restriction for 6 months after injection.[10,89]

Table 2
Characteristics of post-PRP protocols involving lower limb tendinopathy

	NSAID Restriction		Immediate Post-PRP Restrictions					Post-PRP Rehabilitation		
Author, y	Pre-PRP	Post-PRP	Movement	Orthosis/ Crutches	Type	Weight Bearing	Activity Limitation	Range of Motion/Stretching	Strengthening	Return to Play
Achilles tendon										
Albano et al, 2017[48]	-	-	-	<2 d	Crutches	<2 d	<2 d	-	-	Restricted
Boesen et al, 2017[49]	-	-	<30 min	-		-	2-7 d	-	<7 d	<4 wk
Deans et al, 2012[50]	-	-	-	>7 d	Pneumatic boot	-	>7 d	>7 d	>13 d	-
de Jonge et al, 2011[51]	-	-	-	-		-	-	>7 d	>13 d	4-6 wk
Filardo et al, 2014[52]	-	<7 d	-	-		-	No restriction	Restricted	Restricted	>6 wk
Gaweda et al, 2010[53]	-	-	-	2-7 d	Elbow crutches	2-7 d	>7 d	2-7 d	>13 d	-
Guelfi et al, 2015[54]	-	-	>60 min	2-7 d	Crutches	2-7 d	<2 d	-	>13 d	>6 wk
Krogh et al, 2016[55]	-	-	-	-		-	2-7 d	Restricted	Restricted	-
Monto, 2012[56]	-	>13 d	-	2-7 d	CAM boot	-	2-7 d	-	Restricted	-
Murawski et al, 2014[57]	-	-	-	>7 d	CAM boot	-	No restriction	Restricted	>13 d	>6 wk
Oloff et al, 2015[58]	-	-	-	-		-	-	2-7 d	>13 d	-
Owens et al, 2011[59]	-	-	-	>7 d	Walking boot	-	-	-	-	4-6 wk
Gluteal tendons										
Fitzpatrick, 2019[4]	-	-	-	-		-	2-7 d	-	>13 d	>6 wk
Jacobson et al, 2016[60]	>13 d	>13 d	-	-		-	2-7 d	-	-	-
Lee et al, 2016[61]	-	>13 d	-	-		-	>7 d	-	>13 d	-
Hamstring tendons										
Davenport et al, 2015[62]	-	-	-	-		-	-	-	-	-
Levy et al, 2018[63]	-	-	-	-		-	-	-	-	-
Hamid et al, 2012[64]	-	>13 d	<30 min	-		-	2-7 d	-	Restricted	-
Park et al, 2018[65]	-	-	-	-		-	-	-	-	-
Wetzel et al, 2013[66]	-	-	-	>7 d	CrutchesHip abduction brace	-	>7 d	>7 d	>13 d	-
Patellar tendon										
Charousset et al, 2014[67]	-	Restricted	-	-		-	<2 d	<2 d	<7 d	>6 wk
Dragoo et al, 2014[68]	>13 d	>13 d	-	-		-	-	Restricted	Restricted	-
Filardo et al, 2010[69]	<7 d	-	-	-		-	No restriction	Restricted	Restricted	4-6 wk
Gosens et al, 2012[70]	-	Restricted	-	-		-	No restriction	<2 d	>13 d	4-6 wk
Kaux et al, 2015[71]	-	>13 d	-	-		-	2-7 d	Restricted	7-13 d	4-6 wk
Kon et al, 2009[72]	<7 d	<7 d	<30 min	-		-	<2 d	Restricted	Restricted	4-6 wk
Vetrano et al, 2013[73]	-	Restricted	<30 min	-		-	No restriction	2-7 d	7-13 d	4-6 wk
Pes anserine tendon										
Rowicki et al, 2014[74]	-	>13 d	-	-		-	-	2-7 d	>13 d	-
Plantar fascia										
Baz et al, 2017[75]	-	-	-	-		2-7 d	2-7 d	2-7 d	-	4-6 wk
Chew et al, 2013[76]	-	-	-	-		-	No restriction	Restricted	-	-
Gogna et al, 2016[77]	-	-	<30 min	-		-	-	-	-	<4 wk
Jain et al, 2018[78]	-	Restricted	-	-		-	2-7 d	-	-	-
Jimenez-Pérez et al, 2018[79]	-	Restricted	-	-		2-7 d	>7 d	-	-	-
Kim and Lee, 2014[80]	7-13 d	Restricted	30-59 min	-		-	2-7 d	-	-	<4 wk
Mahindra et al, 2016[81]	7-13 d	>13 d	-	-		-	-	Restricted	-	-
Martinelli et al, 2013[82]	-	-	-	-		-	No restriction	-	-	4-6 wk
Monto et al, 2014[83]	-	>13 d	-	>7 d	CAM boot	-	-	Restricted	Restricted	-
Othman et al, 2015[84]	-	Restricted	-	-		-	2-7 d	2-7 d	>13 d	4-6 wk

(Continues)

Table 2.
Continued

Author, y	NSAID Restriction		Immediate Post-PRP Restrictions			Post-PRP Rehabilitation				
	Pre-PRP	Post-PRP	Movement	Orthosis/ Crutches	Type	Weight Bearing	Activity Limitation	Range of Motion/Stretching	Strengthening	Return to Play
Ragab and Othman, 2012[85]	-	Restricted	<30 min	-		-	2-7 d	2-7 d	>13 d	4-6 wk
Tiwari and Bhargava, 2013[86]	7-13 d	Restricted	-	-		-	<2 d	-	-	-
van Egmond et al, 2015[87]	-	-	-	-		>7 d	-	>7 d	-	4-6 wk
Wilson et al, 2014[88]	7-13 d	>13 d	-	2-7 d	Boot crutches	2-7 d	>7 d	-	>13 d	>6 wk

"Strengthening" indicates any protocol activity beyond range of motion and stretching.
"Return to play" indicates protocol completion of all physical activity restrictions.
"No restriction" indicates protocol specifically reported no restriction of involved medication or task.
"Restricted" indicates protocol reported restriction of medication or task, without specifics on duration.
*Dash (-) indicates topic was not mentioned in protocol.
CAM, controlled ankle movement; NSAID, nonsteroidal anti-inflammatory drug; PRP, platelet-rich plasma.

Discussion

Our review found no studies that directly compare post-PRP protocols in patients receiving PRP for the treatment of tendinopathy and highlights the heterogeneity present in postinjection protocols. Despite this, some consensus exists among the protocols studied regarding the timing of the various aspects of the post-PRP period (Table 4). Based on our review, the most common features of post-PRP protocols (present in >50% of studies identified) include a short period of weight-bearing restriction for lower limb weight-bearing tendons, a stretching program initiated within 1-2 weeks following injection, a strengthening program initiated approximately 2 weeks after injection, and NSAID restriction for 1-2 weeks following injection. Despite the relative consensus in these features of the post-PRP management, the impact of any specific post-injection protocol on clinical outcomes after PRP has yet to be studied and requires further research.

Soft tissue healing is typically divided into three overlapping stages: inflammation, proliferation, and remodeling. These stages take place in the first few days, weeks, and months after injury, respectively.[90] In refractory tendinosis, the rationale for a PRP injection is to initiate an acute inflammatory response in the target tissue and effectively restart the healing process.[7] The three phases of soft tissue healing align with the common features of post-PRP rehabilitation protocols identified in our review, with features promoting rest and activity restriction during the inflammatory stage; features including stretching and strengthening of the tendon during the proliferation stage; and features involving return to sport in the remodeling phase.[89]

Postprocedure Rest and Weight-Bearing Restrictions

Few protocols included in this review mentioned a postprocedure resting period. Evaluation of temporal growth factor release from PRP suggests that a majority of bioactive growth factors are released within 15 minutes following activation.[90] Theoretically, immediate immobilization after injection may decrease the spread of PRP, prolonging its retention near the tendon and possibly increasing its effects. We found substantial variability between protocols in the use of immobilization, highlighting the poor understanding of the role of immobility in the postinjection period. When specified, protocols indicated periods of immobility ranging from less than 30 minutes to as much as 3 hours after injection.

Similarly, our review showed that weight-bearing restrictions after PRP injections are not consistent between studies. The rationale to limit weight-bearing following tendon injection is to limit the risk of tendon rupture, a well-described risk following corticosteroid injection to weight-bearing tendons, including the patellar[91] and Achilles[92] tendons. To our knowledge, only a

Table 3
Characteristics of post-PRP protocols involving mixed upper and lower limb tendinopathy

		NSAID Restriction		Immediate Post-PRP Restrictions					Post-PRP Rehabilitation		
Author, y	Tendons	Pre-PRP	Post-PRP	Movement	Orthosis/Crutches	Type	Weight Bearing	Activity Limitation	Range of Motion/ Stretching	Strengthening	Return to Play
Dallaudiere, 2013[107]	Achilles Common extensor (elbow) Common flexor (elbow) Patellar Peroneal	-	-	-	-		-	-	-	-	Restricted
Dallaudiere, 2014[108]	Achilles Adductor longus Common extensor (elbow) Common flexor (elbow) Hamstring Patellar Peroneal	-	-	-	-		-	-	-	-	<4 wk
Finnoff[7]	Achilles Biceps Common extensor (elbow) Common flexor (elbow) Gluteal Hamstring Patellar Plantar fascia Popliteus Quadriceps Tibialis posterior Triceps brachii	7-13 d	>13 d	-	>7 d	Boot Crutches Knee immobilizer Sling	>7 d	2-7 d	2-7 d	>13 d	-
Gupta[86]	Common extensor (elbow) Plantar fascia	7-13 d	7-13 d	>60 min	2-7 d	Cuff and collar Micro-cellulose shoe	-	2-7 d	-	-	4-6 wk
Omar[109]	Common extensor (elbow) Plantar fascia	>13 d	Restricted	-	-		2-7 d	2-7 d	-	Restricted	>6 wk

"Strengthening" indicates any protocol activity beyond range of motion and stretching.
"Return to play" indicates protocol completion of all physical activity restrictions.
"Restricted" indicates protocol reported restriction of medication or task, without specifics on duration.
*Dash (-) indicates topic was not mentioned in protocol.
NSAID, nonsteroidal anti-inflammatory drug; PRP, platelet-rich plasma.

Table 4
Most common timing for various PRP protocol elements

Protocol Element	Articles Mentioning Protocol Element (n, %)	Most Common Restricted Time Frame	Number of Protocols Recommending This Duration/Total Number of Protocols Providing Specific Data on This Protocol Element
Restrictions			
NSAIDs pre-PRP	17 (20%)	7-13 d	10/17
NSAIDs post-PRP	47 (56%)	>13 d	18/24
Weight bearing	10 (12%)	2-7 d	7/10
Orthosis/Crutches*	11 (13%)	>7 d	6/11
Activity limitation	42 (50%)	2-7 d	24/42
Initiation			
Range of motion/ stretching	43 (51%)	2-7 d	16/30
Strengthening	45 (54%)	14-21 d	25/33
Return to play	35 (42%)	4-6 wk	19/35

*For lower limb protocols only.
NSAID, nonsteroidal anti-inflammatory drug; PRP, platelet-rich plasma.

single case of tendon rupture following PRP injection has been reported[93] and this occurred 4 months following injection, raising questions about the causative link between the events. Despite a lack of strong support for a connection between PRP injection and tendon rupture in the literature, we found a high rate of controlled ankle movement (CAM) boot or crutch use following PRP injection to the Achilles tendon.

Postprocedure Mobilization and Exercise Initiation

We found the majority of protocols to specify range of motion exercises starting between 2 to 7 days after PRP injection. Early mobilization after tendon injury is associated with improved outcomes.[89,94] However, it is not clear to what extent a PRP injection should be equated to a new tendon injury. Some authors propose that the injection of PRP converts a chronic, nonhealing tendon injury to an acute injury with improved healing potential, especially when combined with a needle tenotomy.[7] Animal studies support this framework and show significant benefit from early mobilization following PRP injection. For instance, in a rat model of Achilles tendinopathy, tendons unloaded by botulinum toxin injection into the calf muscles demonstrated no benefit from PRP injection, whereas tendons subjected to normal activity demonstrated an independent beneficial effect from PRP.[95] Exposure to PRP may improve the early callus properties in the injured tendon so fibroblasts can respond to mechanical loading at an earlier time point.[96] The ideal timing for early mobilization in humans has yet to be determined.

Best practices suggest that once a tendon is relatively pain free at rest, a loading program should be initiated to promote tendon healing.[97-99] Although eccentric loading is the most common type of strengthening used, isometric, concentric, and graduated programs have also been described.[100] However, there is no clear consensus on when to initiate loading after PRP injection. Based on the current review, the majority of studies did not start strengthening exercises until at least 2 weeks after injection.

NSAID Use

The majority of protocols (80%) reviewed did not limit preinjection NSAID use; however, 56% of protocols studied restricted NSAID use post-PRP injection, most commonly for at least 2 weeks. NSAIDs can impair platelet function by inhibiting the function of both COX-1 and COX-2 pathways, which forms the rationale for limiting NSAID use prior to PRP preparation. A number of investigations have demonstrated decreased platelet activation and aggregation following NSAID use both in animal models[101] and humans.[102] This inhibitory effect appears to be decreased with the use of COX-2 selective NSAIDs.[103] The daily use of aspirin prior to PRP preparation also affects the resultant PRP, and leads to a reduction in vascular endothelial growth factor, platelet-derived growth factor-AB, and transforming growth factor-β1.[104]

Arguments exist to limit NSAIDs following PRP administration as well. In a murine model of Achilles tendinopathy, administration of ibuprofen during the inflammatory stage of healing interfered with extracellular matrix remodeling and ultimately led to decreased tensile strength in the healed tendon.[105] Similar results, including abnormal fiber organization and decreased tensile strength, were seen in a rat model of tendinopathy where ibuprofen was delivered in the first week after injury. However, when delivered after 1 week following injury, no detrimental effects were seen, suggesting that NSAIDs interfere in tendon healing in a time dependent manner, most pronounced in the early, inflammatory phase of healing.[106]

The effects of NSAIDs in human tendinopathy are less clear. In chronic Achilles tendinosis, ibuprofen did not affect the expression of collagen by fibroblasts but did decrease DNA synthesis during the proliferative phase of healing.[14] The effect of NSAIDs on human tendon tissue, when given during the inflammatory phase following injury, remains unknown.

Taken together, these results from both animal and human studies form a reasonable rationale to limit NSAIDs both prior to PRP preparation and during the early period following PRP administration.

Limitations

The heterogeneity of protocols described following PRP administration limited our ability to correlate clinical outcomes with particular elements of the protocols. Studies were included regardless of their outcomes after

PRP injection. We also did not stratify outcomes based on specifics of PRP preparation including leukocyte count, inclusion of red blood cells, platelet concentration, number of injections, type of PRP kit, or PRP injection protocol, as this was outside of the scope of this article.

Conclusions

This review reveals some consensus in recommendations in the post-PRP injection period among the protocols studied, although the rationale for these recommendations is limited. The most common time period of relative rest after injection was 2 to 7 days, after which a stretching and range of motion program was typically initiated. Strengthening exercises were most commonly recommended to start at 2 weeks post-injection, with full return to play often was recommended at 4-6 weeks after the injection. Although restriction of NSAIDs was common for 2 weeks after the injection, less consensus exists for NSAID restriction prior to PRP injection. Bracing, orthoses, and weight-bearing restrictions were used uncommonly in the articles reviewed, with little consensus as to an appropriate time period. To the authors' knowledge, no literature currently exists comparing post-PRP protocols. This review may help to form the basis for a future trial comparing different protocols.

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Disclosure

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