Platelet-Rich Plasma for Patellar Tendinopathy

A Randomized Controlled Trial of Leukocyte-Rich PRP or Leukocyte-Poor PRP Versus Saline

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Background: A small number of randomized controlled trials have found ultrasound-guided injection of platelet-rich plasma (PRP) to be no more effective than saline for several tendinopathies; limited information exists for patellar tendinopathy. In addition, different PRP formulations that produce varying concentrations of leukocytes have not been directly compared for patellar tendinopathy.

Purpose/Hypothesis: To determine if a single ultrasound-guided PRP injection, either leukocyte-rich PRP (LR-PRP) or leukocyte-poor PRP (LP-PRP), was superior to saline injection for the treatment of patellar tendinopathy. The null hypothesis was that no treatment would be superior to another for the treatment of patellar tendinopathy.

Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: Athletes with patellar tendinopathy for ≥6 months (Blazina stage IIIB) were assessed for eligibility in a multisite single-blind controlled trial. There were 3 injection arms: LR-PRP, LP-PRP, and saline. Patients received a single ultrasound-guided injection, followed by 6 weeks of supervised rehabilitation (heavy slow resistance training, concentric and eccentric, 3 times per week). Outcome measures—Victorian Institute of Sport Assessment (patellar; VISA-P), pain during activity, and global rating of change—were assessed at 6 and 12 weeks and 6 and 12 months. VISA-P score at 12 weeks was the primary outcome. Fifty-seven patients (19 in each group) were included in an intention-to-treat analysis. Secondary outcome measures included pain during activity and patients' global rating of change.

Results: Study retention was 93% at 12 weeks and 79% after 1 year. There was no significant difference in mean change in VISA-P score, pain, or global rating of change among the 3 treatment groups at 12 weeks or any other time point. After 1 year, the mean (SD) outcomes for the LR-PRP, LP-PRP, and saline groups were as follows, respectively: VISA-P—58 (29), 71 (20), and 80 (18); pain—4.0 (2.4), 2.4 (2.3), and 2.0 (1.9); global rating of change—4.7 (1.6), 5.6 (1.0), and 5.7 (1.2) (P > .05 for all outcomes).

Conclusion: Combined with an exercise-based rehabilitation program, a single injection of LR-PRP or LP-PRP was no more effective than saline for the improvement of patellar tendinopathy symptoms.

Registration: NCT02116946 (ClinicalTrials.gov identifier).

Keywords: knee; patellar tendon; platelet-rich plasma; musculoskeletal; rehabilitation; injection; pain

The patellar tendon is a common location of pain among athletes who engage in repetitive forceful loading of the extensor apparatus, particularly those with a high volume of training (eg, >20 hours per week). Pain that is localized to the patellar tendon, exacerbated by tendon loading, and associated with reduced function is known as patellar tendinopathy. Patellar tendinopathy is frequently accompanied by imaging changes, such as tendon thickening, increased blood flow, and signal intensity changes, although these also occur among asymptomatic athletes.
The prevalence of patellar tendinopathy has been reported to be highest among sports involving jumping, such as volleyball (44%) and basketball (32%). The prevalence has been reported as 28% among elite track and field athletes. The condition results in substantial pain and reduced performance in sports and activities of daily living. The majority of patients report persistent pain and disability, with some experiencing long-term, career-ending symptoms. Current state-of-the-art treatment emphasizes exercise, load management, and biomechanical interventions with eventual referral to surgery for severe long-standing cases. Placebo-controlled studies have not consistently demonstrated a clear benefit of noninvasive treatments for patellar tendinopathy, such as shockwave, ultrasound, patellar straps, or topical glyceryl trinitrate. Ultrasound-guided injections of corticosteroids and polidocanol have been reported to be superior to placebo, yet both strategies leave a substantial number of patients with persisting symptoms. An alternative approach that has attracted some attention in recent years is the injection of autologous platelet-rich plasma (PRP) at the site of the lesion under ultrasound guidance. Depending on the centrifugation protocol, leukocyte-rich PRP (LR-PRP) and leukocyte-poor PRP (LP-PRP) preparations may result and laboratory studies suggest that LR-PRP induces a greater short-term inflammatory and fibrotic response than LP-PRP. Dragoo et al suggested that “the inclusion of the WBC [white blood cell] fraction in PRP preparations may increase GF [growth factor] yield but may also lead to increased inflammation and possibly a delayed healing response.” Many centers administer a single PRP injection for patellar tendinopathy, although other centers may provide multiple injections.

In 2010, the International Olympic Commission medical committee suggested that while PRP is not likely to be harmful, its efficacy should be established with robust clinical trials. Since that time, several randomized controlled trials have not demonstrated any difference in outcomes between those treated with single PRP injections and saline for Achilles, elbow, and shoulder tendinopathy. Currently, there is limited information for the patellar tendon. Therefore, the purpose of this study was to determine if a single PRP injection, either LR-PRP or LP-PRP, is superior to saline for the treatment of patellar tendinopathy.

METHODS

Study Design

We conducted a parallel randomized single-blind saline-controlled study at 3 sites: the University of Washington Sports Medicine Center (Seattle, United States), the Olympiatoppen (Oslo, Norway), and the Rizzoli Orthopaedic Institute (Bologna, Italy). Patients were recruited primarily through local caseloads, supplemented by advertising the study through local contact networks at each medical center. All patients provided written informed consent. The study was approved by the local ethics committees of all recruiting centers. The trial was registered at clinicaltrials.gov (NCT02116946).

Changes to Study Design After Commencement

The study was designed as a double-blind study, with masking of the care providers. However, it was evident that providers were unblinded during the ultrasound-guided injection procedure, so we changed it to a single-blind study.

Patients

All patients were between 18 and 50 years old and were diagnosed by the physician investigators using standard diagnostic criteria: history of exercise-related pain located at the proximal part of the patellar tendon or its patellar...
insertion, tenderness to palpation of the tendon substance, and a positive result from an ultrasound scan performed by the treating physician investigator (fusiform swelling and/or hypoechoic areas). Symptoms had to be present for at least 6 months, and patients had to have already attempted to resolve their conditions with exercise-based rehabilitation for a minimum of 6 weeks. Patients were excluded if they had a history of knee or patellar tendon surgery or any inflammatory or prominent degenerative joint condition affecting the knee (i.e., physical examination and history suggestive of osteoarthritis or chondral lesions). Patients with bilateral patellar tendinopathy were not excluded; the most symptomatic knee was used in the analysis. Patients had to have normal hematology results (red blood cell, platelet, and WBC counts), as determined by the local laboratory at each site with its equipment (Hematology Analyzer Coulter LH 750, Beckman Coulter; pocHi-100i Hematology Analyzer, Sysmex).

Randomization and Enrollment

After clinical assessment of the eligibility criteria (with the exception of ultrasound scan), the baseline information was entered into a custom online database (Tenalea; FormsVision). After the patient was registered, an allocation code was automatically generated (saline, LR-PRP, or LP-PRP). Randomization was performed using an automatic system (Tenalea in balanced blocks of 6 (1:1:1 ratio), stratified by age (18-34 and 36-50 years) and site. The participants were enrolled in and allocated to their treatment groups by the study coordinator at each treatment site independent of the authors.

Blinding

Allocation was concealed from each patient (single-blind) and physical therapist by referring to the treatment via a letter (A, B, or C). The study coordinator at each site knew the groups to which participants were allocated and coordinated with the laboratory to prepare the PRP and saline in opaque syringes. However, the blinding of PRP versus saline was not successful, and some of the physicians may have become unblinded. We conducted an exit questionnaire with patients to assess the success of blinding by asking them to state which treatment group they thought they were assigned to and how confident they felt about their answer. The physical therapists were not told about the participants’ allocations.

PRP Preparation and Characterization and Similarity of Interventions

PRP was prepared on-site by local laboratory technicians with the Angel Cytomedix system (ABS-10060; Arthrex) with 2% and 15% hematocrit settings to produce LP-PRP and LR-PRP, respectively. Venous blood (52 mL) was drawn, added to 8 mL of anticoagulant citrate dextrose solution–solution A, and then run through the collection system. At 1 study site (University of Washington), an aliquot of the PRP was sent for hematological analysis by the local laboratory to determine the platelet and WBC counts (n = 6, LR-PRP; n = 6, LP-PRP). The results of this analysis showed that before centrifugation, the platelet counts—reported here as mean (SD) of 6 samples in units of 1000 counts per milliliter—were 230,000 (51,000) and 227,000 (43,000) in the LR-PRP and LP-PRP groups, respectively, and corresponding WBC counts before centrifugation were 6700 (1900) and 6100 (1500). After centrifugation, the platelet concentration was significantly increased in both PRP preparations: the mean fold change in platelets was 3.8 for LR-PRP and 3.0 for LP-PRP, with a range of 2.3 to 6.1. The fold change in WBCs was significantly different for the 2 types of PRP (Welch t test, P = .017) with a fold change of 1.3 (0.6) for LR-PRP and 0.6 (0.2) for LP-PRP. The same volume of PRP and saline (3.5 mL) was used to control for mechanical effects of the injected fluid, and patients assigned to saline also had blood withdrawn (then discarded) to maintain participant blinding.

Interventions

Patients were positioned supine with the knee slightly flexed. The area was steriley prepared, and 2 mL of lidocaine without epinephrine was injected into the soft tissues around the patellar tendon. The patellar tendon defect was identified with ultrasound and a 22-gauge needle placed directly adjacent to the defect. After injection of up to 3.5 mL of PRP or saline, the patient lay quietly with the knee extended for 15 minutes. Ice was applied for pain as desired by the patient. For 48 hours after injection, patients were instructed to refrain from exercise. After 1 week, rehabilitation began. All patients engaged in a supervised gym-based rehabilitation program based on the slow heavy loading program (concentric and eccentric) described by Kongsgaard et al. They trained in the rehabilitation facility 3 times per week for 6 weeks. At least 1 session per week was directly supervised by a physical therapist.

Outcome Measures

The primary outcome was change in Victorian Institute of Sport Assessment (patellar; VISA-P) score at 12 weeks. The VISA-P is a patient-rated outcome measure of patellar tendinopathy severity that captures pain and limitation with activity and sports. We also used a numeric pain rating scale from 0 to 10, with 0 being no pain and 10 being the worst pain imaginable, asking for a rating of the mean pain with activity over the past week. The patients’ perception of change was assessed with a 7-point Likert scale for global rating of change, from “very much improved” to “very much worse,” with the middle score representing “no change.” All outcomes were scored independently by the participant, either written or online. At the 12-week and 1-year follow-up, we asked patients about any other medications and treatments that they had pursued and any adverse effects experienced. In our initial protocol, we had the primary endpoint as 6 months, but this changed before the start of the trial to 12 weeks, to coincide
with the end of the intervention period. There were no changes to trial outcomes after the start of the trial.

Sample Size Calculation

For a patient undergoing physical therapy, the minimum clinically important difference has been estimated as a 13-point VISA-P improvement, or a 14% to 27% relative improvement depending on the starting score. We hypothesized that after 12 weeks, the difference in mean VISA-P score between LR-PRP and the other 2 groups would be at least 15 points, with an SD of approximately 15. A sample size calculation for a post hoc $t$ test between groups at 12 weeks (power, 0.80; alpha, .05) yielded a required sample size of 16 per group. We exceeded this sample size to minimize loss of statistical power from dropouts (Figure 1).

Statistical Analysis

Data are presented to 2 significant figures with the SDs in parentheses. Welch $t$ test was used to compare the fold change in platelets and WBCs in the LR-PRP and LP-PRP groups.

For the primary and secondary outcome measures, an independent blinded statistical analysis was conducted by a professional statistician. For the 3 main outcome measures (VISA-P, numeric pain rating scale, and global rating of change), linear mixed effect modeling was employed to incorporate the repeated nature of the measurements. For the primary endpoint of VISA-P at 12 weeks, we used a model of $VISA_{12} = \text{intercept} + VISA_{\text{baseline}} + \text{treatment}$. For the secondary outcomes, we used a model of outcome $score_{\text{time}} = \text{patient} + \text{baseline score} + \text{treatment} + \log(\text{time})$. Time was included in the model, as most participants were expected to improve; $\log(\text{time})$ was used because the change in scores appeared large in the short term versus the long term. Models with age as an explanatory variable were also fitted; however, there was no significant effect, and so it was left out of the analysis. Analysis was based on intention to treat, with the exception of 3 participants (1 in each group) who did not receive their allocated intervention (see Figure 1). All available data for all patients who received their
allocated treatment were included in the analysis, regardless of whether their data set was complete. We did not impute or replace any missing values but rather fitted all the available data to the model.

We conducted 2 additional analyses of emergent trends, which were not planned, as follows: we ran a $\chi^2$ test on the proportion of people who experienced a minimal clinically important difference in the VISA-P score at 12 weeks and a Fisher exact test on the proportion of people who experienced a worsening of their symptoms in each group at 6 weeks.

RESULTS

Participants

Recruitment began on March 20, 2014, and was completed on June 28, 2017. The trial ended when the last enrolled patient completed 1-year follow-up on June 28, 2018.

The 3 groups of 19 participants (Figure 1) were demographically and clinically similar (Table 1). The majority of participants in all groups were engaged in recreational sports (basketball, volleyball, soccer, rowing, swimming, running, skiing, tennis, cycling, badminton, weight training, and handball). One patient in the LR-PRP group had received a corticosteroid injection in the tibial tubercle region in the remote past (for Osgood-Schlatter disease). Three patients used nonopioid medications for tendon pain: 2 from the LR-PRP group and 1 from the saline group.

Success of Blinding

Blinding appeared to be successful in concealing the allocation of treatment from the participants. Fifty-six randomized participants received their allocated intervention (1 missing data point). When asked, “Do you know which treatment you received?” 14 did not provide a response; 31 replied “don’t know”; and 5 replied correctly (2 saline, 2 LP-PRP, 1 LR-PRP). Of the 14 who did not provide a response, 6 received LR-PRP, 4 LP-PRP, and 4 saline.

The blinding was not successful in concealing the allocation from the treating physicians. Physicians noted that they could sometimes tell what was being injected given the different appearance on ultrasound, even when the syringes were masked. We did not formally track or count the incidences of unblinding among the physicians, because this was an unexpected occurrence during the study; rather, we simply downgraded the study from double-blind to single-blind.

Missing Data

Most missing data were a result of participants’ leaving the study (ie, all subsequent measurements after a certain time point were missing), yielding a retention rate of 93% at 12 weeks and 79% at 1 year. By 1 year, the number of participants who had left the study were 6 (LR-PRP), 3 (LP-PRP), and 3 (saline). Missing data points also occurred at a particular time point for some participants: 1 at baseline, 2 at 6 weeks, 2 at 12 weeks, and 2 at 24 weeks. For the VISA-P score, the data set was 90% complete over the 1-year follow-up period, and 69% of the missing values were due to participants’ leaving the study. There were 2 instances where 1 outcome measure was missing at a particular time point but the other 2 were available (at baseline and week 24), and there was 1 instance where a single outcome was missing at weeks 24 and 52. The linear modeling did not impute missing values but fitted all available data to the model. All analysis was completed by the original assigned group.

Primary Endpoint: VISA-P at 12 Weeks

The majority (58%) of patients experienced an improvement in VISA-P score from 0 to 12 weeks, regardless of their assigned treatment group and with no significant difference among treatments (Table 2). Of the LR-PRP group,
35% of the participants improved by at least 13 VISA-P points, as opposed to 72% (LP-PRP) and 71% (saline) ($\chi^2$ test, $df = 2, P = .059$, exploratory analysis). The $\chi^2$ analysis was not part of the original statistical plan but was conducted when a possible difference in the proportion of patients improving was observed in the data; however, this difference was not statistically significant.

### Secondary Outcomes

There were no significant differences observed among the treatment groups (Table 2, Figure 2) for VISA-P or any of the other secondary outcomes. A nonsignificant trend for poorer outcomes was noted in the LR-PRP group.

### Side Effects

After 6 weeks, 8 participants rated themselves as worse (global rating of change ≤3): 3 from the LR-PRP group, 5 from the LP-PRP group, and none from the saline group (Fisher exact test, $P_\lambda = .0423$, exploratory analysis). One side effect was recorded by 1 participant in the LP-PRP group: localized patellar tendon pain that prevented participation in the rehabilitation program after the injection.

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**Table 2**

Secondary Outcome Measures of Patients Treated for Patellar Tendinopathy

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 wk</th>
<th>12 wk</th>
<th>24 wk</th>
<th>52 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>VISA-P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LR-PRP</td>
<td>49 (16)</td>
<td>55 (22)</td>
<td>63 (22)</td>
<td>58 (22)</td>
<td>58 (29)</td>
</tr>
<tr>
<td>LP-PRP</td>
<td>45 (18)</td>
<td>57 (24)</td>
<td>67 (21)</td>
<td>71 (19)</td>
<td>71 (20)</td>
</tr>
<tr>
<td>Saline</td>
<td>49 (14)</td>
<td>63 (19)</td>
<td>69 (18)</td>
<td>74 (18)</td>
<td>80 (18)</td>
</tr>
<tr>
<td>NPRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LR-PRP</td>
<td>4.4 (2.0)</td>
<td>3.6 (2.0)</td>
<td>3.4 (1.9)</td>
<td>3.3 (1.5)</td>
<td>4.0 (2.4)</td>
</tr>
<tr>
<td>LP-PRP</td>
<td>5.9 (2.2)</td>
<td>4.0 (2.4)</td>
<td>2.7 (2.1)</td>
<td>2.1 (1.8)</td>
<td>2.4 (2.3)</td>
</tr>
<tr>
<td>Saline</td>
<td>5.0 (2.0)</td>
<td>3.4 (2.2)</td>
<td>2.9 (2.1)</td>
<td>3.1 (2.1)</td>
<td>2.0 (1.9)</td>
</tr>
<tr>
<td>GROC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LR-PRP</td>
<td>—</td>
<td>4.6 (1.2)</td>
<td>4.9 (1.2)</td>
<td>5.0 (1.3)</td>
<td>4.7 (1.6)</td>
</tr>
<tr>
<td>LP-PRP</td>
<td>—</td>
<td>4.8 (1.7)</td>
<td>5.3 (1.3)</td>
<td>5.6 (1.3)</td>
<td>5.6 (1.0)</td>
</tr>
<tr>
<td>Saline</td>
<td>—</td>
<td>5.1 (0.9)</td>
<td>5.6 (1.0)</td>
<td>5.4 (1.0)</td>
<td>5.7 (1.2)</td>
</tr>
</tbody>
</table>

*Values are presented as mean (SD). —, not applicable; GROC, global rating of change; LP-PRP, leukocyte-poor platelet-rich plasma; LR-PRP, leukocyte-rich platelet-rich plasma; NPRS, numeric pain rating scale; VISA-P, Victorian Institute of Sport Assessment (patellar).*

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**Figure 2.** Change in VISA-P at the primary endpoint (12 weeks). The following linear model was used: VISA-P12 = intercept + VISA-Pbaseline + treatment. LP-PRP, leukocyte-poor platelet-rich plasma; LR-PRP, leukocyte-rich platelet-rich plasma; VISA-P, Victorian Institute of Sport Assessment (patellar).
The participant’s rated condition was “minimally worse” at 6 weeks and “minimally improved” 6 months as compared with baseline.

Nonprotocol Treatments

Nine participants reported taking additional treatments while enrolled in the study. These were distributed among the 3 groups and included medication (analgesia), therapeutic massage, and 2 instances of physical therapy (details of treatment not provided).

DISCUSSION

This study failed to demonstrate a significant benefit of LP-PRP or LR-PRP over and above saline injection to patients who were engaged in a rehabilitation program for the treatment of patellar tendinopathy. The improvements in the saline and LP-PRP groups were highly comparable with the effects reported previously with rehabilitation alone. There was a trend toward more recipients of PRP experiencing a worsening of their conditions at 6 weeks as compared with saline and a trend toward fewer patients in the LR-PRP group experiencing a significant improvement at 12 weeks. It could be speculated that the introduction of WBCs into the region of patellar tendinopathy exacerbates the pathology by inducing a localized inflammatory response.

A misconception that occasionally arises among readers of clinical trials is that any observed improvement over time (ie, in comparison with baseline) represents a treatment effect: this misconception can sometimes lead to mistaken interpretations of treatment effectiveness. Improvement over time is to be expected in many conditions regardless of treatment, including recalcitrant tendinopathy: improvements can be attributed to a variety of nonspecific effects, including gradual recovery and regression to the mean, as well as a host of placebo effects. Such a meta-analysis might reveal whether the introduction of WBCs into the region of tendinopathy exacerbates the pathology by inducing a localized inflammatory response.

We addressed this limitation by stratifying allocation by site and observed similar trends in treatment response at the various sites (Figure 2). The exercise sessions were supervised by physical therapists at each site; however, the therapists did not provide us with documentation of the volume and progression of exercise—thus, dose of exercise may have varied among the 3 groups. Some patients (eg, the more physically active ones) were perhaps more successful in carrying out the rehabilitation program, but it is impossible to make any definitive statements about this. It is the nature of a randomized controlled trial to attempt to limit the effect of such natural and unknown variation through the process of randomization. We were able to test only 2 PRP formulations in this study, and we examined the effect of a single injection rather than multiple injections. However, the interventions and injection techniques delivered in this study are analogous to those that are widely used.

Our results are in contrast to a previous randomized controlled trial that concluded that a single ultrasound-guided injection of LR-PRP (Biomet GPS III System) is superior to control (dry needling with no injection). In that study, patients were randomized to receive dry needling of the patellar tendon only (n = 12) versus dry needling plus a single PRP injection (n = 12); as in the current study, VISA-P score at 12 weeks was the primary outcome. Because our current study did not use dry needling, the results are not comparable. All 3 treatment groups in our study undertook a gym-based rehabilitation program, and the improvement in the control group was 18.8 (8.4), as expected.

In conclusion, when combined with an exercise-based rehabilitation program, a single injection of LR-PRP or LP-PRP was no more effective than saline for the improvement of patellar tendinopathy symptoms.

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REFERENCES


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