One-Year Follow-up of Platelet-Rich Plasma Treatment in Chronic Achilles Tendinopathy

A Double-Blind Randomized Placebo-Controlled Trial

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Background: Achilles tendinopathy is a common disease among both athletes and in the general population in which the use of platelet-rich plasma has recently been increasing. Good evidence for the use of this autologous product in tendinopathy is limited, and data on longer-term results are lacking.

Purpose: To study the effects of a platelet-rich plasma injection in patients with chronic midportion Achilles tendinopathy at 1-year follow-up.

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

Methods: Fifty-four patients, aged 18 to 70 years, with chronic tendinopathy 2 to 7 cm proximal to the Achilles tendon insertion were randomized to receive either a blinded injection containing platelet-rich plasma or saline (placebo group) in addition to an eccentric training program. The main outcome was the validated Victorian Institute of Sports Assessment-Achilles score. Patient satisfaction was recorded and ultrasound examination performed at baseline and follow-up.

Results: The mean Victorian Institute of Sports Assessment-Achilles score improved in both the platelet-rich plasma group and the placebo group after 1 year. There was no significant difference in increase between both groups (adjusted between-group difference, 5.5; 95% confidence interval, -4.9 to 15.8, P = .292). In both groups, 59% of the patients were satisfied with the received treatment. Ultrasonographic tendon structure improved significantly in both groups but was not significantly different between groups (adjusted between-group difference, 1.2%; 95% confidence interval, -4.1 to 6.6, P = .647).

Conclusion: This randomized controlled trial showed no clinical and ultrasonographic superiority of platelet-rich plasma injection over a placebo injection in chronic Achilles tendinopathy at 1 year combined with an eccentric training program.

Keywords: Achilles tendon; tendinopathy; therapy; platelet-rich plasma (PRP); growth factors
growth factors are also increased. Growth factors act on different aspects of tendon repair, including angiogenesis, chemotaxis, and cell proliferation by activating intracellular signal-transduction pathways.\(^5\),\(^13\)

Sports orthopaedic physicians have increasingly been using PRP as treatment for tendinopathy. A recent systematic review showed that high-quality randomized clinical trials and midterm and long-term follow-up results are lacking.\(^16\) Of the few studies reporting high success rates for PRP treatment in tendinopathy,\(^19\),\(^24\),\(^27\),\(^32\) only 1 trial had an adequate control group with 1-year follow-up.\(^24\) None of these publications included a standardized ultrasonographic evaluation of tendon structure. The short-term results of the current study were reported earlier. No additional effects of PRP injection to eccentric exercises were found after 6 months.\(^17\) However, biologic agents could bring forth a response that becomes pronounced over time. In a recent randomized controlled trial on the effects of PRP in lateral epicondylitis, there was no difference in outcome between PRP injections and corticosteroid injections at 3 months, whereas at 1 year the PRP group did significantly better.\(^22\)

Ultrasonography can be used for the evaluation of therapy in tendinopathy.\(^7\) Recently, ultrasonographic tissue characterization (UTC) was introduced as a reliable method for quantification of tendon structure.\(^43\) The method calculates the 3-dimensional stability of the echo pattern over continuous cross-sectional images of the tendon and was extensively evaluated in equine studies using histology as the reference. This new technique, with a high inter-observer and intraobserver reliability, can discriminate between symptomatic and asymptomatic human tendons.\(^43\)

Neovascularization score alters during treatment of Achilles tendinopathy. Although the interpretation of neovascularization remains unclear, different trials used neovascularization as an objective parameter in their results.\(^12\),\(^30\),\(^47\)

In further follow-up of the 6-month clinical results,\(^17\) the aim of the current study is to evaluate both the clinical and the ultrasonographic tissue effects of a PRP injection versus placebo in patients with chronic Achilles tendinopathy after 1 year.

MATERIALS AND METHODS

This is a 1-year follow-up study of a randomized controlled trial.\(^17\) Materials and methods were as extensively described in the article by de Vos et al\(^17\) and reported in the study protocol registered at clinicaltrials.gov (Identifier: NCT00761423).

Patients

Patients were recruited in a large district hospital at the department of sports medicine. Inclusion criteria were patients with the clinical diagnosis of Achilles tendinopathy with a minimal duration of symptoms of 2 months. Patients were excluded if they already had performed a full eccentric exercise program or already received a PRP injection in the Achilles tendon. Other exclusion criteria were known presence of a systemic illness, presence of other musculoskeletal injury (such as insertion disorder or tendon rupture), use of fluoroquinolones, and presence of pregnancy.

Procedures

Both the PRP injection (4 mL) and a saline injection (4 mL) were prepared for each patient. For the PRP injection, 54 mL of whole blood was collected from the cubital vein; 6 mL of citrate was added to prevent clotting. The collected blood was centrifuged for 15 minutes using the Recover Platelet Separation Kit (type Gravitational Platelet Separation III), and 0.3 mL of 8.4% sodium bicarbonate buffer was added.\(^18\) No calcium chloride or thrombin was added to activate the platelets before injecting because we assumed that platelets are also activated by collagen.\(^29\)

Randomization

A block randomization was performed with a block size of 12 participants. The patients were randomized into 1 of the treatment groups by choosing a blank sealed envelope. The content of this envelope was only visible for 1 unblinded independent sports medicine physician (A.W.) who selected the randomized injection and blinded it with a covering sleeve.

Intervention

First, the skin and subcutaneous tissue were anesthetized with 2 mL of 0.5% Marcaine. The injection was performed under ultrasonographic guidance by an experienced sports physician who was also blinded to the allocated treatment. At 3 different needle locations, 5 little aliquots were injected (with a total amount of 4 mL). After the injection, patients had to avoid sports activities for 4 weeks; in the second week, they performed a stretching program. After this, all patients started an eccentric exercise program for 12 weeks.\(^3\)

Follow-up

Recruitment, inclusion, and follow-up contacts at 6, 12, and 24 weeks after injection were performed by one researcher (R.J.d.V.). One-year follow-up was performed by another researcher (S.d.J.) who was also blinded for the allocated intervention. Both clinical and ultrasonographic outcomes were assessed at all time points. Patients remained blinded until 1-year follow-up.

Clinical Outcome Measures

The primary outcome was the Victorian Institute of Sports Assessment–Achilles (VISA-A) score (validated questionnaire for outcome in Achilles tendinopathy). Other outcome measures were subjective patient satisfaction (scored as moderate, poor, good, or excellent) and return
to sports activity (scored as not active in sports, no return to sports, returning to sport but not in desired sport, returning to desired sport but not at the preinjury level, or returning to preinjury level in the desired sport). For analysis of patient satisfaction, patients reporting good or excellent satisfaction were reported as satisfied. For return to sports activity, cutoff was made for return to desired sport on preinjury level.

Sonographic Evaluation

Tendon structure was evaluated quantitatively by means of UTC (UTCimaging, Stein, the Netherlands). With the ankle joint in 15° of dorsal flexion, a 10-MHz linear-array transducer (Smartprobe 10L5, TeraSon 2000, TeraTech, Rockville, Maryland) was moved automatically along and perpendicular to the Achilles tendon's long axis over a distance of 9.6 cm. The transverse images collected at regular distances of 0.2 mm were used to reconstruct a 3-dimensional data block. The stability of the echo pattern over contiguous images was analyzed by means of custom-designed algorithms (UTCimaging) and results in discrimination of 4 echo types: Echo types I and II represent more or less organized (secondary) tendon bundles; echo types III and IV represent smaller, disorganized, and more amorphous or fibrillar structures. In transverse and sagittal planes of view, the maximum anterior-posterior diameter was determined and measured. At 5 points around this thickest part, from 1.5 cm proximal to 1.5 cm distal to the maximum anterior-posterior diameter, the border of the tendon was marked and intermediate borders interpolated, creating a volume with an overall length of 3 cm. Proportions of the 4 echo types were measured within this volume. The sum of echo types I and II, representing more or less organized secondary tendon bundles, was used for statistical analysis. Ultrasound examination at the 1-year follow-up was performed by another researcher (S.d.J.). The interobserver reliability between the 2 examiners (R.J.d.V. and S.d.J.) was tested in 17 tendons at 2 different time points within 1 week. The reliability appeared to be excellent, with an intraclass correlation coefficient of 0.89 and a mean difference of 0.9%.

Neovascularization

Neovascularization was scored using the modified Öhberg scoring system. In this scoring system, scores were determined as 0 (no vessels), 1+ (1 vessel, mostly anterior to the tendon), 2+ (1 or 2 vessels throughout the tendon), 3+ (3 vessels throughout the tendon), or 4+ (more than 3 vessels throughout the tendon). The degree of neovascularization can be measured with an excellent interobserver reliability (intraclass correlation, 0.86). This color Doppler ultrasonography examination was performed with a linear high-frequency 12- to 15-MHz transducer (MyLab80, Esaote Piemedical, Maastricht, the Netherlands) with Doppler gain at 79% and Doppler frequency at 6.6 MHz. Patients were laying prone on the examination table with their feet hanging over the edge. The neovascularization of the tendon was scored in longitudinal and transverse planes.

RESULTS

Patients

At baseline, 54 of the 99 eligible patients were willing to participate, met the inclusion criteria, and were randomized into the 2 treatment groups. The mean age was 49.7 years (range, 26-70 years); mean body mass index (weight in kg/height [m]²) was 26.5 (range, 20.2-35.3), and the mean duration of symptoms was 62.6 weeks (median, 32 weeks; range, 8-620 weeks). There were no significant differences in baseline characteristics between the 2 groups.

No patients were lost to follow-up (Figure 1). One patient was not able to visit the center for ultrasonographic examination but did complete the clinical outcome measures by mail. After 24 weeks, 4 patients in the PRP group decided to undergo another treatment because of failure to improve. These treatments included orthotics (n = 1), extracorporeal shockwave therapy (n = 3), and glyceryl trinitrate patches (n = 1). In the placebo group, 1 patient received glyceryl trinitrate patches. No complications were reported between 24-week and 1-year follow-up.

Clinical Outcome

At 1-year follow-up, the VISA-A score improved significantly by 31.6 points (95% confidence interval [CI], 22.2-40.9) from 46.7 (95% CI, 40.3-53.1) at baseline to 78.2 (95% CI, 68.0-88.5) in the PRP group and by 26.0 (95% CI, 18.0-32.0) points from 52.6 (95% CI, 45.1-60.2) to 77.6 (95% CI, 70.8-84.4) in the placebo group. In the general linear model, adjustments were made for baseline VISA-A score (P = .023) and duration of symptoms (P = .023). The adjusted between-group difference at 1-year follow-up was not significant (6.5 points on VISA-A score; 95% CI, −4.9 to 15.8). The VISA-A scores at all follow-up moments for both groups are shown in Figure 2.
After 1 year in both groups, 16 patients (59.3%) were satisfied with their allocated treatment. Adjusted between-group difference for subjective patient satisfaction after 1 year was −2.7% (95% CI, −23.5 to 18.1; P = .801).

In the PRP group, 56.5% of the patients returned to their previous sports levels in the desired sport, compared with 41.7% in the placebo group. The adjusted between-group difference for return to sports at 1-year follow-up was 1.8% (95% CI, −24.5 to 28.1; P = .394).

Sonographic Outcome

The percentages of the more or less organized echo types I and II increased 7.2% (95% CI, 3.4-11.0) in the PRP group from 76.9% (95% CI, 72.6-81.1) at baseline to 83.7% (95% CI, 79.6-87.9) at 1-year follow-up. In the placebo group, these echo types increased 8.4% (95% CI, 3.1-13.6) from 72.1% (95% CI, 67.7-76.5) to 81.3% (95% CI, 77.3-85.3). In the general linear model, adjustments were made for baseline value echo type I and II (P < .001). Between-group difference at 1-year follow-up was 1.2% (95% CI, −4.1 to 6.6; P = .647). Alterations in all echo types in the PRP group (Figure 3A) and control group (Figure 3B) are plotted in Figure 3.

Maximum anterior-posterior diameter of the Achilles tendon decreased in the PRP group from 9.8 mm (95% CI, 9.1-10.5) at baseline to 9.0 mm (95% CI, 8.2-9.8) at 1-year follow-up. This was not significantly different from the decrease in the placebo group from 9.8 mm (95% CI, 8.6-11.1) to baseline to 8.6 mm (95% CI, 7.6-9.5) after 1 year. Between-group difference was 0.4 mm (95% CI, −0.8 to 1.7; P = .457).

Mean neovascularization score increased in the PRP group in the first 12 weeks from 2.3 (95% CI, 1.8-2.7) to 3.0 (95% CI, 2.6-3.5) and in the placebo group from 2.2...
Figure 3. A, changes in UTC echo types in PRP group. Echo type I increased over time, whereas echo type II remained stable. Echo types III and IV decreased slightly. B, changes in UTC echo types in placebo group. Echo type I increased over time, whereas echo type II remained stable. Echo types III and IV decreased slightly.

(95% CI, 1.6-2.7) to 2.5 (95% CI, 2.1-2.9). From 12 weeks to 1-year follow-up, a decrease was found in both groups, to 1.4 (95% CI, 0.8-2.0) in the PRP group and 1.2 (95% CI, 0.7-1.7) in the placebo group. Between-group difference at 1-year follow-up was 0.1 point (95% CI, -0.6 to 0.9; P = .714). Mean neovascularization scores for both groups are shown in Figure 4.

**DISCUSSION**

In this double-blind randomized placebo-controlled clinical trial with 1-year follow-up, no clinical or sonographic benefit of a PRP injection was found. These results are in line with the findings after 6 months. This is the first trial using standardized sonography in 1-year clinical results of PRP therapy in Achilles tendinopathy.

In different types of tendinopathy, promising results for PRP therapy have been published recently. Two pilot studies reported high patient satisfaction and pain reduction after PRP therapy, the group sizes of these studies, however, were small, and a control group was lacking. Filardo et al selected a control group with patients with moderate patellar tendinopathy receiving a regular physical therapy program versus patients with nonresponding patellar tendinopathy receiving multiple PRP injections. They found equal clinical improvements after 6 months in both groups. In a recent publication, Gaweda et al studied the effect of PRP in 14 patients with Achilles tendinopathy without the use of a control group and found significant improvement in VISA-A score after 18 months.

The only other randomized controlled trial on PRP therapy in tendinopathy showed a significant benefit of PRP injection in wrist extensor tendinopathy compared with corticosteroid injection after 1 year. Comparing the pattern of visual analog scale score with the VISA-A score in our study, the deviating course in the control group of Peerbooms et al is remarkable. Unlike our study, the control group received a corticosteroid injection instead of a placebo injection, which very well may have negatively affected the outcome in the control group. In addition, there may be differences in the natural healing response between load-bearing tendons, such as the Achilles tendon, and non-load-bearing tendons, such as the wrist extensors. Although a tennis elbow is a self-limiting injury, Achilles tendinopathy seems not to be.

It is possible that the needling during the injection could influence the outcome in both groups. Brown et al compared aprotinin injections and eccentric exercises with
a saline injection and eccentric exercises. They found similar improvement in both the aprotinin and placebo groups. A healing response can be initiated by needle trauma or local bleeding. Another hypothesis for the positive effects in both groups is the increase in peritendinous volume, thereby destroying the vascular and neural growth that is thought to be the source of pain. The increase of neovessels after the injection contradicts this theory. It is not certain that the injected volume stays intratendinous for a sustained period or leaks, for example, to the peritendinous space. Using an injection procedure similar to the procedure in this study, Wiegerinck et al. showed an equal distribution of intratendinously injected volumes in the Achilles tendons of human cadavers. The assumption that PRP only has great potency in traumatic lesions is invalidated by Schepull et al. They found no benefit of PRP in treatment of Achilles tendon rupture. Cell therapy has recently been proposed as the most promising therapy for degenerated tendons, but further research in this field is required.

The sample size of this study was calculated to detect a minimal clinically relevant difference of 12 points on VISA-A score. After 1 year, this difference lies within the 95% CI of the adjusted between-group difference (−4.9 to 15.8). Although we cannot exclude a clinically relevant effect of PRP, which was the case at 6 months of follow-up, the chance of such an effect at long term with this CI seems unlikely.

Furthermore, no beneficial effect of PRP on ultrasonographic tendon structure and neovascularization was found in our study. Both the PRP group and placebo group improved tendon structure, but no significant differences between the groups were found. These results are in line with the ultrasonographic changes after 6 months. In equine studies, a correlation between UTC and histologic findings was reported. In humans, UTC can differentiate between symptomatic and asymptomatic tendons, however, a clear correlation between tendon structure measured with UTC and clinical outcome after 6 months cannot be found (de Vos et al., unpublished data). In both groups, neovascularization continued decreasing after the increase at the 12-week follow-up. The same pattern was described by Alfredson and Ohberg, reporting neovascularization after sclerosing injections for Achilles tendinopathy. In a previous study on splinting in addition to eccentric exercises, such a pattern was not shown, suggesting that the fluctuations in vascularization may be a direct response to needle trauma.

A limitation of this study is that the exact composition of the PRP is unknown. The platelet separation system used in this trial has been examined in other studies that reported sufficient platelet counts. However, there are a variety of methods for preparing PRP and various forms in which it can be administered. The value of altering variables like platelet count, injected volume, number of injections, preactivation, and presence of leukocytes could not be determined in this study due to the design. More research will be needed to assess the effects of altering these variables on the clinical outcome. At this point in time, there are 7 level 1B studies on PRP in acute and chronic tendon or ligament injuries. In all these studies, very differing preparation and administration techniques were used. None of these high-quality studies showed a statistically significant superior effect compared with placebo.

Some researchers believe PRP should only be reserved for use in severe cases. In the field of tendinopathy research, there is, however, no validated classification for the severity of complaints. Our study population had a mean duration of symptoms of 16 months (range, 2-130 months). In our analysis, the duration of symptoms and baseline VISA-A score were found to be important predictors for VISA-A improvement. For this reason, adjustments were made for these values in the analysis. It is questionable whether PRP treatment can only play a role in patients with resistant tendinopathy that fails to respond to eccentric loading or that the eccentric exercise program dominates the effect of PRP. An animal study revealed that PRP needs to be combined with mechanical stimulation to achieve tendon healing. Furthermore, all published studies on PRP treatment in tendinopathy combined it with strengthening programs.

Based on the current results, no benefit of an injection with PRP, in addition to eccentric exercises in patients with chronic midportion Achilles tendinopathy, was shown at 1-year follow-up.

CONCLUSION

A PRP injection in addition to eccentric exercises did not result in clinical improvement and/or improved structure reorganization on ultrasound after 1 year in chronic midportion Achilles tendinopathy, compared with a placebo injection.

REFERENCES