Positive Effect of Platelet-Rich Plasma on Pain in Plantar Fasciitis

A Double-Blind Multicenter Randomized Controlled Trial

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Background: When nonoperative treatment for chronic plantar fasciitis fails, often a corticosteroid injection is given. Corticosteroid injection gives temporary pain reduction but no healing. Platelet-rich plasma (PRP) has proven to be a safe therapeutic option in the treatment of tendon, muscle, bone, and cartilage injuries.

Purpose: To determine the effectiveness of PRP as compared with corticosteroid injections for chronic plantar fasciitis.

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

Methods: Patients with chronic plantar fasciitis were allocated to have steroid injection or PRP. The primary outcome measure was the Foot Function Index (FFI) Pain score. Secondary outcome measures were function, as scored by the FFI Activity, FFI Disability, and American Orthopaedic Foot & Ankle Society, and quality of life, as scored with the short version of the World Health Organization Quality of Life (WHOQOL-BREF). All outcomes were measured at baseline and at 4, 12, and 26 weeks and 1 year after the procedure.

Results: Of the 115 patients, 63 were allocated to the PRP group, of which 46 (73%) completed the study, and 52 were allocated to the control group (corticosteroid injection), of which 36 (69%) completed the study. In the control group, FFI Pain scores decreased quickly and then remained stable during follow-up. In the PRP group, FFI Pain reduction was more modest but reached a lower point after 12 months than the control group. After adjusting for baseline differences, the PRP group showed significantly lower pain scores at the 1-year follow-up than the control group (mean difference, 14.4; 95% CI, 3.2-25.6). The number of patients with at least 25% improvement (FFI Pain score) between baseline and 12-month follow-up differed significantly between the groups. Of the 46 patients in the PRP group, 39 (84.4%) improved at least 25%, while only 20 (55.6%) of the 36 in the control group showed such an improvement (P = .003). The PRP group showed significantly lower FFI Disability scores than the control group (mean difference, 12.0; 95% CI, 2.3-21.6).

Conclusion: Treatment of patients with chronic plantar fasciitis with PRP seems to reduce pain and increase function more as compared with the effect of corticosteroid injection.

Registration: NCT00758641 (ClinicalTrials.gov identifier).

Keywords: plantar fasciitis; platelet-rich plasma; corticosteroids; pain; function

Chronic plantar fasciitis is the most common cause of foot complaint in the United States. Up to 11% to 15% of these complaints require professional care among adults. The incidence of plantar fasciitis peaks in persons between the ages of 40 and 60 years, with no bias toward either sex. The underlying condition that causes plantar fasciopathy is a degenerative tissue condition that occurs near the site of origin of the plantar fascia at the medial tuberosity of the calcaneus. In acute cases, plantar fasciitis is characterized by classic signs of inflammation, including pain, swelling, and loss of function. For more chronic conditions, however, inflammation is not the underlying tissue disruption. In fact, histology of chronic cases has shown no signs of inflammatory cell invasion into the affected area. Instead, the tissue is characterized histologically by infiltration with macrophages, lymphocytes, and plasma cells; tissue destruction; and repair involving immature vascularization and fibrosis. The normal fascia tissue is replaced by an angiofibroblastic hyperplastic tissue, which spreads itself throughout the surrounding tissue, creating a self-perpetuating cycle of degeneration.

Numerous methods have been advocated for treating plantar fasciitis, including rest, nonsteroidal anti-inflammatory medication, night splints, foot orthosis, stretching protocols, and extracorporeal shock wave therapy.
injections are a popular method of treating the condition as well, but they seem to have only small and short-term effects. Other various types of surgical procedures have been recommended. The use of corticosteroids is particularly troubling since several studies have linked plantar fascia rupture to repeated local injections of a corticosteroid. When rest, activity restriction, and nonoperative treatments do not result in a satisfactory outcome, the patient is often interested in treatment options other than surgery.

Platelet-rich plasma (PRP) is promoted as an ideal autologous biological blood-derived product that can be exogenously applied to various tissues, where it releases high concentrations of platelet-derived growth factors that enhance wound healing, bone healing, and tendon healing.

When platelets become activated, growth factors are released and initiate the body's natural healing response. In animals, the addition of growth factors to ruptured tendon has been shown to increase the healing of the tendon. In humans, it has been shown that the injection of platelets into the tendon decreases pain. In a double-blind randomized trial, we investigated whether an injection of PRP improves the outcome of patients with chronic plantar fasciitis more than corticosteroid injections. The primary outcome parameter was pain. Secondary parameters were function and quality of life.

**METHODS**

**Study Design**

Peerbooms et al published the study design in the journal *BMC Musculoskeletal Disorders* in 2010. Double-blind randomization was performed after patients were deemed eligible and provided informed consent. Patients were randomly allocated to the concentrated autologous platelet group (PRP group) or the corticosteroid group (control group). A randomization schedule was created by computer-based block randomization of 10 patients. Treatment assignments (placed in sequentially numbered opaque envelopes) were assigned by the trial managers, who also arranged the facilities needed for the procedure. The investigator who assessed the outcomes was blinded to the treatment that the patient received. The treatment was given by another investigator, who also prepared the 2 injections (J.C.P., H.M.S., T.G.). For both groups, blood was given by another investigator, who also prepared the treatment that the patient received. The treatment that the patient received. The treatment was given by another investigator, who also prepared the 2 injections (J.C.P., H.M.S., T.G.). For both groups, blood was given by another investigator, who also prepared the treatment that the patient received.

All patients with plantar fasciitis who were admitted to 1 of the participating hospitals and met the inclusion criteria were asked to join the study. Plantar fasciitis was defined as pain at the point of the fascia plantaris origin at direct palpation. All patients with plantar fasciitis were screened with a radiograph of the calcaneus for bony abnormalities and to differentiate for subtalar arthritis. Sonography and magnetic resonance imaging were not used standardly.

The medical ethical committee of the Netherlands approved the study design, procedures, and informed consent.

**Study Population**

The study was conducted at the orthopaedic departments of the HAGA Ziekenhuis Den Haag, Alrijne Ziekenhuis Leiden, Albert Schweitzer Ziekenhuis Dordrecht, Maastricht University Medical Centre, and St Elisabeth Ziekenhuis Tilburg (the Netherlands) between November 2008 and January 2015. J.C.P. and T.G. were responsible for the data and safety monitoring. Patients aged >18 years with plantar fasciitis (at least 6 months’ duration) and failed nonoperative treatment were included. Patients were able to understand the informed consent. The Foot Function Index (FFI) Pain score in the morning should be >5 (0-10 scale).

Patients were excluded from the study when they had received local steroid injections within 6 months, physical/occupational therapies within 4 weeks, or nonsteroidal anti-inflammatory drugs within 1 week before randomization. In addition, patients were excluded for any of the following reasons: inability to fulfill follow-up criteria; significant cardiovascular, renal, or hepatic disease; pregnancy; (local) malignancy; history of anemia (hemoglobin <5.0); previous surgery for plantar fasciitis; active bilateral plantar fasciitis; diagnosis of vascular insufficiency or neuropathy related to heel pain; hypothyroidism; and diabetics.

**Interventions**

*Platelet Concentrate Preparation.* Fifty-five milliliters of whole blood was collected from the uninvolved arm into a 60-mL syringe that contained 5 mL of sodium citrate. A peripheral complete blood count was also collected at the
time of the initial blood draw. The blood was then prepared according to the Gravitational Platelet Separation (GPS) instructions (Zimmer Biomet). This device is a desktop-size centrifuge with disposable cylinders for the blood, from which approximately 0.05 mL of platelet concentrate is obtained for each patient. Autologous platelet concentrate contains concentrated white blood cells and platelets suspended in plasma. Since an acidic anticoagulant is introduced to the whole blood used to produce the platelet concentrate, the platelet concentrate must be buffered to increase the pH to normal physiologic levels. This was accomplished with 8.4% sodium bicarbonate solution, added at a ratio 0.05 mL of sodium bicarbonate solution to 1 mL of platelet concentrate. The resulting buffered platelet concentrate contains an approximately 6- to 8-times concentration of platelets as compared with baseline whole blood. No activating agent was used. The total time from blood draw to injection in the patients was about 30 minutes. No specialized equipment other than the GPS machine was required.

Corticosteroid. The type of steroid that was used during the study is Kenacort (40 mg/mL of triamcinolone acetonide).

Injection Technique. Initially, bupivacaine was injected into the skin and subcutaneous tissue of both groups as a local field block. Approximately 0.05 mL was also injected directly into the area of maximum tenderness. Then, either 5 to 6 mL of platelet concentrate or 5 to 6 mL of corticosteroid was injected with a 22-gauge needle into the plantar fasciitis with a peppering technique. This technique involved a single skin portal and then 5 penetrations of the fascia.

Postprocedure Protocol. Immediately after injection, patients in both groups were kept in a sitting position without moving the foot for 15 minutes. Patients were referred to the physical therapist to be instructed in stretching exercises. Patients were sent home with instructions to limit their use of the feet for approximately 48 hours, and they used hydrocodone or acetaminophen for pain. The use of nonsteroidal medication was prohibited. After 48 hours, patients were given a standardized stretching protocol to follow for 2 weeks. A formal strengthening program was initiated after this stretching. At 4 weeks after the procedure, patients were allowed to proceed with normal sporting or recreational activities as tolerated. Any type of foot orthosis was not allowed.

Study Endpoints

Pain. The primary outcome, pain, was measured with a visual analog scale of the FFI at all time points.4,14 The FFI Pain score records the patient’s reported pain with a scale of 0 (pain-free) to 10 (worst pain imaginable). The scale is a 10-cm line, and the score is marked at the point on the line corresponding with the patient response.

Treatment was considered a success if patients showed a FFI Pain score reduction of 25% between baseline and 12-month follow-up. In addition, patients should not have required other therapies or pain medication beyond the protocol-defined allowable period. Patients who obtained a different treatment were classified as unsuccessful. To determine the percentage of change, first the baseline pain score was subtracted from the endpoint pain score. Subsequently, this difference score was divided by the baseline pain score and multiplied by 100. If a patient was lost to follow-up, the last available measurement was used to determine treatment success.

Function and Quality of Life. The secondary outcome measures of this study were FFI Disability, FFI Activity,2,4,14 and American Orthopaedic Foot & Ankle Society (AOFAS) score.13,26 Last, patients’ quality of life was assessed with the World Health Organization Quality of Life (WHOQOL-BREF).20,31 This is the short version of the WHOQOL-100. The WHOQOL-BREF consists of 4 domains (Physical Health, Psychological Health, Social Relationships, and Environment) and 2 items assessing overall quality of life and general health. The response scale consists of 5-point Likert scales. Higher scores indicate better quality of life. All outcomes in this study were measured at baseline and 1, 3, and 6 months and 1 year after the procedure.

Determination of Sample Size

Our main hypotheses were tested by investigating the interaction effect between treatment and measurement occasion, indicating whether the treatments differ in their change in outcome over time. We are not aware of earlier research comparing PRP with corticosteroid treatments for chronic plantar fasciitis on pain, function, and quality of life with a follow-up of at least 1 year. Therefore, we took a conservative stance by assuming a small partial eta-squared effect size of 0.02 and a correlation between the repeated measurements of 0.3. To detect such effect sizes with a power of 0.80 and a significance level of .05, at least 84 participants are required (42 in each group).

Statistical Analysis

For dichotomous baseline characteristics, frequencies and percentages were reported. Means and standard deviations were calculated for continuous and normally distributed baseline characteristics. For nonnormally distributed continuous characteristics, the median and interquartile range were reported.

To test the null hypothesis that the treatment groups do not differ in their change on the outcome measures over time, linear mixed modeling analyses were used, focusing on the interaction effect between treatment group and time. The influence of dosage on this treatment effect was assessed by inspecting the 3-way interaction effect among treatment group, time, and injection dosage. For all outcome measures, individual differences in growth trajectories were taken into account by allowing the intercept and slope to vary across all patients. Time was modeled continuously, and linear as well as quadratic and cubic time effects were investigated. Any differences between the treatment groups on the baseline scores of the outcome measures were handled with a longitudinal data analysis
that constrained the baseline means of the treatment groups to be equal by omitting the main effect for treatment from the statistical model. Inferences regarding the difference between treatments were based on the interaction effect between treatment group and time. In the linear mixed model analysis, parameters were estimated with restricted maximum likelihood estimation.

Analysis of covariance was used to test the null hypothesis of equal outcome means at the 12-month follow-up, adjusted for baseline differences. The effects of all aforementioned analyses were adjusted for the potential confounders sex, smoking, and duration of symptoms before treatment. Differences between groups in the number of patients showing at least 25% improvement in pain symptoms were assessed with a chi-square test.

P values < .05 were considered statistically significant for the primary outcome measure (FFI Pain), while a Bonferroni correction was applied to adjust for multiple testing of the treatment effects for the secondary and remaining outcome measures. To retain sufficient statistical power, the Bonferroni correction was applied separately to the secondary outcomes (FFI Disability and Activity, AOFAS; significance level = .05 / 3 = .0167) and the remaining outcome measures (WHOQOL-BREF; significance level = .05 / 5 = .01). Confidence intervals were calculated at the 95% level. All data were analyzed by a blinded researcher (P.L.) using SPSS (v 23; IBM).

RESULTS

The flowchart in Figure 1 indicates that of all 115 randomized patients, 63 were allocated to the PRP group and 52 to the control group. Of the 63 patients in the PRP group, 46 completed the study, and 17 were lost during the 12-month follow-up. For logistic reasons, 16 patients were treated with an injection made of the 30-mL PRP kit instead of the 60-mL PRP kit. The influence of dosage on the treatment effect was assessed by inspecting the 3-way interaction effect among treatment group, time, and injection dosage. No differences were seen between the 30- and 60-mL doses. In the control group, 36 patients completed the study, and 16 were lost to follow-up.

Table 1 presents the baseline characteristics for patients allocated to the PRP and control group separately.

Appendix Table A1 (available in the online version of this article) indicates that for all outcome measures, the Little MCAR test (missing completely at random) failed to reach significance, suggesting that the missing values on those outcome measures were likely missing completely at random. This result allowed for handling missing data on the outcome measures by means of maximum likelihood estimation in the mixed model analysis, as this method assumes the missing values to be either missing at random or missing completely at random.

Table 2 presents the results of the linear mixed modeling analysis for all outcome measures. For each outcome, the treatment × time interaction effects in the second column pertain to a model including only a linear time effect, while the similar tests in the third column are derived from a model including linear as well as quadratic and cubic time effects. The linear time models assume that patients change linearly over time on the outcome measures. For these models, the FFI Pain, FFI Disability, FFI Activity, and AOFAS outcomes showed significant interaction effects between treatment and time, suggesting that the treatment groups differed in their change in these outcomes over time. However, when we inspected the results of the models that also included quadratic and cubic time effects, it turns out that the treatment groups showed significant differences in their change on only the FFI Pain scores over time and no longer on the FFI Disability, FFI Activity, and AOFAS outcomes.

Note that in the models including linear, quadratic, and cubic time effects, we report in Table 2 only the interaction effects between treatment and linear time. The interactions between treatment and quadratic and cubic time were included in the model, although their significance was similar to that of the linear time × treatment interaction. We decided to report the results of the linear time × treatment interaction to test the null hypothesis that the 2 groups were equal in their change on the outcome over time, after accounting for nonlinear change in the outcome measure. This is exactly what we were interested in; therefore, we did not report the interactions of treatment with the quadratic and cubic time effects.

A possible explanation for this discrepancy is that the assumption of linear change over time is implausible. If change in an outcome over time is not linear yet time is...
modeled only linearly, then spurious interaction effects between time and other variables may arise. Indeed, the FFI Pain, FFI Disability, FFI Activity, AOFAS, and WHOQOL-BREF Physical Health models showed linear as well as significant quadratic and cubic time effects, suggesting that the change in these outcome measures could not be considered linear. This finding is corroborated by visual inspection of the growth curves of both treatment groups (Figure 2).
The treatment groups did not show differences with respect to their change in quality of life over time, as indicated by the nonsignificant treatment × time interaction effects for all models involving the WHOQOL-BREF outcomes.

Appendix Table A2 (available online) is similar to Table 2, yet it presents the results of the 3-way interaction among treatment group, time, and dosage. This test indicates whether the differences between treatment groups in the change in the outcome measures over time depend on the used injection dosage. For all outcome measures, this interaction effect failed to reach significance, both for models with linear time only and for models with linear, quadratic, and cubic time effects. These results suggest that the injection dosage did not affect the differences between the treatment groups in their change on the outcomes over time.

Based on the mixed model analysis, only the change in FFI Pain scores differed significantly between the
treatment groups. Inspection of Figure 2 indicates that both treatment groups show decreased pain over time. In the control group, the pain scores decreased quickly after the treatment and then remained stable during the follow-up. In the PRP group, the pain reduction was more modest yet reached a lower point at the 12-month follow-up than the control group. This finding is confirmed by the analysis of covariance reported in Table 3. After adjusting for baseline differences in FFI Pain scores, the patients in the PRP group showed significantly lower pain scores than patients in the control group (mean difference, 14.4; 95% CI, 2.3-21.6). Although the mixed model analysis did not indicate a significant treatment effect for the FFI Disability outcome, the analysis of covariance suggests that after adjusting for baseline differences, patients in the PRP group also showed significantly lower FFI Disability scores than patients in the control group (mean difference, 12.66). For all WHOQOL-BREF outcomes, the differences between the treatment groups at the 12-month follow-up failed to reach significance.

Last, Table 4 shows for both treatment groups the number of patients with at least 25% improvement in FFI Pain score between baseline and the 12-month follow-up. It turns out that of the 46 patients in the PRP group, 39 (84.8%) improved at least 25%, while only 20 (55.6%) of the 36 patients in the control group showed such an improvement. This difference was statistically significant ($\chi^2[1] = 8.6; P = .003; \text{odds ratio,} 4.5; 95\% \text{ CI,} 1.6-12.7$).

### DISCUSSION

This randomized study was designed to test the effectiveness of PRP as compared with corticosteroid injections for chronic plantar fasciitis.

There is no standard of care management for chronic recalcitrant plantar fasciitis that is nonresponsive to nonoperative treatment. Many researchers believe that, since plantar fasciitis is a degenerative disease, regenerative potential of PRP could help. The treatment of a degenerative tendon disease with an injection of concentrated autologous platelets may be a nonoperative alternative. By utilizing the GPS system, the patient’s own platelets can be collected into a highly concentrated formula. We postulate that the concentrated growth factors work in a synergetic manner to initiate a tendon healing response. This hypothesis is supported by in vitro research in the literature. Transforming growth factor $\beta1$ is shown to significantly increase type I collagen production by tendon sheath fibroblasts. This same mechanism is likely to be active in chronic plantar fasciitis.

In this study, we followed the patients for 1 year after intervention; pain at the end of 1 year was our primary end point, as assessed with the FFI Pain scale. Function and quality of life were the secondary outcome measures.
Our results show that the 2 treatments differed in their change in pain score over time. Patients in the PRP group showed significantly lower pain and disability scores than patients in the control group after adjusting for baseline differences. Differences between the treatment groups at 1-year follow-up were not found with respect to function (FFI Activity and AOFAS) and quality of life (WHOQOL-BREF). A larger percentage of patients showed at least a 25% improvement in pain score between baseline and the 1-year follow-up in the PRP group (84.8%) than in the control group (55.6%). Our findings in this study, with a decrease in pain and disability after a PRP injection, compared well with other published studies on treatment of plantar fasciitis.29 It also showed similar outcomes when compared with a previous study where the same GPS and injection techniques were used for patients with chronic lateral epicondylitis.23 Here the authors also concluded that the corticosteroid group was initially better and then declined, whereas the PRP group progressively improved.

According to Gonnade et al10 in their recent article, previous observational studies and a few randomized clinical trials on plantar fasciitis have concluded that PRP is an effective therapy in chronic cases, but still there is controversy owing to a lack of level 1 evidence. In a single-blinded prospective randomized longitudinal case series of 40 patients, Monto21 concluded that PRP injection is more efficacious and long-lasting than cortisone injection in the long-term management of severe chronic plantar fasciitis. One trial by Shetty et al18 also compared PRP with cortisone, but they found no difference between the two. The drawback of Shetty et al’s study is the short follow-up of only 3 months. The most recent study by Mahindra et al18 found that PRP and cortisone are better than placebo, but at 3 months of follow-up, PRP injection was significantly better than corticosteroid injection.

To our knowledge, this is the first randomized study that compared PRP with corticosteroids in >100 patients with plantar fasciitis. Treatment of patients with chronic plantar fasciitis with PRP seems to reduce pain and increase function as compared with the effect of corticosteroid injection. Our findings are comparable with other studies, but this study had a 1-year follow-up. All other randomized studies had a maximum follow-up of 3 months.10

There are some limitations of our study. First, we have to address the violation of protocol. Sixteen patients were treated with a 30-mL PRP kit instead of the 60-mL PRP kit as described in the protocol. This was due to logistic reasons and occurred in only 1 of the treating centers. Because the results suggest that the injection dosage did not affect the differences between the treatment groups in their change on the outcomes over time, we did not exclude them from this study. Our statistical analyses were also adjusted to accommodate for this protocol violation. Furthermore, there is large heterogeneity among systems with regard to the concentrations of platelets, leukocytes, and growth factors in PRP. The choice for the most appropriate type of PRP should be based on the specific clinical field of application,22 but there is no significant difference between the concentrations of PRP obtained with the GPS II (30-mL blood) and GPS III (60-mL blood) systems.12 Second, we did not use ultrasound-guided injections for both groups. There is always a debate about the fact that injections would not have been given at the exact spot where they were needed. Ultrasound-guided technique is advocated in previous studies.10 Kane et al11 showed no advantages of ultrasound guidance over direct palpation of the most tender area for guidance for the injections. A final limitation is that we have no data on the characteristics between the study group and the 8 patients who were not suitable for further allocation. Potentially, this could lead to a bias.

In conclusion, this report describes the first comparison of an autologous platelet concentrate with corticosteroids as a treatment for chronic plantar fasciitis in patients who have undergone failed nonoperative treatment, with a follow-up of 1 year. It demonstrates that a single injection of concentrated autologous platelets improves pain and function more so than corticosteroid injection. These improvements were sustained over time with no reported complications. Future decisions for application of the PRP for plantar fasciitis should be confirmed by further follow-up from this trial and should take into account possible costs and harms as well as benefits.

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