Platelet-Rich Plasma in Patients With Partial-Thickness Rotator Cuff Tears or Tendinopathy Leads to Significantly Improved Short-Term Pain Relief and Function Compared With Corticosteroid Injection: A Double-Blind Randomized Controlled Trial

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Purpose: To perform a randomized controlled trial comparing platelet-rich plasma (PRP) with standard corticosteroid (CS) injection in providing pain relief and improved function in patients with rotator cuff tendinopathy and partial-thickness rotator cuff tears (PTRCTs). **Methods:** This double-blind randomized controlled trial enrolled patients with ultrasound-proven or magnetic resonance imaging–proven PTRCTs who received either an ultrasound-guided PRP or CS injection. Patients completed patient-reported outcome assessments at baseline and at 6 weeks, 3 months, and 12 months after injection. The primary outcome was improvement in the visual analog scale (VAS) score for pain. Secondary outcomes included changes in American Shoulder and Elbow Surgeons (ASES) and Western Ontario Rotator Cuff Index (WORC) scores. Treatment failure was defined as subsequent injection, consent to undergo surgery, or operative intervention. **Results:** We followed up 99 patients (47 in the PRP group and 52 in the CS group) until 12 months after injection. There were no differences in baseline patient demographic characteristics including age, sex, or duration of symptoms. Despite randomization, patients in the PRP group had worse baseline VAS (46.0 vs 34.7, $P = .01$), ASES (53.9 vs 61.8, $P = .02$), and WORC (42.2 vs 49.5, $P = .03$) scores. At 3 months after injection, the PRP group had superior improvement in VAS (−13.6 vs 0.4, $P = .03$), ASES (13.0 vs 2.9, $P = .02$), and WORC (16.8 vs 5.8, $P = .03$) scores. There were no differences in patient-reported outcomes at 6 weeks or 12 months. There was no difference in the rate of failure ($P = .31$) or conversion to surgery ($P = .83$) between groups. **Conclusions:** Patients with PTRCTs or tendinopathy experienced clinical improvement in pain and patient-reported outcome scores after both ultrasound-guided CS and PRP injections. Patients who received PRP obtained superior improvement in pain and function at short-term follow-up (3 months). There was no sustained benefit of PRP over CS at longer-term follow-up (12 months). **Level of Evidence:** Level I, randomized controlled trial.

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Rotator cuff pathology is ubiquitous in the general population and encompasses a wide spectrum of disease ranging from early tendinosis to cuff tear arthropathy. Although the surgical treatment of full-thickness tears has yielded excellent results in the literature,[1] several factors contribute to the success or failure of such treatment, and debate persists regarding the quality and integrity of tendon healing after surgical repair.[2,3] When considering this controversy and a proportionally higher prevalence of partial-thickness tears,[4] attention has been drawn to addressing early disease in an effort to slow progression and/or promote healing.

First-line treatment of early rotator cuff disease may consist of activity modification, stretching and strengthening exercises, oral anti-inflammatory medications, and/or corticosteroid (CS) injections.[1] CS injections are often used as an inexpensive and effective treatment to reduce pain and improve motion in all stages of rotator cuff disease. Despite common use and reported success,[5] the mechanism of action of CSs may only be of symptomatic benefit and may not address tendon pathology or promote healing. When considering the degenerative pathology of rotator cuff disease, much study has been devoted to discovering new nonoperative treatments to promote tendon biology.

Several biological treatments have been trialed as either isolated therapies or augmentations in both nonoperative and operative settings. One of the most commonly used injectable biological agents is platelet-rich plasma (PRP).[6] Such injections have been found to increase the local concentrations of platelets and growth factors, including platelet-derived growth factor, vascular endothelial growth factor, transforming growth factor β, and epidermal growth factor, which have been implicated as important factors in the early healing process.[7] PRP injections have shown promising results in the treatment of lateral epicondylitis, knee osteoarthritis, and shoulder disorders,[8-11] including in early intervention for rotator cuff disease and in the setting of surgical repair.[12,13] However, the true benefit of PRP injections remains controversial.

Rotator cuff tendinopathy and partial-thickness rotator cuff tears (PTRCTs) are treated similarly and have been investigated together to assess the efficacy of nonoperative interventions. Several small cohort studies and randomized controlled trials have examined the clinical benefit of PRP to treat both PTRCTs and tendinopathy; however, their results have been confounded by small numbers, variable reporting or under-reporting of PRP preparations, and short-term follow-up.[14-17] A recent meta-analysis suggested that additional high-quality randomized controlled trials were needed to further investigate the benefits of PRP in early rotator cuff disease.[18]

The purpose of this study was to perform a randomized controlled trial comparing PRP with standard CS injection in providing pain relief and improved function in patients with rotator cuff tendinopathy and PTRCTs. We hypothesized that PRP would provide improved pain relief and function in patients with PTRCTs when compared with the standard treatment of CS injection.

Methods

Patients

Eligible patients were aged 18 years or older and had magnetic resonance imaging or ultrasound (US) tendinopathy or PTRCTs involving the supraspinatus tendon at the time of screening. Patients must have been symptomatic for a minimum of 3 months, and an adequate course of nonoperative treatment including, but not limited to, home or outpatient physical therapy, oral analgesics, and/or shoulder injections must have been exhausted. Patients who had not completed a course of physical therapy prior to presentation were provided with a detailed home exercise program previously described by Boorman et al.[19]

Patients were excluded if they had undergone prior surgical intervention on the affected shoulder or had a full-thickness rotator cuff tear, concomitant ipsilateral shoulder pathology (i.e., osteoarthritis or inflammatory arthritis) on initial imaging, or confounding cervical neck pain or radiculopathy. A maximum of 3 previous CS injections were permitted, with none in the 6 months prior to the study intervention. Elite-level athletes, Workers' Compensation patients, and patients with associated litigation or secondary-gain issues were excluded. Patients unwilling or unable to provide informed consent or complete patient-reported outcome measures were also excluded.

Study Design, Randomization, and Blinding

This study was a single-center, double-blind randomized controlled trial. On inclusion, patients were randomized to either CS or PRP injection. Block randomization was used to ensure that the groups remained relatively equal over time. Group allocation was assigned sequentially by study number from a sealed envelope that the radiologist opened immediately after the pre-injection US and confirmation of the patient's eligibility. Both the treating surgeon and patient were blinded to the intervention. All patients had venous blood drawn prior to injection and received injections by a similar method to obviate the effects of needling in the PRP group. All injections were performed under US guidance by 1 of 2 musculoskeletal radiologists who were unblinded to the intervention.

Intervention

Prior to final inclusion and on the same day as the intended intervention, patients underwent a repeated US of the rotator cuff to confirm the diagnosis of tendinopathy or PTRCT. If the tear had progressed to a full-thickness tear from the time of initial screening, the patient was excluded from randomization and analysis. Confirmed PTRCTs were described based on location as either tendinopathy, articular, intrasubstance, bursal, combination, or indeterminate on the basis of the US findings. In both patient groups, approximately 10 mL of venous blood was drawn with a similar time delay for centrifugation prior to injection.

For patients in the CS group, the blood sample was discarded and 1 mL of 40-mg/mL triamcinolone was suspended in 2 mL of 0.5% bupivacaine. Injection was performed through a lateral subacromial approach after needle fenestration of the supraspinatus tendon under US visualization. CS was infiltrated into the subacromial bursa and not the tendon itself. In the PRP group, patients received an injection with a volume of 3 to 5 mL at the site of tendon pathology, with the remainder of the PRP preparation infiltrated into the subacromial space, under US guidance. Patients were informed about possible adverse reactions to both injections. Patients were permitted to proceed with activity as tolerated after injection and were encouraged to continue with a home exercise program.

PRP Preparation

In the PRP group, a leukocyte-poor preparation was used from a pre-packaged kit (RegenLab, Lausanne, Switzerland). The samples were centrifuged at 1,500*g* for 5 minutes to yield approximately 5.5 mL of 80% platelets at 1.6× concentration. The manufacturer has reported filtration rates of 99.7%, 87% to 89%, 70% to 75%, and 96.5% of red blood cells, white blood cells, mononuclear cells, and granulocytes, respectively. The supernatant was then resuspended by inverting the tube several times and was drawn into a separate 5-mL syringe for subacromial injection.

Outcomes

The primary outcome was the visual analog scale (VAS) score for pain at 6 weeks, 3 months, and 12 months. Secondary patient-reported outcomes included the American Shoulder and Elbow Surgeons (ASES) shoulder score and the Western Ontario Rotator Cuff Index (WORC) score, which were collected at the same time points. Outcome scores were measured as the change from the baseline score. Failure rates were calculated, with failure defined as one of the following: (1) a patient requesting a subsequent shoulder injection, (2) signing a surgical consent form, or (3) undergoing surgery. Post-injection US was completed at 3 and 12 months to assess for progression to a full-thickness rotator cuff tear.

Statistical Analysis

This study was powered to 80% ($\beta = .20$) to detect the minimal clinically important difference (MCID) in the primary outcome of VAS pain score. The MCID has been previously described in the setting of rotator cuff disease as 1.4 cm with a standard deviation of 2.41 cm on a 10-cm scale for pain in the dominant shoulder.[20] By use of these parameters in a superiority formula, a sample size of 49 patients per group was calculated, for a total of 98 patients.

Baseline patient characteristics were summarized and compared between groups using a cross-tabulation analysis; tear classification was analyzed using the Fisher exact test. Final outcome data were analyzed as the change in outcome scores from baseline using independent-samples *t* tests assuming equal variance. Failure rates were analyzed using cross-tabulation analysis by group on surgical consent, actual surgery, and request for repeated injection. An independent-samples *t* test was performed to determine any difference in failure rates between the 2 groups. This study was approved by the Conjoint Health Research Ethics Board at the University of Calgary (REB14-0570).

Results

Demographic Characteristics

We assessed 382 patients for study eligibility. Ultimately, 104 patients were randomized and received either PRP or CS injections. A total of 5 patients, 3 in the PRP group and 2 in the CS group, were excluded after randomization (Fig 1). All remaining data were included for analysis. There was no difference between the 2 groups in age, sex, tear etiology, or duration of symptoms (Table 1). Tear types were classified as either tendinopathy, articular sided, intrasubstance, or bursal sided or as a combination thereof and showed no difference between the 2 groups ($P = .55$) (Table 2).

Pain

Despite randomization, there was a statistically significant difference in baseline pain scores between groups, with the PRP group having more pain prior to intervention ($P = .01$) (Table 3). Overall, patients reported pain improvement from baseline at all time points after both interventions, with the exception of 3

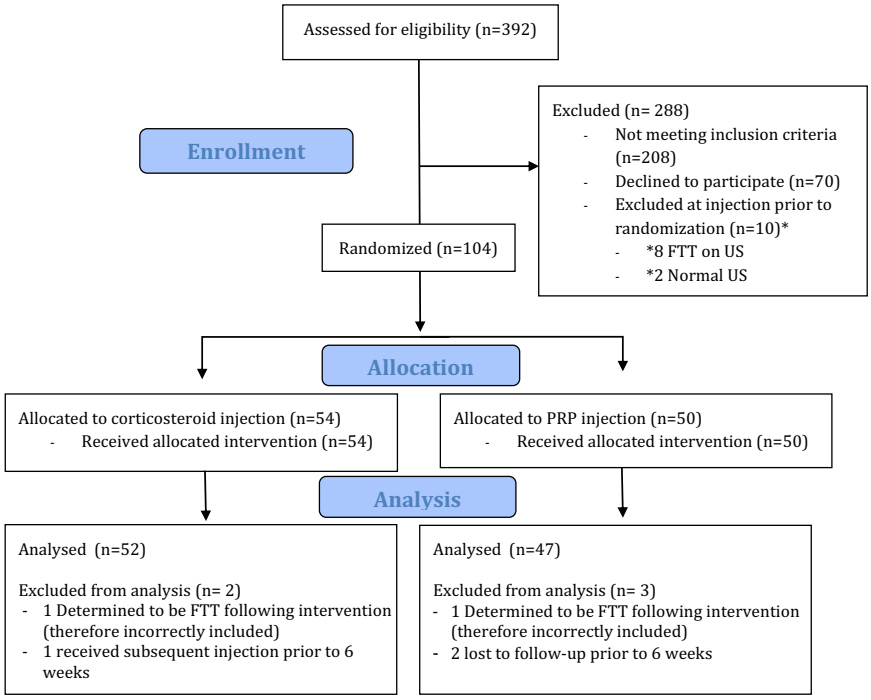

Fig 1. Consolidated Standards of Reporting Trials (CONSORT) flowchart. (FTT, full-thickness tear; PRP, platelet-rich plasma; US, ultrasound.)

months after CS injection (Fig 2A). At 3 months, there was a significant difference in pain reduction favoring PRP over CS injections ($P = .02$). No difference in pain reduction was detected between the 2 groups at any other time point (Table 3). The MCID for pain (1.4 cm or 14/100) was achieved at 12 months after injection in the PRP group; however, it was not achieved at any time point in the CS group.

Secondary Patient-Reported Outcomes

The baseline ASES and WORC scores were significantly worse in the PRP group than in the CS group. After injection, the ASES and WORC scores showed statistically significant differences at 3 months favoring PRP over CS injection (Table 3). There were overall improvements in ASES and WORC scores from baseline at all time points for both interventions (Fig 2 B and C). The MCID for the ASES score (6.4) was reached at all time points in both groups, with the exception of 3 months in the CS group.[21] For the WORC score, the MCID of 11.7 was similarly reached at all time points in both groups, with the exception of 3 months after injection in the CS group.[22]

Failure

The overall failure rate within 12 months of injection was 28.3%. The PRP and CS groups had failure rates of 23.4% and 32.6%, respectively ($P = .31$). There was no statistically significant difference in failure—defined by a patient requesting a subsequent injection, consenting to undergo surgery, or actually undergoing surgery—between groups. Twenty-three patients underwent surgical intervention after injection, for failure rates of 23.4% and 23.1% in the PRP and CS groups, respectively ($P = .83$) (Table 4). No adverse events were reported in either group.

Table 1. Patient Demographic Characteristics

Parameter	PRP Group	CS Group	*P* Value
Age, mean (SD), yr	49.94 (9.70)	49.08 (9.54)	.66
Sex: F/M, n	31/16	33/19	.80
Dominant hand, n	3	27	.24
Tear etiology, n			
Degenerative	34	39	
Traumatic	12	13	.90
Duration of symptoms, mean (SD), yr	33.69 (77.11)	24.82 (26.52)	.44
Total, n	47	52	

CS, corticosteroid; F, female; M, male; PRP, platelet-rich plasma; SD, standard deviation.

Table 2. Tear Types (Supraspinatus Tendon) Between Groups

	PRP Group, n (%)	CS Group, n (%)	*P* value
Tear type			.55
Tendinopathy	5 (11)	9 (17)	
Articular sided	11 (23)	12 (23)	
Intrasubstance	3 (6)	3 (6)	
Bursal sided	1 (2)	2 (4)	
Combination	24 (51)	26 (50)	
Indeterminate	3 (6)	0	
Total	47 (100)	52 (100)	

CS, corticosteroid; PRP, platelet-rich plasma.

Table 3. Baseline Outcome Scores and Changes in Outcome Scores at Each Time Point

	Baseline		6 wk		3 mo		12 mo	
	Mean (SD)	*P* Value	Mean (SD)	*P* Value	Mean (SD)	*P* Value	Mean (SD)	*P* Value
VAS score								
PRP group	46.0 (21.6)		−13.9 (25)		−13.6 (24.4)		−21.6 (24.4)	
CS group	34.7 (22.3)	.01*	−12.0 (25)	.70	0.4 (27.9)	.03*	−10.5 (26.2)	.07
ASES score								
PRP group	53.9 (15.8)		13.2 (19.3)		13.0 (18.7)		19.2 (19.4)	
CS group	61.8 (17.2)	.02*	14.1 (17.9)	.82	2.9 (22.5)	.02*	11.9 (23.3)	.15
WORC score								
PRP group	42.2 (15.6)		14.6 (19.6)		16.8 (19.0)		22.3 (25.2)	
CS group	49.5 (17.2)	.03*	20.0 (21.9)	.22	5.8 (25.1)	.03*	15.1 (21.8)	.19

ASES, American Shoulder and Elbow Surgeons; CS, corticosteroid; PRP, platelet-rich plasma; SD, standard deviation; VAS, visual analog scale; WORC, Western Ontario Rotator Cuff Index.
*Significant difference ($P < .05$).

Repeated US

Follow-up US was available at 3 months in 98 of 99 patients (unavailable in 1 patient in the CS group). Eighty-five percent of patients in each group were re-evaluated by US at 12 months after injection to assess for tear progression. At 3 months, progression to a full-thickness rotator cuff tear had occurred in 1 patient in the PRP group and 2 patients in the CS group, for tear progression rates of 2% and 4%, respectively. At 12 months, progression to a full-thickness tear had occurred in 2 (4%) and 3 (6%) additional patients in the PRP and CS groups, respectively.

Discussion

The findings of this study show that patients receiving either a US-guided CS or PRP injection for a PTRCT or tendinopathy experienced decreased shoulder pain and improved ASES and WORC outcome scores. When CS and PRP injections were directly compared, patients in the PRP group experienced statistically superior results at 3 months in all patient-reported outcomes. However, the benefit of PRP over CS injections did not persist at 12 months. Both groups experienced improvements in ASES and WORC scores throughout the course of the study.

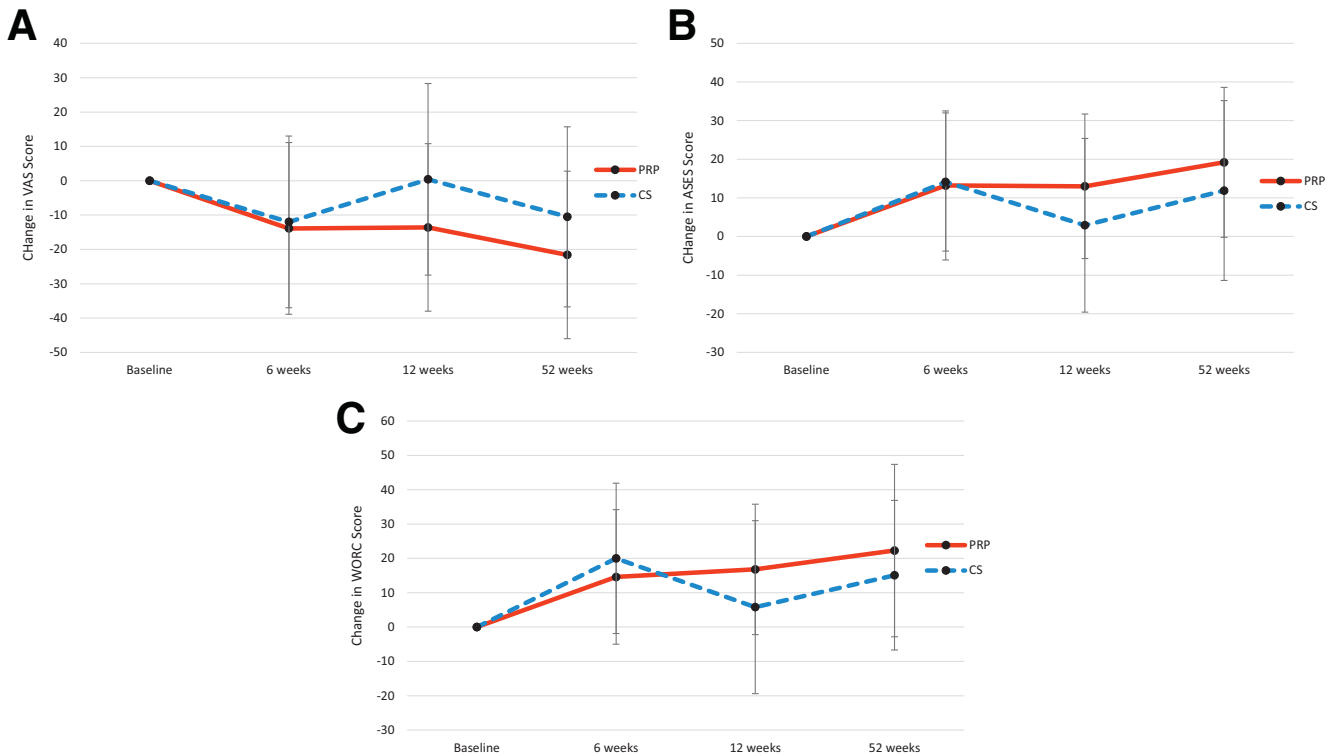

Fig 2. Change in baseline scores in platelet-rich plasma (PRP) group versus corticosteroid (CS) group. (A) Visual analog scale (VAS) score. (B) American Shoulder and Elbow Surgeons (ASES) score. (C) Western Ontario Rotator Cuff Index (WORC) score. Error bars show standard deviations.

Table 4. Post-injection Treatment Failure Rates

	PRP Group, %	CS Group, %	*P* Value
Failure	23.4	32.6	.31
Surgery	23.4	23.1	.83

NOTE. Failure was defined as requesting a subsequent injection, consenting to undergo surgery, or actually undergoing surgery prior to 12 months.

CS, corticosteroid; PRP, platelet-rich plasma.

Recently, Hurley et al.[18] performed a systematic review of all randomized controlled trials examining PRP as a treatment for PTRCTs. Treatment in the control groups varied from a saline solution injection, dry needling, or CS injection to an exercise program. Overall, Hurley et al. concluded that PRP injections may not be effective at providing short-term improvements in patients with PTRCTs; however, limitations in this review included the lack of reporting of PRP preparations and the high risk of bias in the studies included. The findings of the only included study comparing PRP directly with CS were consistent with the results of our study and revealed statistically better VAS, ASES, Simple Shoulder Test, and Constant scores in the PRP group at 3 months; however, the differences between groups did not persist at 6 months.[17] Our study is also consistent with existing literature when considering the CS control group alone. A 2017 meta-analysis by Mohamadi et al.[12] investigated the effect of CS injection in patients with rotator cuff tendinosis and found that although there were slight improvements in pain compared with placebo up to 2 months after injection, there was no difference at 3 months. Thus, we consider the sustained benefits of PRP over CS at 3 months after injection to be an important finding of our study.

CS injections have been used widely as a nonoperative treatment modality for a variety of shoulder disorders. Several studies have shown the efficacy of CS injections in providing short-term relief in patients with subacromial impingement syndrome and PTRCTs.[12,23] However, recent literature has called into question the safety of CS injections and described possible deleterious effects.[24] Several animal models have shown decreased rotator cuff tendon quality after CS injection,[25-27] whereas some human studies have reported higher revision rates after CS injection.[28,29] Weber et al.[29] performed a large database study examining revision rates in patients undergoing rotator cuff repair with and without preceding CS injection. On the basis of their large retrospective review, they concluded that preoperative CS injection was strongly correlated with increased rates of revision rotator cuff repair. Despite these potential risks, CS is still commonly used in practice as clinicians search for more effective nonoperative treatment modalities. With few reports of adverse effects after PRP injection in the literature,[30] it has become an attractive option for circumventing the potential risks of CS. No new cases of significant adverse events related to PRP or CS were reported in this study.

Such a course of formal or home-based physical therapy had previously failed in all patients, this study did not institute a supervised rehabilitation program after intervention. However, patients were encouraged to independently continue a home exercise program. Previous studies have shown physical therapy to be an effective and beneficial tenet of nonoperative treatment.[31-34] Although optimal management of rotator cuff pathology is undoubtedly a multimodal approach, the focus of this study was to investigate the effects of PRP versus CS. By not restricting or enforcing participation in physical therapy, we believe that the results of this study are more generalizable to standard clinical practice.

A criticism common to all studies examining the effects of PRP pertains to the variability of its preparation. Our study used a leukocyte-poor PRP preparation that was in use at our institution at the time of study design. Some authors have speculated that a leukocyte-rich preparation with a higher platelet concentration is favorable in the setting of tendinopathy to promote a better healing response.[35] In contrast, other authors have cautioned against the increased catabolic effects incited by leukocytes and have recommended leukocyte-poor preparations.[36-38] Currently, there is no conclusive evidence supporting the superiority of leukocyte-poor over leukocyte-rich PRP in the clinical setting.[39] Because our study did not include a leukocyte-rich PRP treatment group, we were unable to provide further insight as to the ideal leukocyte profile or specific PRP concentration.

This study has several important strengths. First, its experimental design was a double-blind randomized controlled trial with a large sample size. Second, all injections were performed under US guidance by 1 of 2 experienced musculoskeletal radiologists. Third, strict inclusion criteria were used based on time-zero US to include only patients with tendinopathy and PTRCTs. Finally, the 12-month follow-up period is as long as or longer than the periods in previously performed randomized trials in the literature.[18,40]

Limitations

This study was subject to several limitations that should be considered in the interpretation of these results. Despite randomization, there were significant differences in the baseline outcome scores in the PRP group compared with the CS group, which could have confounded the study results. When examining these differences, we noted that overall, the PRP group started with more pain and worse patient-reported outcome scores than the CS group. Although this

does introduce heterogeneity into the 2 groups, it is noted that the PRP group achieved better improvements at 3 months and similar overall outcome scores even in the context of worse baseline rotator cuff symptoms.

In addition, we were unable to report detailed radiographic follow-up on tendon quality after injection. The data obtained from repeated US were only sufficient to categorize tears as partial or full thickness owing to the inherent limitation of US in its ability to assess small changes in tear size in the setting of PTRCTs.[41]

Finally, it would have been ideal to include a control group that received a saline solution injection alone because previous studies have shown clinical improvement after such injections.[14] However, owing to the chronicity of patient symptoms, the 12-month follow-up period expected from study participants, and the standard practice of CS injections at our institution, we believed that the proposition of a placebo group (i.e., saline solution) would have negatively affected patient recruitment.

Conclusions

Patients with PTRCTs or tendinopathy experienced clinical improvement in pain and patient-reported outcome scores after both US-guided CS and PRP injections. Patients who received PRP obtained superior improvement in pain and function at short-term follow-up (3 months). There was no sustained benefit of PRP over CS at longer-term follow-up (12 months).

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