

Efficacy of Platelet-Rich Plasma for Chronic Tennis Elbow

A Double-Blind, Prospective, Multicenter, Randomized Controlled Trial of 230 Patients

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Background: Elbow tenderness and pain with resisted wrist extension are common manifestations of lateral epicondylar tendinopathy, also known as tennis elbow. Previous studies have suggested platelet-rich plasma (PRP) to be a safe and effective therapy for tennis elbow.

Purpose: To evaluate the clinical value of tendon needling with PRP in patients with chronic tennis elbow compared with an active control group.

Study Design: Randomized controlled trial; Level of evidence, 2.

Methods: A total of 230 patients with chronic lateral epicondylar tendinopathy were treated at 12 centers over 5 years. All patients had at least 3 months of symptoms and had failed conventional therapy. There were no differences in patients randomized to receive PRP ($n = 116$) or active controls ($n = 114$). The PRP was prepared from venous whole blood at the point of care and contained both concentrated platelets and leukocytes. After receiving a local anesthetic, all patients had their extensor tendons needled with or without PRP. Patients and investigators remained blinded to the treatment group throughout the study. A successful outcome was defined as 25% or greater improvement on the visual analog scale for pain.

Results: Patient outcomes were followed for up to 24 weeks. At 12 weeks ($n = 192$), the PRP-treated patients reported an improvement of 55.1% in their pain scores compared with 47.4% in the active control group ($P = .163$). At 24 weeks ($n = 119$), the PRP-treated patients reported an improvement of 71.5% in their pain scores compared with 56.1% in the control group ($P = .019$). The percentage of patients reporting significant elbow tenderness at 12 weeks was 37.4% in the PRP group versus 48.4% in the control group ($P = .143$). Success rates for patients at 12 weeks were 75.2% in the PRP group versus 65.9% in the control group ($P = .104$). At 24 weeks, 29.1% of the PRP-treated patients reported significant elbow tenderness versus 54.0% in the control group ($P = .009$). Success rates for patients with 24 weeks of follow-up were 83.9% in the PRP group compared with 68.3% in the control group ($P = .037$). No significant complications occurred in either group.

Conclusion: No significant differences were found at 12 weeks in this study. At 24 weeks, however, clinically meaningful improvements were found in patients treated with leukocyte-enriched PRP compared with an active control group.

Keywords: platelet-rich plasma (PRP); tennis elbow; lateral epicondylitis; tendinopathy; platelet

Pain with resisted wrist extension and local elbow tenderness are the characteristic complaints of patients who present with chronic lateral epicondylar tendinopathy (tennis elbow). This pain has been ascribed to microtears within the extensor carpi radialis brevis muscle and the subsequent development of angiofibroblastic dysplasia.³¹ Other theories about the source of the pain include altered neurogenic pathways and up-regulation of substance P.^{21,47} Recently, an association with an abnormal vascular

response within the extensor carpi radialis brevis muscle has also been reported.⁴⁰

Since this common disorder was first described in 1883, a wide variety of treatments has been proposed.²³ Rest, activity or equipment modification, nonsteroidal anti-inflammatory medication, bracing, and physical therapy have all been described as initial interventions. If these treatments fail to improve the pain and tenderness, second-line treatments such as cortisone injections, prolotherapy, autologous blood injections, platelet-rich plasma (PRP) injections, and needling of the extensor tendon origin have been recommended. If patients continue to report pain and dysfunction despite these measures, surgery is then considered. Only 10% to

15% of patients with chronic lateral epicondylar tendinopathy consider surgery. Surgical options include open tendon debridement and repair, percutaneous or open tendon release, and arthroscopic debridement. Reviews of the surgical literature note few differences in the outcomes of these approaches overall, with a success rate of approximately 85%.²²

Platelets are, in part, mediators of the coagulation process, but they also contain more than 300 bioactive cytokines and growth factors that act via autocrine and paracrine mechanisms to help coordinate cellular communication.⁷ Platelets also release vasoactive substances such as serotonin, calcium, histamine, and adenosine via their dense granules.^{27,29} Importantly, several preclinical studies suggest that PRP enhances human tendon cell proliferation, differentiation, and maturation.^{16,41-43}

It is crucial to note that not all PRPs are the same. Some preparations contain only concentrated platelets in a small volume of plasma. Others contain various concentrations of platelets and white blood cells. Equally important is the influence of platelets on the behavior and function of white blood cells.³⁹ Activation of the platelets with thrombin and/or calcium to initiate release of the contents of the granules *ex vivo* has been recommended in the wound healing literature.³⁷ Recent information, however, strongly suggests that PRP without activation promotes a better healing response.³⁷ All these different formulations of PRP make comparison between studies difficult and have led to the development of a PRP classification system²⁵ (Table 1). This system has 4 types and incorporates white blood cell concentration, activation status, and platelet concentration (A: >5 times the baseline platelets; B: <5 times the baseline platelets). Such classification now permits investigators and clinicians to replicate research results and standardize the use of different formulations of PRP for various conditions.

In 2006, Mishra and Pavelko²⁶ published a pilot study suggesting that unactivated concentrated platelets with concentrated white blood cells may be effective for patients who had failed nonoperative treatment for lateral epicondylar tendinopathy and who were considering surgery. That specific formulation of PRP consisted of unactivated platelets concentrated at about 5 times the baseline with concentrated white blood cells (type 1 PRP²⁵). In a small

TABLE 1
Platelet-Rich Plasma Classification System

Type	White Blood Cells	Activated?
1	Increased over baseline	No
2	Increased over baseline	Yes
3	Minimal or no white blood cells	No
4	Minimal or no white blood cells	Yes
	A: Platelets >5× baseline	
	B: Platelets <5× baseline	

group of patients (n = 15), there were statistically significant improvements compared with an active control group (bupivacaine with epinephrine, n = 5) at 8 weeks and a 93% reduction in pain scores for the PRP-treated patients at an average of 25.6 months.

That investigation was followed by a study by Gosens et al¹³ and Peerbooms et al³³ using the same techniques and indications in a prospective, randomized trial of PRP versus cortisone in 100 patients. The results were published in 2 separate works.^{13,33} At 2 years, the PRP-treated patients reported an improvement of 69% in pain scores compared with only 36% for patients treated with corticosteroid injections ($P < .0001$). When the patients were evaluated via the Disabilities of the Arm, Shoulder and Hand (DASH) scores at 2 years, the PRP group had an improvement of 67.6% compared with 15.7% in the cortisone group ($P < .0001$).

The pilot study of Mishra and Pavelko²⁶ was underpowered and only suggested some value for unactivated PRP in patients with chronic lateral epicondylar tendinopathy who were considering surgery when all other nonoperative measures had failed. The studies of Gosens et al¹³ and Peerbooms et al³³ had excellent methodology and execution but have been criticized for using cortisone as a control group because of its potential negative effects. Overall, however, these 2 controlled studies reported no safety issues and supported the use of unactivated PRP with leukocytes as an alternative to surgery. The second set of studies also clearly showed that cortisone has little or no long-term value in the treatment of chronic tennis elbow.

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One or more of the authors has declared the following potential conflict of interest or source of funding: This study was sponsored by Biomet Biologics. A.K.M. receives royalties for patents from Biomet and ThermoGenesis and owns stock in BioParadox and ThermoGenesis. N.V.S. has received payment for speaking and as a consultant from Auxilium and receives research support from Biomet, DePuy, Ferring Pharmaceuticals, Biomemetic, Pfizer, Smith & Nephew, Zimmer, and Wyeth. S.G.E. is a paid consultant and receives research support from Medartis, owns stock or stock options in Mylad, and receives research support from Biomet. G.L.J. is an unpaid consultant for Arthrotek and receives research support from Biomet and Genzyme. S.S. has made presentations for Sonosite. D.A.V. has made presentations for Genzyme and receives research support from Biomet. M.L.R. receives royalties from and is a paid consultant for Integra (Ascension) and Zimmer and has made presentations for Arthrex. D.C.K. is an employee of and receives royalties from Greyledge Technologies. A.C.R. receives research support from Biomet.

Needling of the extensor tendon under a local anesthetic has been described in the literature as an effective treatment for chronic tennis elbow.²⁴ The objective of the present investigation was to evaluate the efficacy of needling with and without a specific type of PRP as a treatment for chronic lateral epicondylar tendinopathy. We hypothesized that the addition of PRP would result in more improvement in pain and lower levels of tenderness at the elbow compared with needling alone.

MATERIALS AND METHODS

The study design was a double-blinded, prospective, multicenter, randomized trial (ClinicalTrials.gov trial number: NCT 00587613). The study sponsor, physician-evaluators, and patients were blinded to the treatment assignment and results until the end of the investigation. Thirteen investigational sites received local institutional review board approval for this study. Twelve sites enrolled patients. Trained study site personnel entered the source information into an electronic database, and informed consent was obtained from all patients.

Patient Selection

The patients had to fail at least 1 conventional therapy as listed below. There was considerable variability in the types and amount of treatment. The inclusion criteria, however, were uniformly applied to both the PRP and active control groups.

The following inclusion criteria were employed:

1. Pain by palpation at the lateral epicondyle of the elbow
2. Baseline elbow pain ≥ 50 mm/100 mm using a visual analog scale (VAS) during resisted wrist extension
3. History of elbow pain for at least 3 months
4. Pain unresponsive to 1 of 3 conventional therapy programs (local steroid injections, physical/occupational therapy, nonsteroidal anti-inflammatory medications)
5. Patient-informed consent

The following exclusion criteria were employed:

1. Pregnancy
2. Age <18 years
3. History of anemia
4. History of bleeding disorder
5. History of carpal tunnel syndrome on the affected side within 1 year before randomization
6. Cervical radiculopathy
7. Systemic disorders such as diabetes, rheumatoid arthritis, or hepatitis
8. Uncooperative patient or patient with neurological disorders who is incapable of following directions or who is predictably unwilling to return for follow-up examinations
9. Previous surgery for elbow tendinosis
10. Active bilateral elbow tendinosis within 4 weeks before randomization
11. Hypothyroidism

12. History of any blood disorder
13. Hemoglobin <11 g/dL
14. Hematocrit <33%
15. Platelet count outside of the normal range of 150 to 400 \times 1000/uL
16. Participation in a workers' compensation program or planning to apply for the program and/or any ongoing, pending, or planned legal action as a result of elbow pain
17. History of arthritis or fracture of the affected elbow
18. Received local steroid injections within 6 weeks, physical/occupational therapy within 4 weeks, or nonsteroidal anti-inflammatory medications within 1 week of randomization
19. Intolerance to acetaminophen

Informed consent was obtained from 301 patients; 48 failed initial screening, and 22 dropped out before any treatment. The remaining 231 patients were then randomized via a computerized protocol. There were no differences between the 2 groups with regard to weight, age, height, sex, or race. The mean patient age in the active control group was 47.4 years compared with 48.4 years in the PRP group ($P = .375$). All patients had normal radiograph findings. Baseline measurements of pain and forearm function were also not different. One patient was excluded because of blood draw failure. Therefore, a total of 230 patients with chronic lateral epicondylar tendinopathy received treatment. The investigation was conducted over a period of 5 years from 2006 to 2011. Two patients (1 PRP, 1 active control) were treated and voluntarily withdrew with no postbaseline measurements. Three patients (all PRP) were treated but were lost to follow-up. This left 225 patients (97.8% of the total) with postbaseline data that were included in the analysis (Figure 1).

PRP Preparation and Procedure Technique

Approximately 30 mL of whole blood was drawn from a peripheral vein of each patient. In the PRP group, the blood was mixed with an anticoagulant (ACD-A) and placed into a sterile separator canister (GPS, Biomet Biologics, Warsaw, Indiana). The canister was then placed in a desktop-sized centrifuge and processed for 15 minutes at 3200 rpm (Figure 2). This method of preparation produces type 1A PRP (leukocyte-enriched PRP with platelets $5 \times$ baseline used in an unactivated manner). The PRP was then removed and buffered to physiological pH using 8.4% sodium bicarbonate to neutralize the acidic ACD-A in the PRP. The injection site was blocked using 0.5% bupivacaine with epinephrine, and then, 2 to 3 mL of the prepared PRP was injected into the extensor carpi radialis brevis tendon and surrounding area using a peppering technique. This technique consisted of 5 penetrations of the tendon as the PRP was injected via a single skin penetration. The active control group was injected with 2 to 3 mL of bupivacaine using the same peppering technique as the PRP group. To maintain blinding in both groups, the entire 10-mL syringe including the needle hub was wrapped in black tape to obscure its contents. The patient's

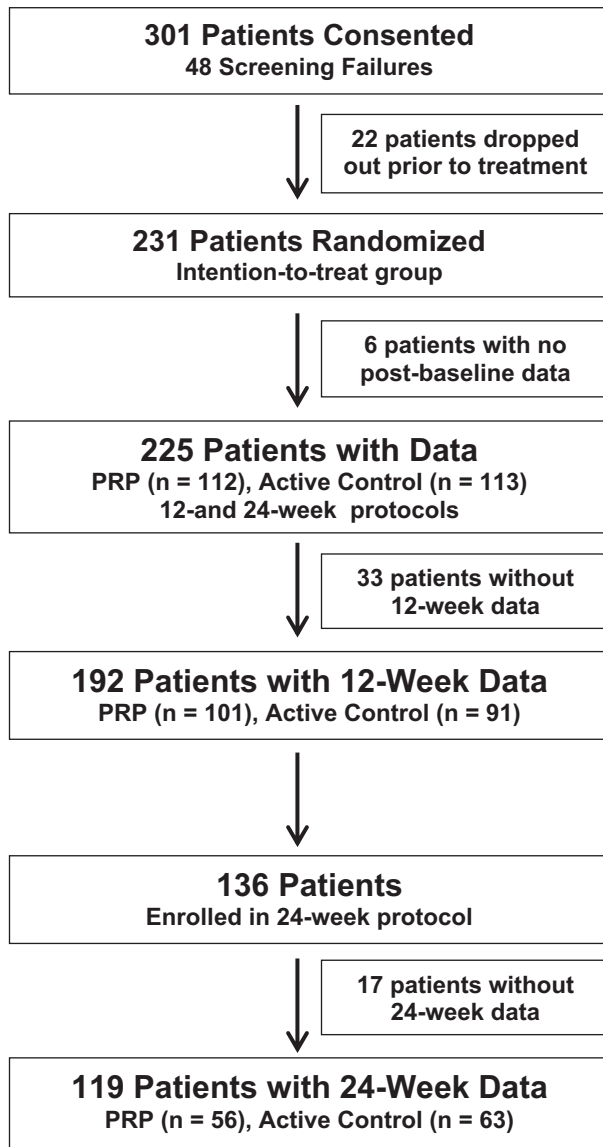


Figure 1. Flow diagram of the study patients.

arm was also draped to prevent inadvertent unblinding of the patient during the injection.

Outcome Measurements and Statistical Analysis

The primary outcome measure was defined based on the VAS with resisted wrist extension (VASRWE). Patients indicated their pain score on a 100-mm VAS. A successful outcome was defined as 25% or greater improvement in this score compared to baseline. This level of improvement was considered clinically meaningful. The study was originally designed to compare the proportion of successfully treated patients at 12 weeks.

The null hypothesis was that the proportion of patients successfully treated with PRP or control would be equal. The alternative 1-sided hypothesis specifically stated that



Figure 2. Disposable cylinder containing blood components after separation.

the proportion of successfully treated patients with PRP would be *greater* than the control group:

$$\begin{aligned} \text{Null hypothesis:} & \quad H_0: \pi_{\text{PRP}} - \pi_{\text{cntl}} = 0 \\ \text{Alternative hypothesis:} & \quad H_A: \pi_{\text{PRP}} - \pi_{\text{cntl}} > 0 \end{aligned}$$

where π is the success proportion in PRP or control.

This prospective hypothesis was designed at the outset to be 1-sided, not 2-sided, based in part on previously published studies^{13,26,33} suggesting that treatment with PRP results in greater improvement in pain scores when compared to controls. In the initial prospective statistical analysis, a 1-sided alpha level of 0.025 was set for the 12-week cohort. The overall success rates, therefore, are reported using a 1-sided Fisher exact test. All other P -values reported are 2-sided.

The Patient-Rated Tennis Elbow Evaluation (PRTEE; formerly known as the Patient-Rated Forearm Evaluation Questionnaire) and extended wrist examination were secondary measurements of outcome. The extended wrist examination evaluates the patient for signs of infection, local tenderness, and sensation. Successful treatment was prospectively defined as a reduction of greater than or equal to 25% of the VASRWE pain score compared to baseline in patients that did not require pain medication beyond 48 hours and did not require escape therapy. There were no differences between the groups in terms of patients requiring pain medication beyond 48 hours (PRP, $n = 21$; active control, $n = 24$) or the need for escape therapy (PRP, $n = 5$; control, $n = 11$).

The original design of this study included only a 12-week follow-up protocol. After the initial study approval, a request was made by the sponsor to add additional investigational sites. During that review, the regulatory agency (FDA) asked

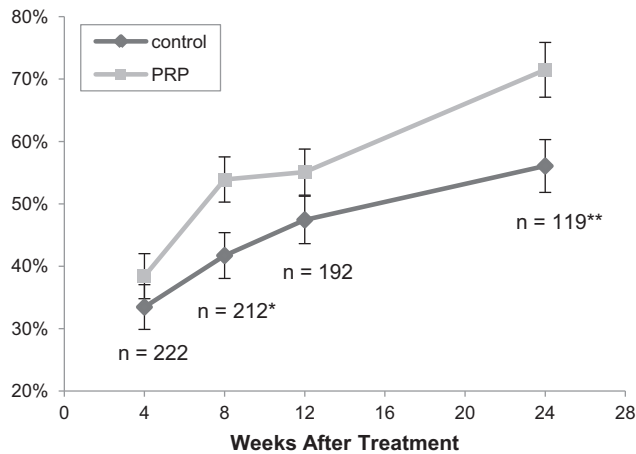


Figure 3. Mean percentage improvement in visual analog scale pain score. *Improvement in pain score at 8 weeks ($P = .023$). **Improvement in pain score at 24 weeks ($P = .019$).

the study sponsor to give serious consideration to adding a longer follow-up visit to better evaluate safety and efficacy. This prompted the sponsor to request the addition of a 24-week follow-up visit, which was approved. No data were evaluated prior to the addition of the 24-week endpoint, and no interim analyses at 12-week or other times were conducted. This was a double-blind study. The sponsor, evaluator, patient, and injecting physician were blinded as to which treatment an individual was assigned throughout the length of the study. Initial and follow-up data collection of VASRWE, PRTEE, and the extended wrist examination including elbow tenderness was conducted by a blinded evaluator without the presence of the treating physician.

A total of 94 patients were enrolled under the 12-week protocol and 136 patients were enrolled under the 24-week protocol. It was therefore not possible to fully evaluate all of the 94 patients in the initial cohort, as they had already passed the 24-week follow-up period when the study was modified. Thus, the incomplete data at 24 weeks is not a result of dropouts or related to the outcome. Furthermore, there was no statistical difference in the mean baseline pain scores in those patients with 24-week data versus those patients without 24-week data, providing evidence that there has been no violation of the missing at random assumption needed for 24-week comparisons to be fair.

The repeated-measures analysis of variance (ANOVA) model was used to analyze the mean percentage pain score comparisons between the two groups. Fisher exact test was used to evaluate other measurements as appropriate. A sample size of 115 patients in each treatment group was calculated to have 87.7% power to detect a difference in treatment success percentage between PRP and bupivacaine injections assuming a rate of 50% for PRP, that the true difference is 20%, and that the type I error rate is a 1-sided alpha significance level of 0.025. Similarly, a sample size of 115 patients in each treatment group was calculated to have a 99.1% power to detect a difference in the treatment success percentage between PRP and bupivacaine injections

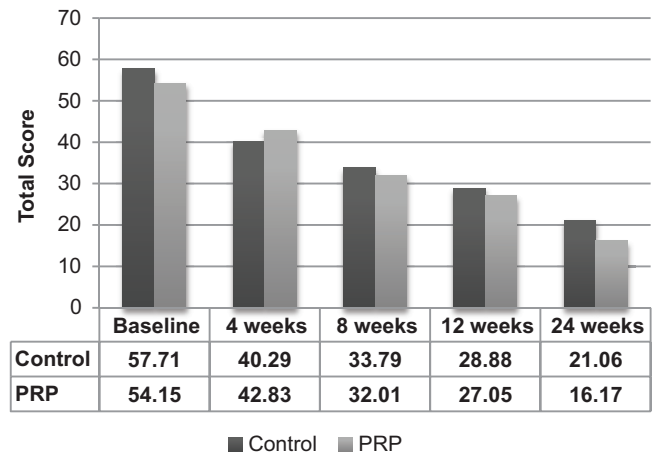


Figure 4. Tennis elbow questionnaire. Both the platelet-rich plasma-treated and active control groups had improved functionality over baseline at each follow-up as measured by the Patient-Rated Tennis Elbow Evaluation.

assuming a rate of 47.1 for PRP, that the true difference is as large as 26.5%, and that the type I error rate is a 1-sided alpha significance level of 0.025. Ideally, there would have been 115 patients in each group with 24 weeks of follow-up according to power calculations designed with at least 80% power to detect a treatment success rate difference of 20%. Unfortunately, only 119 patients (PRP, $n = 56$; control, $n = 63$) had 24-week data available for analysis. Clinicians and patients may not consider a 25% improvement clinically meaningful at 24 weeks. Success rates as defined by 50% or more improvement are therefore also reported.

RESULTS

Safety

A total of 5 significant adverse events were reported during the study. Two PRP-treated patients had severe pain (1 for 2 days, 1 for 4 days). These events were reported as probable or likely related to the treatment. The remaining 3 events were reported as unlikely or not related to the treatment. They included 1 patient in the PRP group with unstable angina 4 months after treatment and 2 patients in the active control group; one patient had a radial/ulnar fracture, and the other underwent shoulder arthroscopic surgery with decompression.

Total adverse events, pain being the most common, occurred in 18% ($n = 20$) of the active control patients and 19% ($n = 22$) of the PRP-treated patients. There were no statistical differences between the active control and PRP groups in the incidence of adverse events, need for pain medication beyond 48 hours, or escape therapy.

Pain Scores (VAS With Resisted Wrist Extension)

Patients reported a baseline level of pain with resisted wrist extension. This value was then compared with their

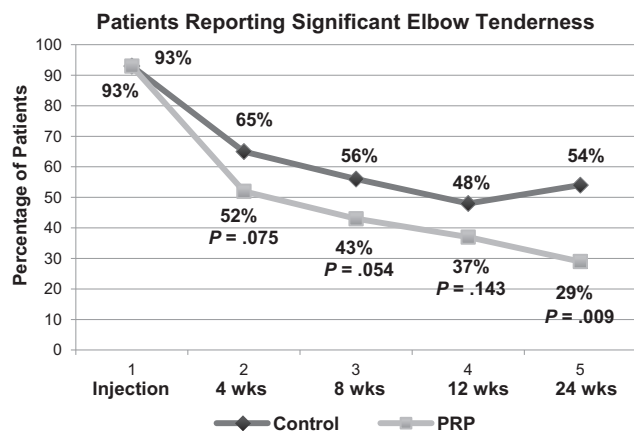


Figure 5. Percentages of patients reporting elbow tenderness were significantly lower in the platelet-rich plasma-treated group versus active control group at 24 weeks ($P = .009$). The differences were not significant at 4 weeks ($P = .075$), 8 weeks ($P = .054$), or 12 weeks ($P = .143$).

reported scores at 4, 8, 12, and 24 weeks. At each follow-up, the PRP-treated patients reported more improvement in their pain scores relative to the active control group. These differences were statistically significant at 8 and 24 weeks. Specifically, at 4 weeks after treatment, the PRP-treated patients reported an improvement of 38.4% compared with 33.5% in the active control group ($P = .324$). At 8 weeks, the PRP-treated patients reported an improvement of 53.9% versus 41.7% in the active control group ($P = .023$). At 12 weeks, the PRP-treated patients reported an improvement of 55.1% compared with 47.4% in the active control group ($P = .163$). At the final follow-up at 24 weeks, the PRP-treated patients reported an improvement of 71.5% compared with 56.1% in the active control group ($P = .019$) (Figure 3).

Tennis Elbow Questionnaire (PRTEE)

There were no major differences in scores between the 2 groups on the patient-rated elbow questionnaire. Both groups showed improvement with time. At 8-, 12-, and 24-week follow-up, the PRP group reported more improvement over baseline, but these differences were not statistically significant (Figure 4).

Extended Wrist Examination

There were no notable differences between the groups in terms of signs of infection or sensation. There were, however, significant differences in terms of local tenderness. At each posttreatment follow-up, the PRP group had a lower percentage of patients reporting significant local tenderness at the elbow. There were, however, no statistical differences at 4, 8, or 12 weeks. At 24 weeks after treatment, 54% of the active control group versus 29% of the PRP group reported significant local tenderness ($P = .009$) (Figure 5).

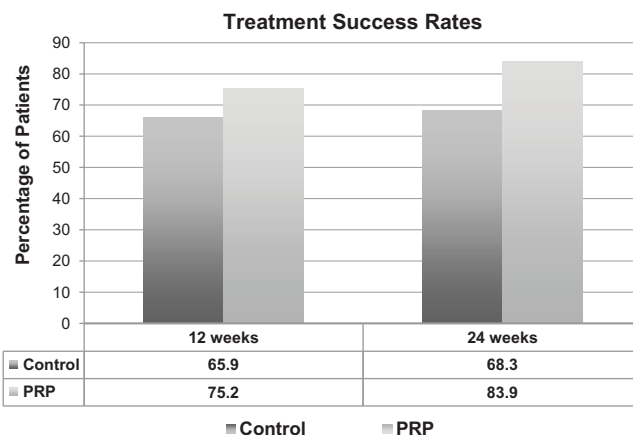


Figure 6. Clinically significant success rates, as measured by a $\geq 25\%$ reduction in pain score versus baseline, were found in platelet-rich plasma-treated patients at 24 weeks after treatment ($P = .037$).

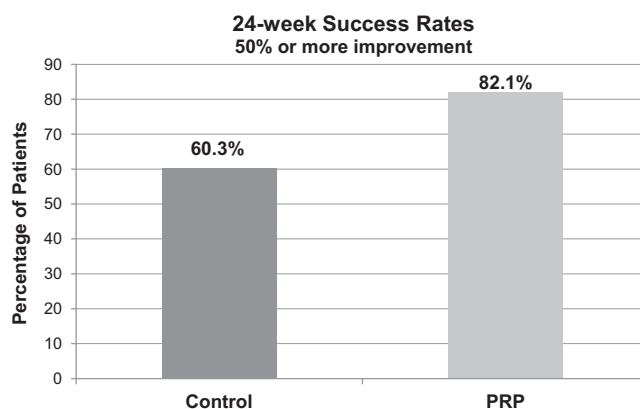


Figure 7. Clinically significant success rates, as measured by a 50% or greater reduction in pain score versus baseline, were found in PRP-treated patients at 24 weeks posttreatment ($P = .008$).

Success Rates

Using the preplanned measurement of success that required combining the results of the 12- and 24-week cohorts, there were no differences between the study sites in success rates (control, 54.0% vs PRP, 63.4%) When all patients with 12-week follow-up data (control, $n = 91$; PRP, $n = 101$) were analyzed for $\geq 25\%$ reduction in pain score compared with baseline, the success rate for the control group was 65.9% compared with 75.2% for the PRP group ($P = .104$, 1-sided; $P = .203$, 2-sided). Evaluating the 119 patients with 24 weeks of follow-up data (control, $n = 63$; PRP, $n = 56$) revealed clinically relevant differences. At this time point, the success rate for the control group was 68.3% compared with 83.9% for the PRP group ($P = .037$, 1-sided; $P = .056$, 2-sided) (Figure 6). Success rates as defined by 50% or more improvement in pain scores were 82.1% in the PRP group compared with

60.1% in the control group at 24 weeks ($P = .008$, 1-sided; $P = 0.015$, 2-sided) (Figure 7).

DISCUSSION

Chronic lateral epicondylar tendinopathy, also known as tennis elbow, is a common problem seen by primary care physicians, physiatrists, and orthopaedic surgeons. It is often self-limiting or responsive to nonoperative measures such as rest, anti-inflammatory medication, physical therapy, and activity modification. Home-based stretching and eccentric strengthening exercises can also be effective if the patient is compliant. In approximately 10% to 15% of patients, however, symptoms of local elbow tenderness and pain with resisted wrist extension persist. In this cohort of patients, corticosteroid injections are often considered. A survey of 400 members of the American Academy of Orthopaedic Surgeons found that 93% had administered a corticosteroid injection for this type of problem.¹⁴ Cortisone injections have demonstrated short-term pain improvements but also result in high rates of symptom recurrence.^{1,20}

Unfortunately, dexamethasone inhibits tenocyte proliferation and tendon progenitor cell recruitment with reduced collagen synthesis.³⁸ Furthermore, dexamethasone depletes the pool of human tendon stem cells, suppresses type I collagen, and enhances fatty and cartilage-like tissue changes that can lead to tendon ruptures.⁴⁸ This treatment can also result in dermal depigmentation and cause subcutaneous atrophy that may exacerbate local elbow tenderness. A plethora of alternative injection treatment options has arisen because of the limited data supporting cortisone. Autologous blood, botulinum toxin, polidocanol, prolotherapy, hyaluronic acid, and PRP injections have all been utilized with varying degrees of success.¹⁷ Autologous blood injections have been shown to have value in some studies, but often, more than 1 injection is needed.¹⁰ Direct comparison of PRP against whole blood also suggests a higher conversion rate to surgery in whole blood-treated patients. The higher levels of growth factors in PRP compared with whole blood help explain some of these clinical differences.²⁷

A recently published study suggested that there is no difference in treatment effectiveness between PRP, cortisone, and saline injections at 12 weeks after treatment.¹⁸ This investigation enrolled patients who had not failed other treatments. A high volume of lidocaine (10-15 mL) was also injected into the tendon before treatment. This treatment protocol is different from the present investigation and previous published studies.^{13,26,33} There were also dramatic differences in outcome when the PRP-treated patients were compared with the steroid-treated patients at 6 months and 1 year in favor of significantly more pain reduction in the PRP group ($P = .005$ and $P = .006$, respectively). The steroid-treated group also was found to have a 15% chance of developing skin atrophy at the injection site. This confirms that steroid injections are not benign and have little long-term value in terms of alleviation of pain.

Surgery is typically recommended for patients with chronic lateral epicondylar tendinopathy who fail to respond

to nonoperative measures. Percutaneous, open, and arthroscopic techniques have been described. Most of the surgical literature consists of case series of fewer than 50 patients (type 4 evidence), reporting varying degrees of success ranging from 80% to 90%.²² Five years after surgery, however, up to 28% of patients may complain of persistent symptoms, and 9% report moderate to severe pain.⁶ A recent prospective, randomized surgical trial in a small number of patients suggested that a simple skin incision at the area of tendon dysfunction may yield the same outcome as a more invasive procedure.¹⁹ In addition, surgical treatment rarely can result in serious complications such as a nerve injury especially with an arthroscopic approach.²

The total cost of a surgical solution must also be addressed. If an equally effective treatment is available with less expense and risk, it should be considered before surgical intervention. An informal poll of the authors of this study found the total charges associated with operative treatment of chronic lateral epicondylar tendinopathy, including surgeon's fees, anesthesiology fees, and surgery center or hospital fees, to be between \$10,000 and \$12,000. Significant cost savings could be realized by payers if they were to initiate coverage of PRP for chronic tennis elbow patients who are contemplating surgery at a total price point of about \$1000.

Successful treatment was predetermined in this investigation to be a greater than 25% reduction in the VAS pain score with resisted wrist extension. This required imputing the results of the 12- and 24-week cohorts to the last recorded endpoint. This is an inherent weakness of the study. Ideally, all patients would have had at least 24 weeks of follow-up. Another weakness was the 24-week follow-up time point. A later evaluation, such as 1 or 2 years after treatment, would have been better. The study would also have been stronger if a standardized rehabilitation protocol was implemented. None was used because it was not possible to confirm compliance across so many centers.

The multicenter approach was one of the strong points of the study. By standardizing the PRP preparation, using the same separation device and injection protocol, the study was able to enroll patients in 12 different centers. There were no differences in success rates across these centers. Therefore, this technique can be translated beyond a single investigator or center. Reproducibility of results across multiple centers is crucial if a new therapy is to become available and useful to a wide range of patients. However, the results from this clinical trial using type 1A PRP may not be generalizable to types of PRP that differ from the one used in this study.

Another strength of the study was the complete blinding of the study sponsor, treating physician, evaluator, and patient by masking the syringes and drawing blood from all patients. Using the active control of needling the extensor origin without PRP also enhanced results. This study confirms the value of needling alone, but the clinical importance may be limited because 54% of the active control group still reported significant elbow tenderness compared with 29% in the PRP group ($P = .009$) at 6 months. Longer follow-up level I studies would be helpful in clarifying the relative value of needling alone.

In the present investigation, superior results were demonstrated when PRP was added to the needling technique. It would not have been practical or ethical to deny treatment to patients still complaining of pain and tenderness despite other nonoperative treatments. Therefore, a control group of doing nothing would not have been possible.

Similar to previous studies, this investigation fails to explain how PRP improves pain. It has been postulated that the bioactive molecules within PRP enhance or improve the tendon physiology in a manner that allows for improved function and decreased pain. Some small series have suggested that PRP can improve the morphological characteristics of the tendon as evaluated by ultrasound.⁵ Large studies, however, have not yet shown any significant structural changes when patients are treated with PRP. Pain reduction may also be the result of some alteration in neural pain responses or substance P metabolism. Also, PRP may enhance the microvascular circulation within the tendon and surrounding muscle, therefore decreasing pain. This theory is supported by studies confirming enhanced capillary density and angiogenesis when unactivated PRP is applied to wounds.³⁷ A previous report has also shown how specific formulations of PRP can enhance myocardial function after an ischemic injury.²⁸ Recent data further suggest that an intratendinous injection of the same type of PRP used in this study may lead to a systemic elevation of vascular endothelial growth factor for several days.⁴⁴ Together, these reports support the hypothesis of PRP working to improve blood flow into and around the tendon and surrounding muscle. Further investigation of these potential mechanisms of action is still needed.

Platelet-rich plasma has also been used as a primary or adjuvant treatment for a variety of musculoskeletal injuries and disorders. Several formulations have been used in rotator cuff disease with conflicting results.^{3,15,34,36,45} A recent randomized controlled trial, however, revealed the value of PRP over dry needling for this problem.³⁵ Treatment of patellar tendinopathy, Achilles tendinopathy, and knee osteoarthritis with PRP has also been investigated with variable results based on the specific degree of pathological changes.^{4,9,11,12,30,32} Graft donor site and anterior cruciate ligament healing using PRP have also been studied.^{8,46}

In this study, the primary endpoint of at least 25% improvement in VAS pain scores was not statistically significant at 12 weeks. The 24-week results are clinically meaningful despite not reaching the 0.025 alpha level for a minimum 25% improvement. Specifically, significant differences existed at 24 weeks for pain score percentage improvement ($P = .019$), elbow tenderness ($P = .009$), and success rates if the minimum improvement is set at 50% ($P = .008$). Importantly, whether the success rate is defined as 25% or 50% improvement, twice as many patients failed in the active control group. Treatment failure with minimum 25% improvement was 32% in the active control group versus 16% in the PRP group. Treatment failure with minimum 50% improvement was 40% in the active control group versus 18% in the PRP group.

The present study, in combination with the prospective, randomized controlled trial of PRP versus cortisone by Gosens et al¹³ and the initial pilot study by Mishra and Pavelko,²⁶ provides clinicians and patients with evidence

supporting the use of this type of PRP and device for patients who have failed standard nonoperative treatments. Together, these 3 studies have evaluated a total of 350 patients in a prospective, controlled fashion using the same treatment protocol. Additional studies of this type of PRP compared with surgical intervention have already been initiated. Future investigations should also consider utilizing ultrasound guidance for enhanced needle placement and noninvasive means of measuring tendon remodeling.

There is now more than a decade of experience using PRP to effectively treat chronic tennis elbow with a safe biological protocol at the point of care. Based on these data, it is now possible to recommend treating patients with unactivated, leukocyte-enriched PRP (type 1 PRP) before considering surgical intervention primarily because it provides a similar rate of success with lower cost and less risk. Individual clinicians may continue to disagree whether the differences presented in this paper are clinically meaningful. We also do not expect for this paper to end the controversy over the value of PRP as a treatment for musculoskeletal disorders. We hope, however, that it will contribute to the worldwide discussion about how to best conduct and analyze trials of biological treatments. Clinicians, researchers, and patients must be cautioned that positive results may take more than 12 weeks and are specific to chronic lateral epicondylar tendinopathy using the techniques and the PRP system discussed in this article.

ACKNOWLEDGMENT

The authors acknowledge Patti Davis, a professional editor, who assisted with the proofreading and reference formatting of this paper; Jennifer Woodell-May, director of Research at Biomet Biologics, who assisted with the statistical analysis of the original paper; and Jeffrey Gornbein, UCLA Department of Biomathematics, who assisted with the revision of the paper.

REFERENCES

1. Bisset L, Beller E, Jull G, Brooks P, Darnell R, Vicenzino B. Mobilisation with movement and exercise, corticosteroid injection, or wait and see for tennis elbow: randomized trial. *Br Med J*. 2006;333(7575):939-941.
2. Carofino BC, Bishop AT, Spinner RJ, Shin AY. Nerve injuries resulting from arthroscopic treatment of lateral epicondylitis: report of 2 cases. *J Hand Surg*. 2012;37(6):1208-1210.
3. Castricini R, Longo UG, De Benedetto M, et al. Platelet-rich plasma augmentation for arthroscopic rotator cuff repair: a randomized controlled trial. *Am J Sports Med*. 2011;39(2):258-265.
4. Cerza F, Carni S, Carcangiu A, et al. Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. *Am J Sports Med*. 2012;40(12):2822-2827.
5. Chaudhury S, de La Lama M, Adler RS, et al. Platelet-rich plasma for the treatment of lateral epicondylitis: sonographic assessment of tendon morphology and vascularity (pilot study). *Skeletal Radiol*. 2013;42(1):91-97.
6. Cohen MS, Romeo AA. Open and arthroscopic management of lateral epicondylitis in the athlete. *Hand Clin*. 2009;25:331-338.
7. Coppinger JA, Cagney G, Toomey S, et al. Characterization of the proteins released from activated platelets leads to localization of novel platelet proteins in human atherosclerotic lesions. *Blood*. 2004;103(6):2096-2104.

8. De Almeida AM, Demange MK, Sobrado MF, Rodrigues MB, Pedrinelli A, Hernandez AJ. Patellar tendon healing with platelet-rich plasma: a prospective randomized controlled trial. *Am J Sports Med.* 2012;40(6):1282-1288.
9. de Vos RJ, Weir A, van Schie HT, et al. Platelet-rich plasma injection for chronic Achilles tendinopathy: a randomized controlled trial. *JAMA.* 2010;303(2):144-149.
10. Edwards SG, Calandruccio JH. Autologous blood injections for refractory lateral epicondylitis. *J Hand Surg Am.* 2003;28(2):272-278.
11. Filardo G, Kon E, Della Villa S, Vincentelli F, Fornasari PM, Marcacci M. Use of platelet-rich plasma for the treatment of refractory jumper's knee. *Int Orthop.* 2010;33(6):909-915.
12. Filardo G, Kon E, Di Martino A, et al. Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial [published online November 23, 2012]. *BMC Musculoskelet Disord.* doi:10.1186/1471-2474-13-229.
13. Gosens T, Peerbooms JC, van Laar W, den Ouden BL. Ongoing positive effect of platelet-rich plasma versus corticosteroid injection in lateral epicondylitis: a double-blind randomized controlled trial with 2-year follow-up. *Am J Sports Med.* 2011;39(6):1200-1208.
14. Hill JJ, Trapp RG, Colliver JA. Survey on the use of corticosteroid injections by orthopedists. *Contemp Orthop.* 1989;18:39-45.
15. Jo CH, Kim JE, Yoon KS, et al. Does platelet-rich plasma accelerate recovery after rotator cuff repair? A prospective cohort study. *Am J Sports Med.* 2011;39(10):2082-2090.
16. Kajikawa Y, Morihara T, Sakamoto H, et al. Platelet-rich plasma enhances the initial mobilization of circulation-derived cells for tendon healing. *J Cell Physiol.* 2008;215(3):837-845.
17. Krogh TP, Bartels EM, Ellingsen T, et al. Comparative effectiveness of injection therapies in lateral epicondylitis: a systematic review and network meta-analysis of randomized controlled trials [published online September 12, 2012]. *Am J Sports Med.* doi:10.1177/0363546512458237.
18. Krogh TP, Fredberg U, Stengaard-Pedersen K, Christensen R, Jensen P, Ellingsen T. Treatment of lateral epicondylitis with platelet-rich plasma, glucocorticoid, or saline: a randomized, double-blind, placebo-controlled trial [published online January 17, 2013]. *Am J Sports Med.* doi:10.1177/0363546512472975.
19. Krosiak M. Surgical treatment of lateral epicondylitis: a prospective, randomized, blinded, placebo controlled pilot study. *University of New South Wales.* November 2012. Available at: http://www.unsw.edu.au/primo_library/libweb/action/diDisplay.do?vid=UNSWORKS&docId=unsworks_10864. Accessed December 12, 2012.
20. Lindenhovius A, Henket M, Gilligan BP, Lozano-Calderson S, Jupiter JB, Ring D. Injection of dexamethasone versus placebo for lateral elbow pain: a prospective, double-blind, randomized clinical trial. *J Hand Surg Am.* 2008;33(6):909-919.
21. Ljung BO, Alfredson H, Forsgren S. Neurokinin 1-receptors and sensory neuropeptides in tendon insertions at the medial and lateral epicondyles of the humerus: studies on tennis elbow and medial epicondylalgia. *J Orthop Res.* 2004;22(2):321-327.
22. Lo MY, Safran MR. Surgical treatment of lateral epicondylitis: a systematic review. *Clin Orthop Relat Res.* 2007;463:98-106.
23. Major HP. Lawn-tennis elbow [letter]. *Br Med J.* 1883;2:557.
24. McShane JM, Shah VN, Nazarian LN. Sonographically guided percutaneous needle tenotomy for treatment of common extensor tendinosis in the elbow: is a corticosteroid necessary? *J Ultrasound Med.* 2008;27(8):1137-1144.
25. Mishra A, Harmon K, Woodall J Jr, Vieira A. Sports medicine applications of platelet rich plasma. *Curr Pharm Biotechnol.* 2012;13(7):1185-1195.
26. Mishra A, Pavelko T. Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. *Am J Sports Med.* 2006;33(11):1774-1778.
27. Mishra A, Randelli P, Barr C, Talamonti T, Ragone V, Cabitza P. Platelet-rich plasma and the upper extremity. *Hand Clin.* 2012;28(4):481-491.
28. Mishra A, Velotta J, Brinton TJ, et al. RevaTen platelet-rich plasma improves cardiac function after myocardial injury. *Cardiovasc Revasc Med.* 2011;12(3):158-163.
29. Mishra A, Woodall J Jr, Vieira A. Treatment of tendon and muscle using platelet-rich plasma. *Clin Sports Med.* 2009;28(1):113-125.
30. Monto RR. Platelet rich plasma treatment for chronic Achilles tendinosis. *Foot Ankle Int.* 2012;33(5):379-385.
31. Nirschl RP, Pettrone FA. Tennis elbow: the surgical treatment of lateral epicondylitis. *J Bone Joint Surg Am.* 1979;61(6A):832-839.
32. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial [published online January 17, 2013]. *Am J Sports Med.* doi:10.1177/0363546512471299.
33. Peerbooms JC, Sluimer J, Bruijn DL, Gosens T. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial: platelet-rich plasma versus corticosteroid injection with a 1-year follow-up. *Am J Sports Med.* 2010;38(2):255-262.
34. Randelli P, Arrigoni P, Ragone V, Aliprandi A, Cabitza P. Platelet rich plasma in arthroscopic rotator cuff repair: a prospective RCT study, 2-year follow-up. *J Shoulder Elbow Surg.* 2011;20(4):518-528.
35. Rha DW, Park GY, Kim YK, Kim MT, Lee SC. Comparison of the therapeutic effects of ultrasound-guided platelet-rich plasma injection and dry needling in rotator cuff disease: a randomized controlled trial [published online October 3, 2012]. *Clin Rehabil.* doi:10.1177/0269215512448388.
36. Rodeo SA, Delos D, Williams RJ, Adler RS, Pearle A, Warren RF. The effect of platelet-rich fibrin matrix on rotator cuff tendon healing: a prospective, randomized clinical study. *Am J Sports Med.* 2012;40(6):1234-1241.
37. Scherer SS, Tobalem M, Vigato E, et al. Nonactivated versus thrombin-activated platelets on wound healing and fibroblast-to-myofibroblast differentiation in vivo and in vitro. *Plast Reconstr Surg.* 2012;129(1):46e-54e.
38. Scutt N, Rolf CG, Scutt A. Glucocorticoids inhibit tenocyte proliferation and tendon progenitor cell recruitment. *J Orthop Res.* 2006;24(2):173-182.
39. Sowa JM, Crist SA, Ratliff TL, Elzey BD. Platelet influence on T- and B-cell responses. *Arch Immunol Ther Exp.* 2009;57(4):235-241.
40. Vendung T, Werner M, Ljung BO, Jorfeldt L, Henriksson J. Blood flow to the extensor carpi radialis brevis muscle following adrenaline infusion in patients with lateral epicondylitis. *J Hand Surg Am.* 2011;36(12):1974-1980.
41. Virchenko O, Aspenberg P. How can one platelet injection after tendon injury lead to a stronger tendon after 4 weeks? Interplay between early regeneration and mechanical stimulation. *Acta Orthop.* 2006;77(5):806-812.
42. Visser LC, Arnoczky SP, Caballero O, Kern A, Ratcliffe A, Gardner KL. Growth factor-rich plasma increases tendon cell proliferation and matrix synthesis on a synthetic scaffold: an in vitro study. *Tissue Eng Part A.* 2010;16(3):1021-1029.
43. Wang X, Qiu Y, Triffitt J, Carr A, Xia Z, Sabokbar A. Proliferation and differentiation of human tenocytes in response to platelet rich plasma: an in vitro and in vivo study. *J Orthop Res.* 2012;30(6):982-990.
44. Wasterlain AS, Braun HJ, Harris AH, Kim HJ, Dragoo JL. The systemic effects of platelet-rich plasma injection. *Am J Sports Med.* 2013;41(1):186-193.
45. Weber SC, Kauffman JI, Parise C, Weber SJ, Katz SD. Platelet-rich fibrin matrix in the management of arthroscopic repair of the rotator cuff: a prospective, randomized, double-blinded study. *Am J Sports Med.* 2013;41:263-270.
46. Yoshida R, Murray MM. Peripheral blood mononuclear cells enhance the anabolic effects of platelet-rich plasma on anterior cruciate ligament fibroblasts. *J Orthop Res.* 2013;31(1):29-34.
47. Zeisig E, Ohberg L, Alfredson H. Extensor origin vascularity related to pain in patients with tennis elbow. *Knee Surg Sports Traumatol Arthrosc.* 2006;14(7):659-663.
48. Zhang J, Keenan C, Wang JH. The effects of dexamethasone on human patellar tendon stem cells: implications for dexamethasone treatment of tendon injury. *J Orthop Res.* 2013;31(1):105-110.