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# Ongoing Positive Effect of Platelet-Rich Plasma Versus Corticosteroid Injection in Lateral Epicondylitis

## A Double-Blind Randomized Controlled Trial With 2-year Follow-up

Taco Gosens,<sup>\*†</sup> MD, PhD, Joost C. Peerbooms,<sup>‡</sup> MD, Wilbert van Laar,<sup>‡</sup> and Brenda L. den Ouden,<sup>†</sup> PhD

*Investigation performed at St Elisabeth Hospital, Tilburg, the Netherlands, and Haga Hospital, The Hague, the Netherlands*

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**Background:** Platelet-rich plasma (PRP) has been shown to be a general stimulation for repair and 1-year results showed promising success percentages.

**Purpose:** This trial was undertaken to determine the effectiveness of PRP compared with corticosteroid injections in patients with chronic lateral epicondylitis with a 2-year follow-up.

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

**Methods:** The trial was conducted in 2 Dutch teaching hospitals. One hundred patients with chronic lateral epicondylitis were randomly assigned to a leukocyte-enriched PRP group (n = 51) or the corticosteroid group (n = 49). Randomization and allocation to the trial group were carried out by a central computer system. Patients received either a corticosteroid injection or an autologous platelet concentrate injection through a peppering needling technique. The primary analysis included visual analog scale (VAS) pain scores and Disabilities of the Arm, Shoulder and Hand (DASH) outcome scores.

**Results:** The PRP group was more often successfully treated than the corticosteroid group ( $P < .0001$ ). Success was defined as a reduction of 25% on VAS or DASH scores without a reintervention after 2 years. When baseline VAS and DASH scores were compared with the scores at 2-year follow-up, both groups significantly improved across time (intention-to-treat principle). However, the DASH scores of the corticosteroid group returned to baseline levels, while those of the PRP group significantly improved (as-treated principle). There were no complications related to the use of PRP.

**Conclusion:** Treatment of patients with chronic lateral epicondylitis with PRP reduces pain and increases function significantly, exceeding the effect of corticosteroid injection even after a follow-up of 2 years. Future decisions for application of PRP for lateral epicondylitis should be confirmed by further follow-up from this trial and should take into account possible costs and harms as well as benefits.

**Keywords:** lateral epicondylitis; platelet-rich plasma; corticosteroids; pain; disability

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Lateral epicondylitis is the most commonly diagnosed condition of the elbow and affects approximately 1% to 3% of the population. The condition mostly occurs in patients whose activities require strong gripping or repetitive wrist movements. Individuals between the ages of 35 and 50 years are at high risk. The dominant arm is most frequently affected.<sup>11,12,19</sup>

The cause of lateral epicondylitis is unknown. It is thought that lesions occur in the common origin of the wrist and finger extensors on the lateral epicondyle because of a combination of mechanical overloading and abnormal microvascular responses.<sup>18,29,34</sup>

Numerous methods have been advocated for treating elbow tendinosis, including rest, nonsteroidal anti-inflammatory

medication, bracing, physical therapy, extracorporeal shockwave therapy, and botulinum toxin injection. Injection of corticosteroids, which was considered to be the gold standard before but is actually currently controversial, or whole-blood injections and various types of surgical procedures have also been recommended.<sup>2,6,25,28,35</sup>

In an animal model, the addition of growth factors to the ruptured tendon has been shown to increase the healing of the tendon.<sup>1,16</sup> In humans, the injection of whole blood into the tendon at least decreases pain.<sup>6</sup>

Platelet-rich plasma (PRP) is promoted as an ideal biologic autologous blood-derived product. It can be exogenously applied to various tissues where, upon platelet activation, a release of high concentrations of platelet-derived growth factors occurs. Platelet-rich plasma applications enhance wound healing, bone healing, and also tendon healing.<sup>22</sup> In addition, PRP also possesses antimicrobial properties that may contribute to the prevention of infections.<sup>8</sup> As nowadays various different ways to produce PRP are available, it is of eminent importance to discriminate between leukocyte-enriched or leukocyte-depleted PRP. Accordingly, platelet concentrates have been categorized in either pure PRP (P-PRP), in which leukocytes are purposely eliminated from the PRP, or leukocyte and PRP (L-PRP), containing a high concentration of leukocytes.<sup>5</sup>

We recently published the 1-year results of a double-blind randomized trial showing the improved outcome of patients with epicondylitis after an injection of concentrated autologous leukocytes and platelets compared with corticosteroid injection.<sup>20</sup> Few studies have examined the effectiveness of PRP against corticosteroids. The primary outcome parameters were pain and daily use of the elbow. However, as data on a longer follow-up regarding the effectiveness of PRP are currently lacking, we now present the 2-year follow-up of this trial using the same outcome parameters.

## METHODS

This double-blind randomized trial included 100 consecutive patients with lateral epicondylitis for injection therapy in 2 Dutch training hospitals (St Elisabeth Hospital and Haga Hospital) between May 2006 and January 2008. The PRP preparation was done using the Recover system (Biomet Biologics, Warsaw, Indiana). This device uses a desktop-size centrifuge with disposable cylinders to isolate the platelet and leukocyte-rich fraction from a small volume of the patient's anticoagulated blood drawn at the time of the procedure. Both PRP and corticosteroids were injected into the common extensor tendon using a 22-gauge needle and a peppering technique. Further information on the study design, power analysis, enrollment criteria, and treatment methods can be found in the 1-year follow-up report.<sup>20</sup> The Medical Ethical Committee and the National and Institutional Review Board approved the study. This trial is registered with identifier number 2007-004947-31 at <http://www.clinicaltrials.gov>.

## Instruments

Patients completed 2 self-report instruments at every time point: the Disabilities of the Arm, Shoulder and Hand (DASH) outcome measure and a visual analog scale (VAS) for pain.

The DASH is a 30-item, self-report questionnaire designed to assess physical function and symptoms in persons with any of several musculoskeletal disorders of the upper limbs.<sup>3,32</sup> The items assess the degree of difficulty in performing various physical activities because of an arm, shoulder, or hand problem (21 items), the severity of each of the symptoms of pain, activity-related pain, tingling, weakness, and stiffness (5 items), and the problem's effect on social activities, work, and sleep, and its psychological effect (4 items). The DASH also contains 2 optional 4-item scales concerning the ability to perform sports and/or to play a musical instrument (sport/music scale), and the ability to work (work scale). In this study, the 2 optional scales were not used in the analyses. A 5-point Likert scale ranging from 1 (no difficulty or no symptom) to 5 (unable to perform activity or very severe symptom) is used. The scores for all items are then used to calculate a total scale score ranging from 0 (no disability) to 100 (severest disability). The psychometric properties of the DASH outcome measure are adequate to good.<sup>3,32</sup>

A VAS is a measurement instrument to quantify the amount of pain reported by the patient. Scores can range from 0 (no pain) to 100 (severest pain).

Data concerning type of treatment (corticosteroids or PRP), type of reintervention, complications, side, sex, and age were retrieved from medical files.

## Statistical Analyses

Frequencies were used to present the available sociodemographic and clinical data. Student *t* tests (continuous data) and  $\chi^2$  tests (categorical data) were used to examine differences between (1) the protocol-compliant group and the reintervention patients, (2) the corticosteroid group and the PRP group, and (3) the successfully treated group and the nonsuccessfully treated group. The protocol-compliant group was defined as the group of patients who did not need a reintervention (ie, reinjection, crossover, or surgery). Successful treatment was defined as more than 25% reduction on the VAS pain score and the DASH total scores without a reintervention after 2 years compared with the preinjection scores. This 25% reduction closely resembles the MCID (minimum clinically important difference), which is 10.2 points for the DASH score.<sup>21</sup> To examine differences in VAS pain scores and DASH total scores between the PRP group and the corticosteroid group before and after the intervention, multivariate analyses of variance for repeated measures were used. Multiple post hoc comparisons were corrected with the Bonferroni method. To determine whether the corticosteroid group and PRP group scored significantly different at a specific time point, Student *t* tests were used. The VAS pain score and DASH total scores were analyzed according to the intention-to-treat

principle (based on the allocated intervention) and according to the as-treated principle (based on the received treatment). Missing values are replaced by the last observed value of that variable for each individual (last observation carried forward). All statistical analyses were performed using the Statistical Package for the Social Sciences (version 17.0, SPSS, Chicago, Illinois).

## RESULTS

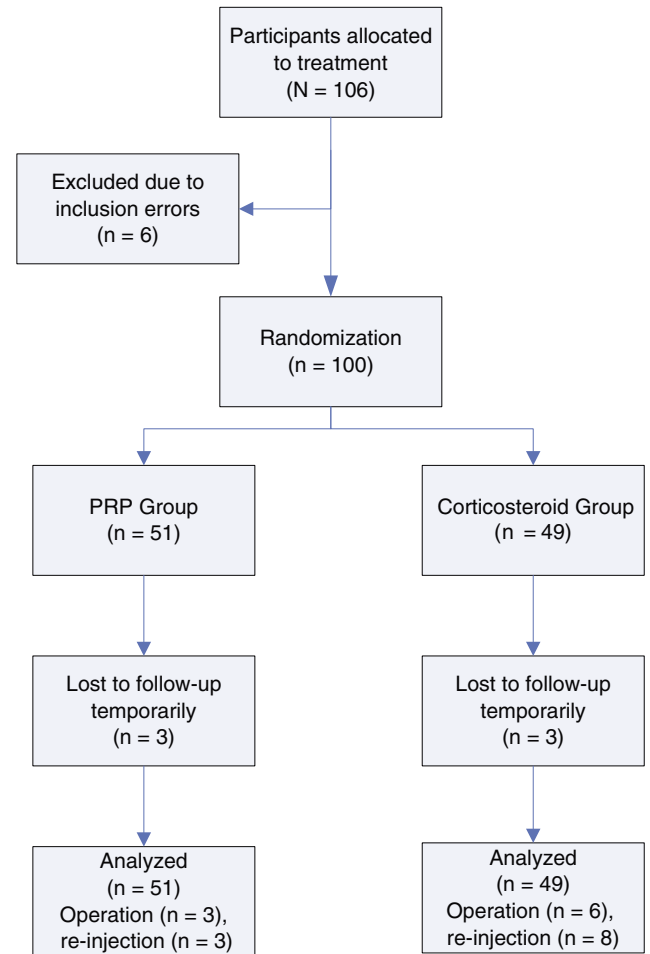
From May 2006 to January 2008, a total of 100 eligible patients with epicondylitis were randomized into either a PRP injection group or a corticosteroid injection group. Six patients were lost to follow-up because of wrongful inclusion (Figure 1). Analysis of the baseline characteristics (age, sex, side, hand dominance, VAS score, DASH score) between the protocol-compliant patients and those lost to follow-up showed no significant differences ( $P > .05$ ). Sociodemographic and clinical characteristics of the participants are shown in Table 1. The PRP group and the corticosteroid group did not differ on demographic or clinical characteristics ( $P > .05$ ). However, at baseline, the PRP group did score significantly higher on the DASH total score compared with the corticosteroid group ( $P < .0001$ ).

### Course of VAS Pain Scores (Intention-to-Treat Principle)

As shown in Figure 2A, the course of the VAS scores across assessment points is different for the group treated with corticosteroids and the PRP group ( $P < .0001$ ). Table 2 shows the mean scores and standard deviations. The baseline scores of the corticosteroid group were significantly higher compared with all subsequent time points ( $P < .0001$ ), except for 26 weeks ( $P = .029$ ). Between 8 weeks and 26 weeks, pain scores temporarily got worse ( $P = .007$ ). In contrast, compared with baseline scores, the scores of the PRP group significantly improved during the entire duration of the study ( $P < .002$ ). Overall, the average VAS scores differed significantly between the 2 groups ( $F_{1,98} = 6.3$ ,  $P = .014$ ). When VAS scores were compared at each assessment point separately, the PRP group scored significantly worse at 4 weeks after the injection ( $P < .023$ ), while the opposite was found at 26 weeks ( $P < .0001$ ), 52 weeks ( $P < .0001$ ), and 104 weeks ( $P < .0001$ ) after treatment. No differences between the PRP group and the corticosteroid group were found at baseline, 8 weeks, and 12 weeks. In general, the results of the intention-to-treat analysis and the as-treated analysis were comparable (Figure 2B).

### Successful Treatment (VAS Score)

In total, 60 of 100 patients were successfully treated, which was defined as a reduction of 25% on the VAS pain score without a reintervention after 2 years. Table 3 shows



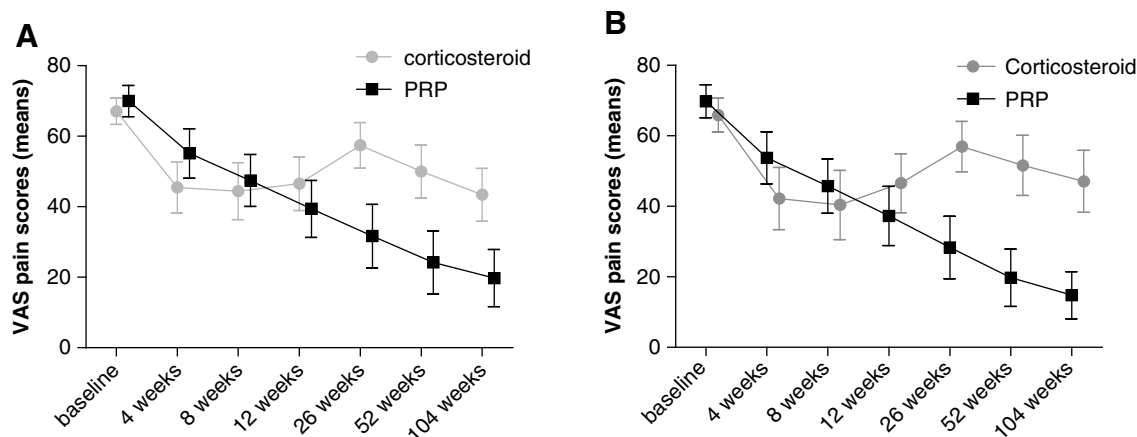
**Figure 1.** Flow diagram of a trial of injection therapy for chronic lateral epicondylitis. The diagram includes the number of patients actively followed up at different times during the trial.

**TABLE 1**  
Baseline Characteristics of the Corticosteroid and Platelet-Rich Plasma Groups<sup>a</sup>

|                                    | Corticosteroid<br>(n = 49) | Platelet-Rich<br>Plasma (n = 51) | P<br>Value |
|------------------------------------|----------------------------|----------------------------------|------------|
| Age, mean ± SD                     | 47.3 ± 7.8                 | 46.8 ± 8.5                       | .780       |
| Male sex, no. (%)                  | 23 (44.2)                  | 23 (47.9)                        | .712       |
| Right side, no. (%)                | 32 (61.5)                  | 30 (62.5)                        | .921       |
| Dominant hand<br>involved, no. (%) | 37 (75.5)                  | 38 (74.5)                        | .908       |
| VAS, mean ± SD                     | 67.1 ± 13.5                | 70.2 ± 15.2                      | .285       |
| DASH, mean ± SD                    | 44.1 ± 16.2                | 56.3 ± 17.7                      | <.0001     |

<sup>a</sup>SD, standard deviation; VAS, visual analog scale; DASH, Disabilities of the Arm, Shoulder and Hand outcome measure.

that the PRP group was more often treated successfully (n = 39) than the corticosteroid group (n = 21;  $P < .0001$ ). However, compared with baseline VAS pain scores, a number of patients (n = 11) had deteriorated in VAS pain scores



**Figure 2.** The course of visual analog scale (VAS) pain scores across assessment points. Bars present 95% confidence intervals. Patients with chronic lateral epicondylitis were randomly assigned to the platelet-rich plasma (PRP) group or the corticosteroid group. A, intention to treat; B, reintervention excluded.

**TABLE 2**  
DASH and VAS Scores for the Corticosteroid Group and the PRP Group at the Various Time Points (Intention-to-Treat Analyses)<sup>a</sup>

| Time      | Intervention   | DASH        |         | VAS         |         |
|-----------|----------------|-------------|---------|-------------|---------|
|           |                | Mean ± SD   | P Value | Mean ± SD   | P Value |
| Baseline  | Corticosteroid | 43.3 ± 16.1 | .002    | 66.2 ± 14.0 | .340    |
|           | PRP            | 54.3 ± 19.5 |         | 69.0 ± 15.9 |         |
| 4 weeks   | Corticosteroid | 31.2 ± 20.8 | .005    | 44.3 ± 26.3 | .023    |
|           | PRP            | 43.1 ± 21.6 |         | 55.7 ± 24.1 |         |
| 8 weeks   | Corticosteroid | 28.3 ± 22.2 | .060    | 43.4 ± 28.9 | .411    |
|           | PRP            | 37.2 ± 24.7 |         | 47.7 ± 25.0 |         |
| 12 weeks  | Corticosteroid | 32.3 ± 21.7 | .813    | 45.5 ± 27.1 | .319    |
|           | PRP            | 21.3 ± 22.0 |         | 40.2 ± 27.5 |         |
| 26 weeks  | Corticosteroid | 37.6 ± 23.1 | .037    | 55.8 ± 24.1 | <.0001  |
|           | PRP            | 27.8 ± 24.7 |         | 32.9 ± 30.8 |         |
| 52 weeks  | Corticosteroid | 36.8 ± 24.0 | <.0001  | 48.8 ± 27.0 | <.0001  |
|           | PRP            | 20.0 ± 23.5 |         | 25.9 ± 30.6 |         |
| 104 weeks | Corticosteroid | 36.5 ± 23.8 | <.0001  | 42.4 ± 26.8 | <.0001  |
|           | PRP            | 17.6 ± 24.0 |         | 21.3 ± 28.1 |         |

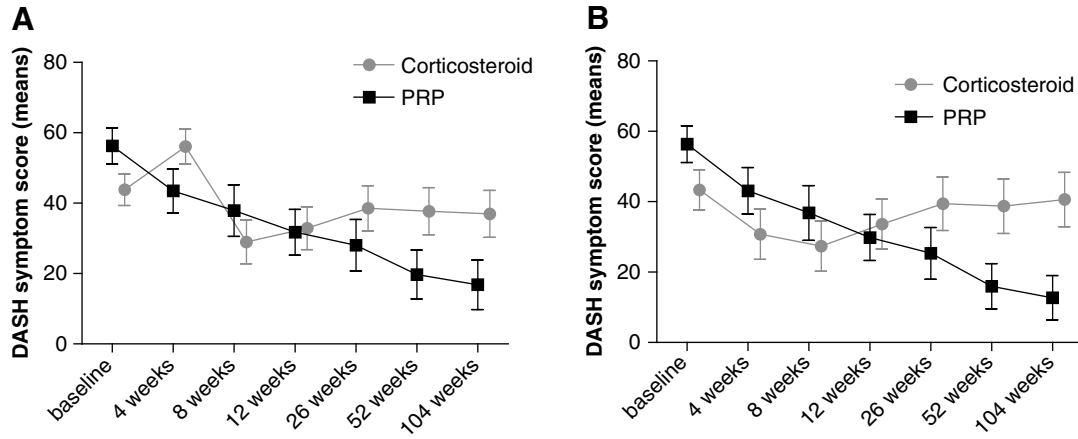
<sup>a</sup>DASH, Disabilities of the Arm, Shoulder and Hand outcome measure; VAS, visual analog scale; PRP, platelet-rich plasma; SD, standard deviation.

at 2-year follow-up. Of these 11 patients, the majority received a corticosteroid injection (n = 9), while 2 patients received a PRP injection (P = .017). Eventually, 1 patient had received a reinjection with corticosteroids, 1 patient crossed over to the PRP group, and 2 patients received surgery.

**Course of DASH Disability Symptom Scores (Intention-to-Treat Principle)**

As shown in Figure 3A, the course of the DASH disability symptom scores showed an overall improvement (F<sub>6,93</sub> = 18.4, P < .0001). The baseline DASH scores of the corticosteroid group were significantly higher compared with the

scores at 8 weeks (P < .0001) and 12 weeks after injection (P < .006). Between baseline and 4 weeks, DASH scores significantly deteriorated (P < .0001). Although differences were not significant, after 12 weeks, DASH scores deteriorated. In contrast, compared with baseline scores, the scores of the PRP group significantly improved during the entire duration of the study (P < .002). Overall, the average DASH disability symptom scores did not differ significantly between the intervention groups (P = .455). However, when DASH scores were compared at each assessment point separately, the PRP group scored significantly worse at baseline and at 4 weeks after the injection (P < .005), while the opposite was found at 26 weeks (P = .037), 52 weeks (P < .0001), and 104 weeks (P < .0001) after treatment.



**Figure 3.** The course of Disabilities of the Arm, Shoulder and Hand (DASH) disability symptom scores across assessment points. Bars present 95% confidence intervals. Patients with chronic lateral epicondylitis were randomly assigned to the PRP group or the corticosteroid group. A, intention-to-treat; B, reintervention excluded.

**TABLE 3**  
Baseline Characteristics of the Successful and Nonsuccessful Groups<sup>a</sup>

|  | Successful (n = 60) | Nonsuccessful (n = 40) | P Value |
|--|---------------------|------------------------|---------|
| Age, mean ± SD                         | 45.9 ± 8.7          | 48.8 ± 7.0             | .084    |
| Sex, male/female, no. (%)              | 29 (48.3)/31 (51.7) | 17 (42.5)/23 (57.5)    | .566    |
| Side, right/left, no. (%)              | 35 (58.3)/25 (41.7) | 27 (67.5)/13 (32.5)    | .355    |
| Treatment, PRP/corticosteroid, no. (%) | 39 (65.0)/21 (35.0) | 9 (22.5)/31 (77.5)     | <.0001  |
| VAS, mean ± SD                         | 67.6 ± 14.4         | 70.2 ± 14.4            | .382    |
| DASH, mean ± SD                        | 52.9 ± 17.9         | 45.5 ± 17.2            | .044    |

<sup>a</sup>SD, standard deviation; PRP, platelet-rich plasma; VAS, visual analog scale; DASH, Disabilities of the Arm, Shoulder and Hand outcome measure.

**TABLE 4**  
Baseline Characteristics of the Protocol-Compliant Group and the Reintervention Group<sup>a</sup>

|  | Protocol-Compliant (n = 80) | Reintervention (n = 20) | P Value |
|--|-----------------------------|-------------------------|---------|
| Age, mean ± SD                         | 46.5 ± 8.2                  | 49.2 ± 7.6              | .206    |
| Sex, male/female, no. (%)              | 41 (51.2)/39 (48.8)         | 5 (25.0)/15 (75.0)      | .015    |
| Side, right/left, no. (%)              | 46 (57.5)/34 (43.5)         | 16 (80.0)/4 (20.0)      | .027    |
| Treatment, PRP/corticosteroid, no. (%) | 45 (56.3)/35 (44.7)         | 6 (30.0)/14 (70.0)      | .036    |
| VAS, mean ± SD                         | 68.1 ± 14.9                 | 70.8 ± 11.9             | .464    |
| DASH, mean ± SD                        | 50.4 ± 18.2                 | 48.2 ± 17.2             | .663    |

<sup>a</sup>SD, standard deviation; PRP, platelet-rich plasma; VAS, visual analog scale; DASH, Disabilities of the Arm, Shoulder and Hand outcome measure.

In general, the results of the intention-to-treat analysis and the as-treated analysis were comparable (Figure 3B). However, when the baseline scores of the corticosteroid group were compared with the 2-year results in the as-treated analysis, no significant difference was found ( $P = .438$ ), indicating that the corticosteroid group returned back to baseline levels. In addition, the deterioration in the corticosteroid group between baseline and 4 weeks disappeared.

**Successful Treatment (DASH Symptom Score)**

In total, 56 of 100 patients (56.0%) were successfully treated, which was defined as a reduction of 25% on the DASH score without a reintervention after 2 years. Patients in the PRP group were more often treated successfully ( $n = 37$ ;  $P < .0001$ ) compared with the corticosteroid group ( $n = 19$ ). However, compared with baseline DASH scores, a number of patients ( $n = 30$ ) had deteriorated at 2-year



follow-up. The majority of patients in this group received a corticosteroid injection ( $n = 23$ ), while 7 patients received a PRP injection ( $P = .001$ ). Eventually, 1 patient received a reinjection, 1 patient crossed over to the PRP group, and 4 patients received surgery.

### Failures (Reinterventions)

Table 4 shows the characteristics of the 20 reinterventions. On average, reinterventions or operations were needed after an average of 6 months (range, 2-14 months). At baseline, 14 patients were allocated to corticosteroids and 6 patients received an injection with PRP ( $P = .036$ ). The protocol-compliant group and the reintervention group differed significantly regarding sex ( $P = .015$ ) and side ( $P = .027$ ).

There were 6 reinterventions in the PRP group: 3 patients who required an operation and 3 patients who required a reinjection with corticosteroids. Except for 1 reinjection, all reinterventions were performed in the first year after the initial treatment; 2 operations and 1 reinjection with corticosteroids occurred within 3 months after the PRP injection. There were 14 reinterventions in the corticosteroid group: 6 patients required an operation, 1 patient required a reinjection with corticosteroids every 3 months and declined surgery, and 7 patients crossed over to have a PRP injection.

In the corticosteroid group, all reinterventions were performed in the first year of follow-up except for 1 crossover patient receiving a PRP injection. Regarding the patients who failed their initial treatment, those who crossed over to the PRP group significantly improved on both VAS pain scores ( $P < .001$ ) and DASH disability symptom scores ( $P = .019$ ). However, patients who received surgery or a reinjection with corticosteroids did not benefit when their VAS and DASH scores at 2 years were compared with their baseline scores. No complications were seen concerning the use of PRP, except for the initial worsening of pain because of the activation of the inflammation cycle, which usually lasted for 1 to 2 weeks.

## DISCUSSION

This randomized, double-blind study was designed to compare the use of concentrated autologous platelets to corticosteroid in patients with lateral epicondylitis; its application proved to be both safe and easy. The corticosteroid group was actually better initially and then declined, returning to baseline level concerning functional impairment, while the PRP group progressively improved. There was a significant difference in decrease of pain and disability of function after the platelet application even after 2 years. Comparing the results presented here with the results of the 1-year follow up, the effect in the corticosteroid group declined, whereas the result in the PRP group was maintained. A remarkable finding was that the PRP group had worse DASH scores before treatment and better ones after 26 weeks of the initial treatment. This adds to the power of our conclusion that that PRP was helpful.

Lateral epicondylitis is a common problem with many available treatment methods. The most commonly recommended treatment is physiotherapy and bracing. Approximately 87% of the patients benefit from this combination of treatment methods.<sup>30</sup> Corticosteroid injection, nowadays seen as controversial, was considered the gold standard in the treatment of lateral epicondylitis. However, studies show it is merely the best treatment option in the short term, when compared with physiotherapy and a wait-and-see policy. Often, poor results are seen after 12 weeks of follow-up.<sup>28</sup> Treatment with corticosteroids has a high frequency of relapse and recurrence, probably because intratendinous injection may lead to permanent adverse changes within the structure of the tendon and because patients tend to overuse the arm after injection as a result of direct pain relief.<sup>28</sup> In our study, the recurrence rate and need for repeated injection or surgery was also larger in the corticosteroid group than in the PRP group. Actually, of the 11% getting worse after the injection, the vast majority was found in the corticosteroid group. Smidt et al<sup>26</sup> showed in a meta-analysis that the effects of steroid injections compared with placebo injection, injection with local anesthetics, injection with another steroid, or another non-operative treatment are not significantly different in the intermediate and long term. However, the studies acknowledging the relatively good results of a wait-and-see policy, physiotherapy, and even corticosteroid injections are studies that included patients who all had nonchronic lateral epicondylitis (ie, patients with complaints of less than 6 months' duration). The current study included patients with a duration of symptoms of >6 months. Smidt et al<sup>27</sup> showed most patients recover from lateral epicondylitis within 1 year but that beyond 6 months, not much natural recovery is seen.

Our original power analysis in the 1-year follow-up paper<sup>20</sup> with an alpha of .05 and a beta of .9 was based on the 93% success in the Mishra and Pavelko<sup>15</sup> study for PRP and the 65% success in the Hay et al<sup>10</sup> study for corticosteroid injection, both obtained after 6 months. Our study presents the results after 2 years so possibly the power at 6 months is correct, but the power after 2 years of follow-up does not need to be, rendering this study underpowered at the 2-year follow-up. However, a beta of .9 is higher than in most studies. More important, there is no additional improvement in symptoms from a wait-and-see policy or a steroid injection beyond 1 year (actually, there seems to be no additional gain in recovery percentages in waiting beyond 6 months).<sup>27</sup> Although we do not know what the success percentages will be at 2 years of natural history or after 1 steroid injection, there is no evidence to suggest it would be very different from what we used for the 6-month power analysis.

For those who do not recover, there are various types of surgical procedures for patients with chronic lateral epicondylitis. Verhaar et al<sup>33</sup> noted an improvement in 60% to 70% of the patients after surgical treatment, although more recently higher success rates (80%-90%) have been reported.<sup>31</sup> Patients remain, however, interested in an alternative to surgical intervention.

Platelet-rich plasma is promoted as an ideal biologic autologous blood-derived product. It can be exogenously applied to various tissues, where after platelet activation, high concentrations of platelet-derived growth factors that enhance tissue healing are released.<sup>8,36</sup> Utilizing the Recover system, the patient's own platelets can be collected into a highly concentrated formula. No activation agent was used during our procedure. The activation of the platelets will occur through the exposure of platelets to the thrombin. The thrombin is produced as a reaction to the injection of the platelets into the tendon tissue using a pepping technique. The exposed collagen may also serve as an activator. Several negative side effects are known when using bovine thrombin as an exogenous activator, limiting its clinical use: undesirable immune responses in humans,<sup>13</sup> and inhibition of cell proliferation and viability in vitro.<sup>17</sup> This may be overcome when using an autologous-derived thrombin. Collagen is an attractive alternative to bovine thrombin as it is naturally involved in the intrinsic clotting cascade. Fufa et al<sup>9</sup> measured clinically relevant levels of transforming growth factor beta (TGF- $\beta$ 1), platelet-derived growth factor (PDGF-AB), and vascular endothelial growth factor (VEGF) from both type I collagen-activated as well as bovine thrombin-activated PRP.

During the first 2 days of tendon healing, an inflammatory process is initiated by migration of neutrophils and subsequently macrophages to the degenerative tissue site. In turn, activated macrophages release multiple growth factors, including PDGF, TGF- $\alpha$  and TGF- $\beta$ , interleukin-1, and fibroblast growth factor.<sup>7</sup> Angiogenesis and fibroplasia start shortly after day 3, followed by collagen synthesis on days 3 to 5. This process leads to an early increase in tendon breaking strength, which is the most important tendon healing parameter, followed by epithelialization and the ultimately the remodeling process. This course of repair was confirmed in a previous animal study.<sup>1</sup>

The presence of an elevated concentration of leukocytes in the PRP is a topic of discussion nowadays. Companies that concentrate white blood cells argue that leukocytes are useful in creating an antibacterial response and have the ability to debride dead tendon tissue and jump-start healing (because they also contain growth factors). A basic study in horses showed no lengthening of the inflammation phase when L-PRP was used to treat an acute lesion of the bow tendon when compared to the control group.<sup>4</sup> Companies that purposely eliminate white blood cells from PRP argue that leukocytes have detrimental effects on healing tissue, because of the enzymes from the matrix metalloproteinase family that are released by neutrophils.<sup>24</sup> This is, however, not proven in prospective randomized controlled studies. The treatment of tendinosis with an injection of concentrated autologous platelets may be a nonoperative alternative. Injection of autologous platelets has been shown to improve repair in tendinosis in several animal and in vitro models.<sup>14,23</sup> The effect of 1-injection PRP is shown to last longer than 1 year, while the percentage of success after a single corticosteroid injection drops from 51% at 1 year to 40% after 2 years of follow-up. This figure resembles the number for an invasive placebo treatment. A possible explanation for the long-lasting effect of platelets

could be that platelets improve the very early neotendon properties so that the cells are able to perceive and respond to mechanical loading at an early time point.<sup>1</sup>

In our study, a single percutaneous injection of PRP or corticosteroid was performed, using a pepping technique in both groups. Repeated injections might be beneficial in patients who had suboptimal results after the initial injection, although no evidence for a beneficial effect of more than 1 injection exists. On theoretical grounds, by studying the inflammation cascade in tendon repair, a reinjection after 3 to 4 weeks seems logical because at this stage the cell proliferation and matrix deposition activity will have peaked and can be expected to subsequently decline. However, at this time no true indication of what the result of second injection would be can be determined. Routinely injecting a second time would be unnecessary in 73% of the cases, as they were already successful after 1 injection.

Regarding the patients who failed their initial treatment, those who crossed over to the PRP group significantly improved on both VAS pain scores and DASH disability symptom scores. The decision to proceed to further treatment was based on patient preference. However, patients who received surgery or a reinjection with corticosteroids did not benefit when their VAS and DASH scores at 2 years were compared with their baseline scores. When interpreting these results, strong conclusions regarding these findings are not possible, because the numbers of patients in these reintervention groups was relatively small.

We know that the natural history of nonchronic lateral epicondylitis is benign, resulting in normalization of complaints in the vast majority of patients within 1 year with little gain in recovery between 6 and 12 months.<sup>27</sup> All patients included in this study had complaints for at least 6 months. Patients receiving a corticosteroid injection also have a natural history and because the population was randomized, we can expect that the natural history will have the same influence in both groups. In the current study, 70% of the patients were already injected with corticosteroids at least 6 months before inclusion into this study. The PRP group should have experienced this negative effect also. Whether the positive effect of PRP is in fact the natural course of lateral epicondylitis cannot be determined from the current work. Still, the inclusion of patients with a minimum complaint history of 6 months indicates a chronic patient population was enrolled in the study. The positive effect of PRP compared with a corticosteroid injection on the course of lateral epicondylitis thus seems not be caused by natural history or a negative effect of the corticosteroid injection (which is not present in this study [Figures 2 and 3]). A critique of the original study was that the corticosteroid treatment is not the same as a placebo and might be worse than a placebo. In the Netherlands, the Institutional Review Board would not allow a placebo, and therefore this is a limitation of this study as the corticosteroid injection (and those before inclusion in the study) may have adversely affected the long-term results compared with a true placebo injection or dry needling.

In the Netherlands, a PRP treatment costs approximately twice as much as a corticosteroid treatment and surgery for lateral epicondylitis is twice the cost of a PRP



treatment and thus 4 times as much as a corticosteroid injection. The PRP treatment therefore costs 2 units; a steroid injection costs 1 unit and surgery, 4 units. Thus, in the PRP group 51 patients were treated with PRP, costing 51 times 2 units of money, and in the corticosteroid group, 49 patients were treated, costing 49 times 1 unit. In this study we had 20 reinterventions: 3 surgeries (12 units) and 3 reinjections with corticosteroids (3 units), making a total of 6 reinterventions, costing 15 extra units in the PRP group; and 6 surgeries (24 units), 1 reinjection with corticosteroids (1 unit), and 7 reinjections with PRP (14 units), making a total of 14 reinterventions, costing 39 extra units in the corticosteroid group. Regarding cost, PRP is not cost effective compared with corticosteroid on a short-term basis, but if the costs of those patients failing on the corticosteroid injection who proceed to surgery are taken into account, the differences in cost effectiveness will level out ( $102 + 15 = 117$  units in the PRP group versus  $49 + 39 = 88$  units in the corticosteroid group), especially if the costs for those who failed on corticosteroids were turned into a success by a consecutive PRP injection. This cost analysis does not include all socioeconomic costs of a recurrence, time off work, and the extra efforts reinterventions required from the patient and doctor. Moreover, although it is difficult to draw conclusions from small numbers, those patients who were reinjected with corticosteroids or those who had surgery did not improve compared with baseline, with those who were reinjected with PRP (those who crossed over) showing significant improvement. The crossover patients actually were patients who were offered either an operation or to try the experimental PRP injection; without this offer, an additional 7 patients in the corticosteroid group would have been operated on. Actually, the number of operations in the PRP group might have been less if we had realized that an initial flare-up of inflammation signs (ie, pain) is to be expected when using PRP. Two operations and 1 reinjection with corticosteroids were carried out within 3 months after the PRP injection, whereas in fact these patients still might have been in their inflammation and healing phase. Taking all these incidents into account, the PRP procedure might actually be a cheaper method in the long run, but a formal cost analysis should be performed.

In conclusion, this report demonstrates that a single injection of concentrated autologous platelets improves pain and function more effectively than corticosteroid injection in chronic lateral epicondylitis. These improvements were sustained over a 2-year follow-up time with no reported complications.

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