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JAMA. 2010;303(2):144-149 (doi:10.1001/jama.2009.1986)

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Platelet-Rich Plasma Injection for Chronic Achilles Tendinopathy

A Randomized Controlled Trial

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OVERUSE INJURY OF THE ACHILLES tendon is a frequent problem that often affects sport participants but also inactive middle-aged individuals.^{1,2} An estimated 30% to 50% of all sports-related injuries are tendon disorders.³ Former distance runners have a lifetime risk of 52% for Achilles tendon injury.⁴ Achilles tendon injuries frequently lead to sport cessation for long periods and may interfere with activities of daily living.⁵ Conservative treatment is disappointing and 25% to 45% of patients eventually require surgery.^{1,5} There is a clear need for improved conservative therapy.

Many factors in the etiology and pathogenesis have been reported, but no study has identified a direct cause-effect relationship.^{1,2} Previously, the nomenclature *tendinitis* was generally used for chronic tendon disorders, suggesting the presence of inflammation.^{1,2} Histological studies, however, proved abnormal tissue repair and degeneration, which favored the term *tendinopathy* for the clinical triad of pain, swelling, and decreased activity.^{1,2} Anti-inflammatory agents, previously used for chronic

Context Tendon disorders comprise 30% to 50% of all activity-related injuries; chronic degenerative tendon disorders (tendinopathy) occur frequently and are difficult to treat. Tendon regeneration might be improved by injecting platelet-rich plasma (PRP), an increasingly used treatment for releasing growth factors into the degenerative tendon.

Objective To examine whether a PRP injection would improve outcome in chronic midportion Achilles tendinopathy.

Design, Setting, and Patients A stratified, block-randomized, double-blind, placebo-controlled trial at a single center (The Hague Medical Center, Leidschendam, the Netherlands) of 54 randomized patients aged 18 to 70 years with chronic tendinopathy 2 to 7 cm above the Achilles tendon insertion. The trial was conducted between August 28, 2008, and January 29, 2009, with follow-up until July 16, 2009.

Intervention Eccentric exercises (usual care) with either a PRP injection (PRP group) or saline injection (placebo group). Randomization was stratified by activity level.

Main Outcome Measures The validated Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire, which evaluated pain score and activity level, was completed at baseline and 6, 12, and 24 weeks. The VISA-A score ranged from 0 to 100, with higher scores corresponding with less pain and increased activity. Treatment group effects were evaluated using general linear models on the basis of intention-to-treat.

Results After randomization into the PRP group (n=27) or placebo group (n=27), there was complete follow-up of all patients. The mean VISA-A score improved significantly after 24 weeks in the PRP group by 21.7 points (95% confidence interval [CI], 13.0-30.5) and in the placebo group by 20.5 points (95% CI, 11.6-29.4). The increase was not significantly different between both groups (adjusted between-group difference from baseline to 24 weeks, -0.9; 95% CI, -12.4 to 10.6). This CI did not include the predefined relevant difference of 12 points in favor of PRP treatment.

Conclusion Among patients with chronic Achilles tendinopathy who were treated with eccentric exercises, a PRP injection compared with a saline injection did not result in greater improvement in pain and activity.

Trial Registration clinicaltrials.gov Identifier: NCT00761423

JAMA. 2010;303(2):144-149

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tendinopathies without appropriate efficacy,^{1,6} have now been replaced by eccentric exercises as usual care⁶ that provide some positive effects on tendon collagen synthesis and may result in a decrease of pain.^{1,7}

The recent introduction of platelet-rich plasma (PRP) injections in tendinopathy raised high expectations.⁸⁻¹¹

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See also Patient Page.

Platelets derived from whole blood using simple cell-separating systems provide a release of various growth factors that participate in tissue repair processes.^{9,12,13} Three recent reviews reported promising results of the use of PRP in tendinopathy, although these conclusions were based on laboratory studies and on clinical studies with important limitations.⁹⁻¹¹ Although we are unaware of published data on the prevalence of use of this therapy, 2 recent reviews have suggested that PRP injections for tendinopathy are increasingly used in the clinical setting.^{13,14}

The goal of our double-blind, block-randomized, placebo-controlled trial, the first to our knowledge in this field, was to compare the effects on pain and functional outcome of a PRP injection with a placebo injection, both combined with an eccentric exercise program in patients with chronic midportion Achilles tendinopathy.

METHODS

Study Design

The stratified, block-randomized, double-blind, placebo-controlled trial was performed at the sports medicine outpatient department in a large district general hospital (The Hague Medical Center Antoniusshove, Leidschendam, the Netherlands). The single-center study was announced to general practitioners, sports medicine physicians, orthopedic surgeons, physiotherapists, and the general public with advertisements on several Web sites, folders, and regional radio. The PRP treatment was disseminated as a potentially successful treatment for tendinopathies. According to the study protocol, the primary analysis was performed after 24 weeks of follow-up. After 24 weeks, blinding was disclosed for the primary researcher. Results at 52 weeks will be used as a secondary outcome to describe the long-term results in a future analysis.

The study protocol was approved by the regional Medical Ethics Committee Zuidwest Holland, Voorburg, the Netherlands. All patients provided written informed consent.

Patients

When patients contacted the researcher by telephone or e-mail, detailed information about the study was given and eligibility was evaluated. If patients seemed to be suitable for inclusion in the study after this screening, an appointment was made at the sports medicine outpatients department. One experienced sports medicine physician (J.L.T.) evaluated suitability for inclusion. Inclusion criteria were the presence of chronic midportion Achilles tendinopathy and age of 18 to 70 years. The diagnosis was made based on clinical findings: all patients had a painful and thickened tendon in relation to activity and on palpation. The tendon pain was located approximately 2 to 7 cm proximal to the insertion on the calcaneus. Symptoms had to have been present for at least 2 months.

Exclusion criteria were (1) clinical suspicion of other musculoskeletal (insertional disorders and tendon rupture) injuries, inflammatory internal disorders, or use of specific medications that can cause tendinopathy (fluoroquinolones); (2) previous performance of a complete heavy load eccentric exercise program¹ or inability to perform it; or (3) a previous injection with PRP. Detailed information regarding the inclusion and exclusion criteria is described at clinicaltrials.gov or can be obtained from the corresponding author (R.J.d.V.).

Procedures

A researcher (R.J.d.V.) prepared a PRP injection and a saline injection for every patient. The PRP injection was prepared using the recover platelet separation kit, in accordance with the system instructions.¹² Fifty-four milliliters of venous blood was collected from the cubital vein. The whole blood was mixed with 6 mL of citrate to prevent early clotting. After blood collection and 15 minutes of centrifugation, PRP was obtained. To match the pH of PRP with the pH of the tendon tissue, 0.3 mL of 8.4% sodium bicarbonate buffer was added. One milliliter of PRP was collected for evaluation of possible contamination of the PRP after the prepara-

tion, which was cultured and analyzed on microbial growth by the Department of Medical Microbiology, The Hague Medical Center Antoniusshove, Leidschendam, the Netherlands. Four milliliters of PRP was collected for infiltration and 4 mL of isotonic saline was also prepared in an identical syringe.

Randomization

The preinjury activity level may be a confounder for the primary outcome in this study, because it evaluates pain and activity.¹⁵ Stratification was used to divide the number of active patients between the 2 treatment groups. This stratification was based on the ankle activity score, which objectively quantifies the ankle-related activity.¹⁶ An ankle activity score of 4 or more points indicated a high activity level and a score of less than 4 points indicated a low activity level. Randomization was performed using sealed opaque, identical envelopes. The envelopes were evenly distributed in the high- and low-activity box. The patient was then randomized into 1 of 2 treatment groups by choosing a closed envelope. To ensure balance in the number of patients between the groups, a block randomization was performed (block size of 12 participants).

One unblinded sports medicine physician (A.W.) selected the correct injection and blinded the injection with the use of a covering sheath surrounding the syringe and hub of the needle. To ensure concealment of allocation, data on allocation were stored in a secret location. The content of the injection was blinded for the treating sports medicine physician, researcher, and patients.

Intervention

A blinded sports medicine physician (J.L.T.) performed the injection. First, a local anesthetic was injected (2 mL of 0.5% marcain) in the skin and subcutaneous tissue. Using an ultrasonographic machine (MyLab30; Esaote Piemedical, Maastricht, the Netherlands), the tendon structure was imaged and the blinded fluid was injected using a 22-gauge needle through 3 different

puncture locations. Through each puncture location, 5 small depots were left at several sites in the degenerative area of the main body of the tendon with Color Doppler guidance. Immediately after the injection, the patients lay prone on the examination table for 10 minutes.

All patients received detailed instructions on the standardized rehabilitation program.¹ During the first 48 hours after the injection, patients were only allowed to walk short distances indoors. During days 3 to 7 postinjection, walks up to 30 minutes were allowed. After the first week, the exercise program was started and consisted of 1 week of stretching exercises and then a 12-week daily eccentric exercise program (180 repetitions).¹ Eccentric exercises were done by performing “heel drops” on a step. The specific action of this eccentric exercise movement is the stretch of the Achilles tendon with concurrently contraction of the calf muscle.

All patients were instructed to avoid weight-bearing sporting activities for

the first 4 weeks. After 4 weeks, a gradual return to sports activities was encouraged. The intensity of sports activities could be increased when there was only mild pain (maximum score of 3 on a scale from 0-10, with 0 representing no pain and 10 representing maximum pain) and no increase in morning stiffness.

Patients were instructed to avoid the use of co-interventions within the follow-up period. Acetaminophen (500 mg) could be used as rescue medication.

Outcome Measures

All patients completed a questionnaire consisting of standardized outcome measures at baseline and after 6, 12, and 24 weeks. The primary outcome measure was the Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire, which quantifies the pain and activity level.¹⁷ The VISA-A score ranged from 0 to 100, where 0 denotes no activity and maximum pain and 100 denotes maximum activity and no pain. This is a validated questionnaire, spe-

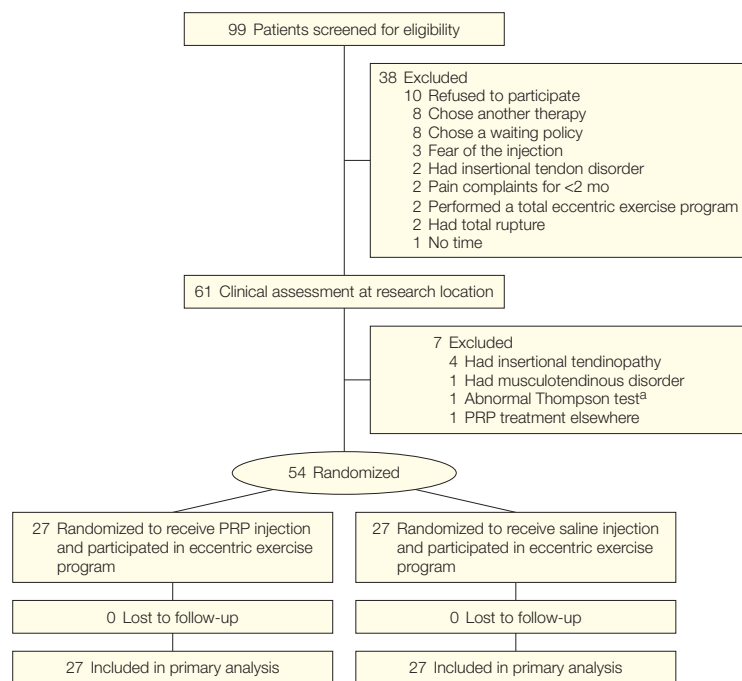
cifically designed for evaluating outcome in Achilles tendinopathy. Secondary outcome measures were subjective patient satisfaction, return to sports, and adherence of the eccentric exercises. Patient satisfaction was subjectively rated as poor, fair, good, or excellent. A good or excellent result was determined as successful. The return to sports level was divided into 5 groups (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, and returning to preinjury level in the desired sport). We determined the patient's return to desired sport, regardless of the level. The patients received forms to keep daily logs for the eccentric exercises. At follow-up, the subjective adherence of the patients was determined by asking which percentage of the prescribed repetitions the patients had accomplished.

Statistical Analysis

Based on previous studies, our alternative hypothesis was that in the group treated with a PRP injection (PRP group), the VISA-A score would be 12 points higher in comparison with the group treated with a saline injection (placebo group).^{15,18,19} The SD of the VISA-A score was estimated at 15 points.¹⁷⁻¹⁹ We calculated that a sample of 27 in each group was required for the study to detect this difference, with a power of 80% with 2-sided testing at a significance level of .05 and assuming 10% loss to follow-up. The patients were analyzed by intention-to-treat. To test for the effect of treatment on the between-group difference in primary outcome, we used the repeated measurement general linear model. Changes from baseline to all follow-up time points were included in the model. Adjustments were made for those variables that influenced the primary outcome with $P < .10$. We evaluated secondary outcomes with use of a generalized estimating equations model.

The researcher (R.J.d.V.) who performed the analyses was blinded to the allocated treatment. The analyses were performed by using SPSS version 16.0.1 (SPSS Inc, Chicago, Illinois).

Figure 1. Flow of Patients Through the Study



PRP indicates platelet-rich plasma.
^aSuggesting a tendon rupture.

RESULTS

Between August 28, 2008, and January 29, 2009, 99 patients contacted the researcher (R.J.d.V.) for information on the study. The flow of patients through the trial is shown in FIGURE 1, and the baseline characteristics of the patients in both treatment groups are shown in TABLE 1. During the study, there were no patients lost to follow-up and there were no missing data. The end of the follow-up period was on July 16, 2009.

The mean VISA-A score improved significantly after 24 weeks within the PRP group by 21.7 points (95% confidence interval [CI], 13.0-30.5) and within the placebo group by 20.5 points (95% CI, 11.6-29.4) (FIGURE 2).

Variables that were considered as important predictors of the primary outcome (VISA-A score) were the baseline VISA-A score ($P = .03$) and duration of symptoms ($P = .06$). After adjustment for these variables, there was no significant difference in improvement on the VISA-A score at 6, 12, and 24 weeks follow-up between these 2 treatment groups; between-group differences were 2.5 (95% CI, -6.9 to 11.9), -1.6 (95% CI, -11.9 to 8.7), and -0.9 (95% CI, -12.4 to 10.6), respectively (positive values favor the PRP group) (TABLE 2).

There was no significant difference in secondary outcome measures. Subjective patient satisfaction (after 24 weeks: -4.1%; 95% CI, -25.8% to 17.7%) and number of patients returning to their desired sport (after 24 weeks: 1.4%; 95% CI, -17.0% to 19.8%) are shown in Table 2 (positive values favor the PRP group).

The mean (SD) percentage of reported adherence for the eccentric exercises in the PRP group was 70.9% (27.0%) and in the placebo group was 74.6% (17.3%). There was no significant difference between both groups (95% CI, -16.1 to 8.7).

One patient in the PRP group used a tendon binding band during the follow-up period and 1 patient in the placebo group applied foot orthotics. The eccentric exercises were continued with a lower frequency after the 12-week program in the PRP group by 15 patients and in the placebo group by 17 patients ($P = .58$).

There was no microbial growth found in the collected PRP samples, and no complications (infections, hematomas, or ruptures) were reported after the treatments.

COMMENT

In this first, to our knowledge, double-blind, block-randomized, placebo-controlled trial on the clinical use of a PRP injection, there was no benefit on pain and function. There were also no

significant differences observed in the secondary outcome measures (subjective patient satisfaction and return to sports activity).

These findings are important and clinically relevant as PRP is thought to be growing in popularity and recent reviews supported its use for chronic tendon disorders.⁹⁻¹¹ These conclusions were drawn based on laboratory studies and small clinical studies. Some of the released growth factors, such as vascular

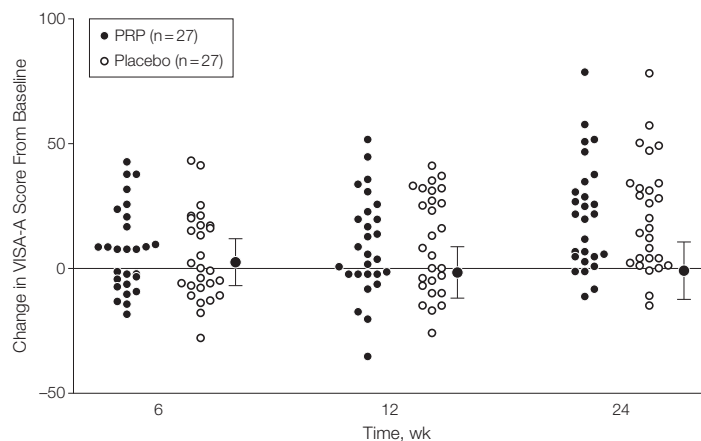
Table 1. Baseline Characteristics of the PRP and Placebo Groups^a

Characteristics	PRP Group (n = 27)	Placebo Group (n = 27)
Age, mean (SD), y	49 (8.1)	50 (9.4)
Sex, male	13 (48)	13 (48)
Duration of symptoms, median (IQR), wk	36 (24-78)	26 (16-104)
Activity		
Active in sports	22 (81)	24 (89)
Sedentary	5 (19)	3 (11)
Level of sports		
Competitive	6 (27)	3 (13)
Recreational	16 (73)	21 (87)
Sports activity at baseline		
Unchanged	2 (9)	9 (37)
Reduced	8 (36)	5 (21)
Ceased	12 (55)	10 (42)
Duration of sports cessation, mean (SD), wk	11 (16)	12 (23)
BMI, mean (SD)	26.8 (3.9)	26.2 (3.5)
VISA-A score, mean (SD)	46.7 (16.2)	52.6 (19.0)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; IQR, interquartile range; PRP, platelet-rich plasma; VISA-A, Victorian Institute of Sports Assessment-Achilles.

^aData are presented as No. (%) unless otherwise specified.

Figure 2. Individual Changes in the VISA-A Score From Baseline in Patients Treated With PRP and Placebo



VISA-A indicates Victorian Institute of Sports Assessment-Achilles; PRP, platelet-rich plasma. Adjusted between-group mean differences from baseline to 6, 12, and 24 weeks are shown with 95% confidence intervals.

endothelial growth factor, platelet-derived growth factor, and transforming growth factor β , have the potential to play a role in regeneration of tendon tissue through increased tendon cell proliferation, collagen synthesis, and vascularization. In *in vitro* and animal studies, positive effects on tendon collagen tissue and vascularization were reported.²⁰⁻²³ However, these studies using healthy tendons or traumatically induced lesions as a good experimental model for tendinopathy is lacking, and it is unknown whether the results of these studies also apply to degenerative tendon disorders. The 2 small clinical studies on PRP in tendinopathy showed a good effect on pain scores and patient satisfaction but had important limitations, such as the lack of a proper control group, disease-specific and validated outcome measurements, and blinding procedure.^{24,25} Treatments in tendinopathy that seem to be effective in

poor quality studies frequently fail to show clinical benefit when assessed in good clinical studies.²⁶

Our study showed no statistically significant difference in outcome between the groups and the CIs did not include the predefined difference used in the power calculation (12 points on the VISA-A score). We defined this clinically relevant difference as 12 points, based on previous studies.^{15,18,19} There is no official agreement on the minimal clinical important difference for the VISA-A score, but on other comparable studies in musculoskeletal medicine, this is reported to be 10% to 15% of the scale.²⁷⁻²⁹ Our predefined clinically relevant difference of 12 points is reasonably located between this accepted minimal clinical important difference of 10% to 15% of the scale. The estimated difference was determined for 24 weeks, but due to the demands of active patients and the claimed fast recov-

ery after PRP administration, we were also interested in the 6- and 12-week results. The reason why both treatment groups show clinical progression in our study, but also in other studies on PRP, is likely due to the fact that exercises were performed. Eccentric exercises have been shown to be effective in previous randomized trials.^{18,30} After 4 months, eccentric exercises proved to improve pain and function in contrast with a wait-and-see policy,³⁰ although there is no convincing evidence that eccentric exercise therapy is more effective than other forms of exercise.^{31,32} Another possible explanation for the improvement in the placebo group might be that the placebo response is amplified when a treatment is invasive and raises high expectations.³³ This has also been demonstrated previously in a study on the value of injection therapy for the treatment of tendinopathy.³⁴

A limitation of our study is that the amount of platelets and the quantity of activated growth factors that were present in the PRP injections was unknown. Nonetheless, good platelet collection efficiency was reported with the use of the platelet separation system used in our study, and a positive correlation between the number of platelets and the harvest of growth factors has been shown.^{10,12} Another variable that may be of interest is the length of time that the platelets remain at the site after injection into the degenerative area. Platelets are slowly activated by exposure to tendon collagen,¹⁰ but it might be that due to the pressure within the tendon a large amount of PRP diffused rapidly out of the tendon, thereby reducing its effect. However, in a laboratory study, an increase in tendon collagen synthesis was also found even with the use of a lower PRP concentration (20%) in healthy human tendon cells, which may be more comparable with the concentration reached during *in vivo* administration.²⁰ Moreover, the PRP preparation and injection was performed as the usual generally accepted procedure in daily clinical practice.¹² The lack of a group that received only a PRP injection without eccentric exercises may be regarded as

Table 2. Main Outcome Measures at 6, 12, and 24 Weeks in the PRP and Placebo Groups

	6 Weeks	12 Weeks	24 Weeks
Primary Outcome Measure			
VISA-A score improvement from baseline, mean (SD) ^a			
PRP group (n = 27)	7.8 (17.1)	9.6 (20.1)	21.7 (22.1)
Placebo group (n = 27)	4.6 (17.6)	10.1 (20.0)	20.5 (22.5)
Absolute between-group mean difference	3.2	-0.5	1.2
Adjusted between-group mean difference (95% CI)	2.5 (-6.9 to 11.9)	-1.6 (-11.9 to 8.7)	-0.9 (-12.4 to 10.6)
Secondary Outcome Measures			
Good/excellent patient satisfaction, No. (%) ^b			
PRP group (n = 27)	8 (30)	7 (26)	15 (56)
Placebo group (n = 27)	8 (30)	8 (30)	17 (63)
Absolute difference, %	0	-4	-7
Adjusted between-group difference, % (95% CI) ^c	-3.4 (-21.6 to 14.8)	-3.2 (-20.7 to 14.2)	-4.1 (-25.8 to 17.7)
Return to desired sport, No./Total No. (%) ^d			
PRP group	11/22 (50)	13/23 (57)	18/23 (78)
Placebo group	14/24 (58)	14/24 (58)	16/24 (67)
Absolute difference, %	-8	-1	11
Adjusted between-group difference, % (95% CI) ^c	1.8 (-21.8 to 25.4)	1.7 (-21.4 to 24.9)	1.4 (-17.0 to 19.8)

Abbreviations: CI, confidence interval; PRP, platelet-rich plasma; VISA-A, Victorian Institute of Sports Assessment-Achilles.

^aThe improvement in VISA-A scores from baseline to 6, 12, and 24 weeks in both treatment groups. The adjusted mean differences were calculated with a repeated measurements general linear model and adjustments were made for the baseline VISA-A score and duration of symptoms. Positive values favor the PRP group.

^bNumber of patients with an excellent or good subjective patient satisfaction divided by the total number of patients in the treatment group.

^cThe adjusted between-group differences between the treatment groups were calculated with a generalized estimating equations model and adjustments were made for duration of symptoms.

^dNumber of patients that returned to their desired sport divided by the total number of sporting patients in the treatment group. This was not applicable to all patients, because not all patients were active in sports participation. The desired sport was defined on the first appointment by the patient.

another limitation of the study. Until now, all studies reporting clinical effects in tendinopathy have used it in combination with exercises. Although it is unlikely that eccentric exercises have had a negative effect on the PRP treatment, as shown by an animal model in which tendon mechanical properties were improved when PRP was combined with mechanical stress, the study design makes it impossible to rule this out.²²

In the future, laboratory studies could examine which fraction of an injected substance remains within the degenerative tendon. This information may be useful for an accurate design of laboratory studies and implementation in clinical research. The Achilles tendon midportion is an ideal location for further clinical research in tendinopathy, because it is not affected by accompanying pathology,⁸ not self-limiting at midterm,³⁰ and there is a disease-specific validated outcome measure.¹⁷

Among patients with chronic midportion Achilles tendinopathy treated with an eccentric exercise program, a PRP injection compared with a saline injection did not result in greater improvement in pain and activity. Therefore, we do not recommend this treatment for chronic midportion Achilles tendinopathy.

Author Contributions: Dr Weir had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: de Vos, Weir, van Schie, Verhaar, Weinans, Tol.

Acquisition of data: de Vos.

Analysis and interpretation of data: de Vos, Weir, Bierma-Zeinstra, Verhaar, Weinans, Tol.

Drafting of the manuscript: de Vos, Weir, Bierma-Zeinstra, Verhaar, Weinans, Tol.

Critical revision of the manuscript for important intellectual content: de Vos, Weir, van Schie, Bierma-Zeinstra, Verhaar, Weinans, Tol.

Statistical analysis: de Vos, Bierma-Zeinstra.

Obtained funding: van Schie, Weinans.

Administrative, technical, or material support: de Vos, Weinans, Tol.

Study supervision: Weir, Verhaar, Weinans, Tol.

Financial Disclosures: None reported.

Funding/Support: This work was funded by Biomet Biologics LLC, Warsaw, Indiana.

Role of the Sponsor: Biomet Biologics LLC had no role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Additional Contributions: We thank Max Reijman, PhD, and Jan H. Waarsing, PhD (Department of Or-

thopedics, Erasmus University Medical Center, Rotterdam, the Netherlands), for their help with the study design, statistical evaluation, and interpretation of the data; Sten P. Willemssen (Department of Biostatistics, Erasmus University Medical Center), for his additional statistical analysis; and Cora van der Heijden, Ank de Vries, and Pauline Verschoor (Department of Sports Medicine, The Hague Medical Center Antoniushove, Leidschendam, the Netherlands), for their logistic help. These individuals were not compensated for their efforts. We thank the patients for their participation and the health professionals for referring them to the study.

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