

Platelet-rich Plasma Injection Reduces Pain in Patients With Recalcitrant Epicondylitis

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abstract

Thirty patients (31 elbows) with epicondylitis unresponsive to nonsurgical treatment (including steroid injection) for >6 months received a single treatment of platelet-rich plasma injected with a peppering technique. Patients were followed using a 5-subcategory visual analog scale (VAS) for pain (0, no pain; 10, worst possible pain), modified American Shoulder and Elbow Surgeons assessment survey, and VAS for patient satisfaction (0, not at all satisfied; 10, very satisfied). Successful treatment was defined as a 25% decrease in worst pain at follow-up with no intervention after 1 year.

Two patients (2 elbows) elected for surgery 1 month postinjection. Of the remaining 29 elbows followed, 28 had a 25% reduction in worst pain at ≥ 1 follow-up visits, for an overall success rate of 90% (28 of 31 elbows). Mean scores for worst pain at baseline, 3 months, and last follow-up (patients with at least 6 months of follow-up; 25 ± 14 months) were 7.2 ± 1.6 ($n=30$ elbows), 4.0 ± 2.2 ($n=23$), and 1.1 ± 1.7 ($n=26$), respectively ($P < .01$ or less comparing follow-up scores to baseline using each patient as his or her own control). Patient satisfaction scores improved from 5.1 ± 2.5 at 1 month to 9.1 ± 1.9 at last follow-up ($P < .01$). Only 1 patient reported no improvement after 6 months. Results suggest that a single platelet-rich plasma injection can improve pain and function scores, thus avoiding surgery.

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This study was funded in part by the Musculoskeletal Transplant Foundation.

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doi: 10.3928/01477447-20101221-05

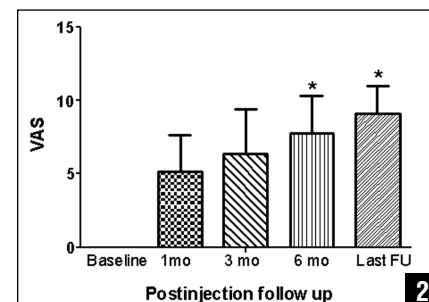
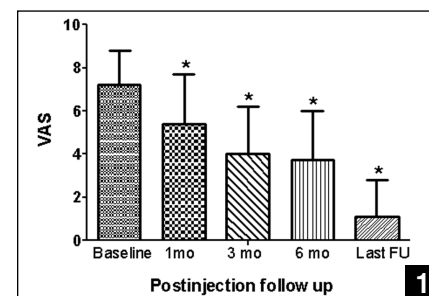


Figure 1: VAS subcategory rating pain at its worst from 0 (no pain) to 10 (worst pain). Data are mean \pm SD. Sample size was $n=30$, 27, 23, 17, and 26 for baseline; 1-, 3-, and 6-month; and last follow-up (FU), respectively (last follow-up range, 6-48 months; mean, 25 ± 14 months). * denotes statistical significance of $P < .01$ or less comparing results for patients at each follow-up time to their own baseline scores. **Figure 2:** Satisfaction with platelet-rich plasma injection from 0 (not at all satisfied) to 10 (very satisfied). Data are mean \pm SD. Sample size was $n=30$, 27, 23, 17, and 26 for baseline; 1-, 3-, and 6-month; and last follow-up (FU), respectively (last follow-up range, 6-48 months; mean, 25 ± 14 months). * denotes statistical significance of $P < .01$ or less comparing results for patients at each follow-up time to their own baseline scores.

The term epicondylitis is misleading in that instead of being an acute inflammatory condition, the lesion may be more accurately described as a degenerative change involving abnormal microvascular responses to the effects of mechanical overloading.¹⁻⁴ A lack of response to conservative treatment may be related to a defect in the normal tendon repair process. Consequently, the condition may more aptly be labeled a type of tendinosis or tendinopathy.³

Historically, typical conservative treatment strategies focused on reducing inflammation with rest, nonsteroidal anti-inflammatory drugs (NSAIDs), bracing, and physical therapy.⁵ Corticosteroid injection is considered a primary treatment, but the rationale and effectiveness is now called into question.⁵⁻⁸ Newer treatment modalities have been tried, such as extracorporeal shock wave treatment, iontophoresis, and injection of botulinum toxin. If conservative treatment fails, the last resort is surgery with the primary objective of relieving pain.^{5,8,9}

One novel treatment strategy is the use of local injection of platelet-rich plasma.^{9,10} Preparation of platelet-rich plasma involves centrifugation of autologous blood to separate and extract plasma and buffy coat portions of blood, which contain high concentrations of platelets. The platelet-rich plasma fraction may then be activated prior to injection by addition of excess calcium and thrombin to saturate all platelet receptors. Alternatively, the platelet-rich plasma fraction may be naturally activated after injection when coming in contact with local tissues. These activated platelets then secrete a variety of growth factors and other signaling molecules, including leukocyte-derived catabolic cytokines and fibrinogen, which collectively influence the tissue-healing processes.^{9,10} Thus, platelet-rich plasma injection is a relatively simple and minimally invasive method of using autologous blood-derived growth factors to promote healing.

Several published studies have reported using local platelet-rich plasma or autologous blood injection to treat epicondylitis of the elbow and various other tendinopathies and orthopedic conditions.¹¹⁻¹⁹ Positive results of platelet-rich plasma injection in patients with epicondylitis have been reported by Mishra and Pavelko¹⁴ in a nonrandomized case series and Peerboms et al¹⁹ in a randomized controlled trial. However, considerable controversy remains about the effectiveness of local platelet-rich plasma injection, which in part may be due to differences in preparation, method of platelet activation, and experimental design, such as how long patients were unresponsive to conservative therapies.

The goal of our study was to follow the outcome of a single local platelet-rich plasma injection in patients with painful medial or lateral epicondylitis of at least 6 months' duration unresponsive to nonsurgical (conservative) treatment, including steroid injection. Our hypothesis was that the platelet-rich plasma injection would stimulate the healing process manifested by a reduction in pain.

MATERIALS AND METHODS

Thirty patients (31 elbows) received a single local injection of platelet-rich plasma in this Institutional Review Board-approved study. All patients had a self-reported history of failed nonsurgical treatment of varying types for at least 6 months. Notably, all patients had a steroid injection as a treatment for the epicondylitis and physical therapy with no sustained relief of pain.

Radiographs of the elbow were obtained. Patients completed a standard physical examination consisting of range of motion; joint stability; pain on resisted flexion, extension, pronation, and supination; pain within their arc of motion; presence of crepitus; and localization of tenderness. A neurological evaluation was performed to check motor sensory function and possible presence of nerve entrapment.

Magnetic resonance imaging (MRI) of the elbow was obtained and read by both a radiologist and the attending physician. The MRIs were performed without contrast with gradient-echo and short tau inversion recovery coronal sequences and fast spin-echo sagittal and axial sequences. The purpose of obtaining the MRIs was to confirm the presence of epicondylitis (increased signal at the common flexor or extensor origin, tearing of tendon fibers if present, and adjacent tissue edema) and also to rule out pathology other than epicondylitis.

Exclusion criteria based on self-reported patient history included patients who were pregnant and patients with severe vascular or neurological disease, severe degenerative bone disease, presence of infection at the site, current tobacco use, active cancer, endocrine disorders, inflammatory disorders, steroid injections within 2 months of enrollment, and history of carpal tunnel syndrome or cervical radiculopathy. Patients taking NSAIDs were asked to stop taking the medication for 2 weeks prior to platelet-rich plasma injection. Patients completed outcome questionnaires prior to the injection.

Platelet-rich Plasma Preparation

Commercially available platelet-rich plasma kits (Cascade Autologous Platelet System; Musculoskeletal Transplant Foundation, Edison, New Jersey) were used to prepare the platelet-rich plasma for injection. Approximately 9 mL of the patient's whole blood was collected from the uninjured arm into a 10-mL blood collection tube containing 1 mL of buffered trisodium citrate and a thixotropic separation gel. The blood collection tube was inverted 7 times to mix the trisodium citrate (anticoagulant) to prevent the blood from clotting prior to being placed in a clinical centrifuge. The process of separating the platelets and plasma from the red and white blood cells involved a 6-minute spin time at 1100 g. After the centrifugation process was complete, the platelets and plasma were sepa-

rated from the red and white blood cells via the separation gel. The blood collection tube was removed and inverted 7 times to resuspend the platelets resting on top of the separation gel prior to recalcification. The platelet-rich plasma was transferred to a 10-mL collection tube containing 0.1 mL of calcium chloride via a male/female luer lock adapter and inverted 7 times. The final concentration of calcium counteracted (neutralized) the sodium citrate anticoagulant, but was not a sufficient concentration to activate the platelets prior to injection.^{9,20} The platelet-rich plasma was then loaded into a 5-mL syringe with a 22-gauge needle. The excess platelet-rich plasma was purged until only 3 mL of platelet-rich plasma remained in the syringe.

Injection Technique

Patients remained in a supine position. Lateral epicondylar tendinopathy patients had their affected arm rest at their side with their elbow flexed to 45° and their hand pronated. Medial epicondylar tendinopathy patients had their affected arm resting comfortably in slight abduction, with their hand supinated. The painful area was then identified with palpation, and the target area was marked with a “tic tac toe” grid so that the center box contained the affected area. The area was prepped with alcohol, followed by betadine. A local anesthetic (1% xylocaine without epinephrine) was used to numb the subcutaneous tissue before platelet-rich plasma injection. The prepared 3 mL of platelet-rich plasma was injected with an 18-gauge needle into the common extensor or flexor tendon as well as the insertions into bone, using a peppering technique.²¹ This technique involved a single skin portal followed by 9 penetrations of the tendon while injecting equal amounts of platelet-rich plasma. The delivered platelets were activated on contact with tendon tissue.

Postinjection Protocol

Patients were instructed to limit extensive use of their arm for the next 24 hours and to use pain medication only if neces-

sary. Patients were given a standardized stretching protocol to follow for 2 weeks, beginning 24 hours after injection. After the stretching program was complete, a formal strengthening program was initiated. Patients were permitted to continue with activities of daily living immediately; however, they were cautioned to refrain from any repetitive activities that reproduced the elbow pain for the next 4 weeks. Return to recreational and/or sporting activity was allowed once the patient was pain free during activities of daily living and asymptomatic during resistive testing.

Outcome Variables

Outcome surveys comprised in part the patient self-evaluation for pain and function from the validated American Shoulder and Elbow Surgeons (ASES) outcome instrument for elbow and selected measures to quantify patient assessment of the effectiveness of the injection.²² Unlike the ASES outcome instrument for shoulder, the elbow instrument does not have a standardized scoring system. Thus, we describe our scoring methods as follows:

Visual analog scale for pain. This was scored in linear fashion from 0 (no pain) to 10 (worst pain ever). Patients were asked to rate their pain in 5 subcategories: (1) when it is at its worst; (2) at rest; (3) lifting a heavy object; (4) when doing a task with repeated elbow movement; and (5) at night. Scores were tallied for each subcategory to produce a composite pain score.

Patient self-evaluation of function. This was the patient self-evaluation of physical function assessment from the ASES assessment tool comprising 12 categories of activities of daily living for which we reported a total score.²² The subcategories were: button a shirt, manage toileting, comb hair, tie shoes, eat with a utensil, carry a heavy object, rise from a chair pushing with arm, do heavy household chores, turn a key, throw a ball. Two additional questions were: do usual work and do usual sport. Each subcategory activity was assessed

with an ordinal scale of 0 (unable to do), 1 (very difficult to do), 2 (somewhat difficult to do), and 3 (not difficult to do), with a composite score maximum of 36.

Patient self-evaluation of satisfaction. This was a visual analog score (VAS) scored in linear fashion from 0 (not satisfied at all) to 10 (very satisfied).

Nirschl staging. This tool rated pain symptoms in 7 phases:

1. Mild pain with exercise; resolves in 24 hours.
2. Pain after exercise; exceeds 48 hours.
3. Pain with exercise; does not alter activity.
4. Pain with exercise; alters activity.
5. Pain with heavy activities of daily living.
6. Pain with light activities of daily living; intermittent pain at rest.
7. Constant pain at rest; disrupts sleep.¹¹

Physical assessment of physical function. We used the ASES elbow assessment form, consisting of physician assessments of motion, stability, strength, and signs.²² We calculated a composite elbow tenderness score (0, no tenderness; 18, severe tenderness at all sites) using a portion of the assessment of signs pertaining to ulnohumeral, radiocapitellar, medial flexor origin, lateral extensor origin, medial collateral ligament, and posterior interosseous nerve tenderness.

Postinjection assessments were planned at 1 week and 1, 3, 6, 12, and 24 months.

Study Design and Definition of Successful Treatment

This was a nonrandomized prospective study, with each patient serving as his or her own control. The rationale was that each patient had chronic epicondylitis refractory to conservative management whose only remaining treatment option was surgery, and thus improvement would be attributable only to platelet-rich plasma injection. We chose a reduction in the worst pain subcategory score of the VAS as the primary objective measure of overall improvement after the platelet-rich plasma injection. Specifically, we adopted the criteria of Peerbooms et al¹⁹

Table	
Patients With >25% Decrease in VAS Pain Score for Worst Pain	
Follow-up	No. Patients With Decrease/Total No. Patients (%)
1 month	12/27 (44)
3 months	16/23 (70)
6 months	13/17 (77)
Last ^a	25/26 (96)

Abbreviation: VAS, visual analog scale.
^a25 ± 14 months.

and defined successful treatment as a 25% reduction in worst pain score at follow-up with no reintervention after 1 year.

Statistical Analyses

Most patients missed ≥1 follow-up visits. As a result, the preferred and intended repeated measures analysis of variance could not be reliably performed for the analysis of serial results. Consequently, we used each patient as his or her own control, comparing follow-up scores to their baseline scores with two-tailed paired *t* tests. This served to avoid the confounding factor of comparing groups of different patients (ie, all the patients who had data at a given time point to the baseline group consisting of all patients), and also kept sample size equity between baseline and follow-up by comparing each patient's baseline to a given follow-up score. However, for simplicity of data presentation, we show the cohort means at each follow-up time (unequal sample size at each time). Further, to account for the hazard of possible type I statistical error with multiple *t* tests, we used *P* < .01 to indicate significance. Data are presented as mean ± standard deviation.

RESULTS

The study group comprised 30 patients (31 elbows): 9 women and 21 men. The

diagnosis was medial epicondylitis in 8 elbows and lateral epicondylitis in 23 elbows. In 22 patients, the dominant arm was affected. Mean patient age was 47.1 ± 14 years (range, 19-67 years). Two patients elected to have surgery by 1-month follow-up. Of the remaining 28 patients (29 elbows), 3 were effectively lost to follow-up after 1 month (1 patient) or 3 months (2 patients). The remaining patients had at least 6 months of follow-up data (3 patients), but the majority had >12-month follow-up (last follow-up, 25 ± 14 months in patients with at least 6-month follow-up; n = 26).

After platelet-rich plasma injection, no patient experienced unexpected adverse effects; specifically, there were no infections, neurovascular changes, or prolonged worsening of epicondylar pain.

Overall effectiveness of the treatment was evident in 27 of the 30 patients (90%) and 28 of the 31 involved elbows (90%), with >25% reduction in worst pain at ≥1 follow-up visits. None of these patients admitted to having other treatments (except occasional use of aspirin or NSAIDs) during the follow-up period. None of the patients who continued the platelet-rich plasma course beyond 1 month had elbow surgery. The Table summarizes the patients with >25% reduction in worst pain at each follow-up visit.

One patient who elected for surgery and was subsequently not followed was a college baseball pitcher, and the other patient played club tennis competitively. Neither had pain relief at 1 month, and both decided they already had a prolonged conservative treatment period and did not want to delay return to play by waiting for possible pain relief from the platelet-rich plasma injection. The followed patient who did not have >25% reduction in worst pain at ≥1 follow-up visits had a consistent decrease in worst pain of 22.2% (reduction of worst pain at baseline of 9 to 7 at all follow-up visits); this patient had a full-time light manual labor job and did not take time from work to rest the affect-

ed elbow. For the 3 patients who were lost to follow-up after 1 and 3 months, worst pain scores had improved dramatically. These patients were eventually contacted by telephone; they confirmed a lasting reduction in pain and satisfaction with the treatment, and did not have further treatment elsewhere after the platelet-rich plasma injection.

For the cohort, actual worst pain elbow scores at baseline; 1-, 3-, and 6-month; and last follow-up were 7.2 ± 1.6 (n = 30), 5.4 ± 2.3 (n = 27), 4.0 ± 2.2 (n = 23), 3.7 ± 2.3 (n = 17), and 1.1 ± 1.7 (n = 26), respectively (Figure 1). Significant decreases were observed beginning at the 1-month follow-up, and scores continued to improve throughout the follow-up period. The composite pain score also decreased in parallel with the subcategory worst pain with cohort scores at baseline; 1-, 3-, and 6-month; and last follow-up of 26 ± 6.0, 20 ± 10, 14 ± 9.1, 10 ± 7.7, and 6.3 ± 1.4, respectively. However, pain did not totally resolve in all patients, with 90%, 83%, 88%, and 38% of patients reporting some level of pain (typically a score of 1 or 2 on one of the 5 subcategory VAS measures of pain) at 1-, 3-, and 6-month and last follow-up, respectively.

Composite patient self-evaluation of physical function scores representing activities of daily living increased (improved) significantly as elbow pain decreased and was evident as early as 3 months after the platelet-rich plasma injection. Scores at baseline; 1-, 3-, and 6-month; and last follow-up were 26 ± 5.5, 28 ± 6.9, 30 ± 4.2, 32 ± 3.3, and 34 ± 7.7, respectively. Individual subcategory scores, such as ability to do usual work or turn a key, were not any more sensitive to healing over time than the composite physical function score, and the data are not presented in this report. Nirschl scores also significantly improved after the platelet-rich plasma injection as shown in Figure 2. Other measures such as range of motion and physician assessments of signs such as flexor or extensor origin tenderness (from the ASES outcome survey) were either not greatly impaired at baseline and

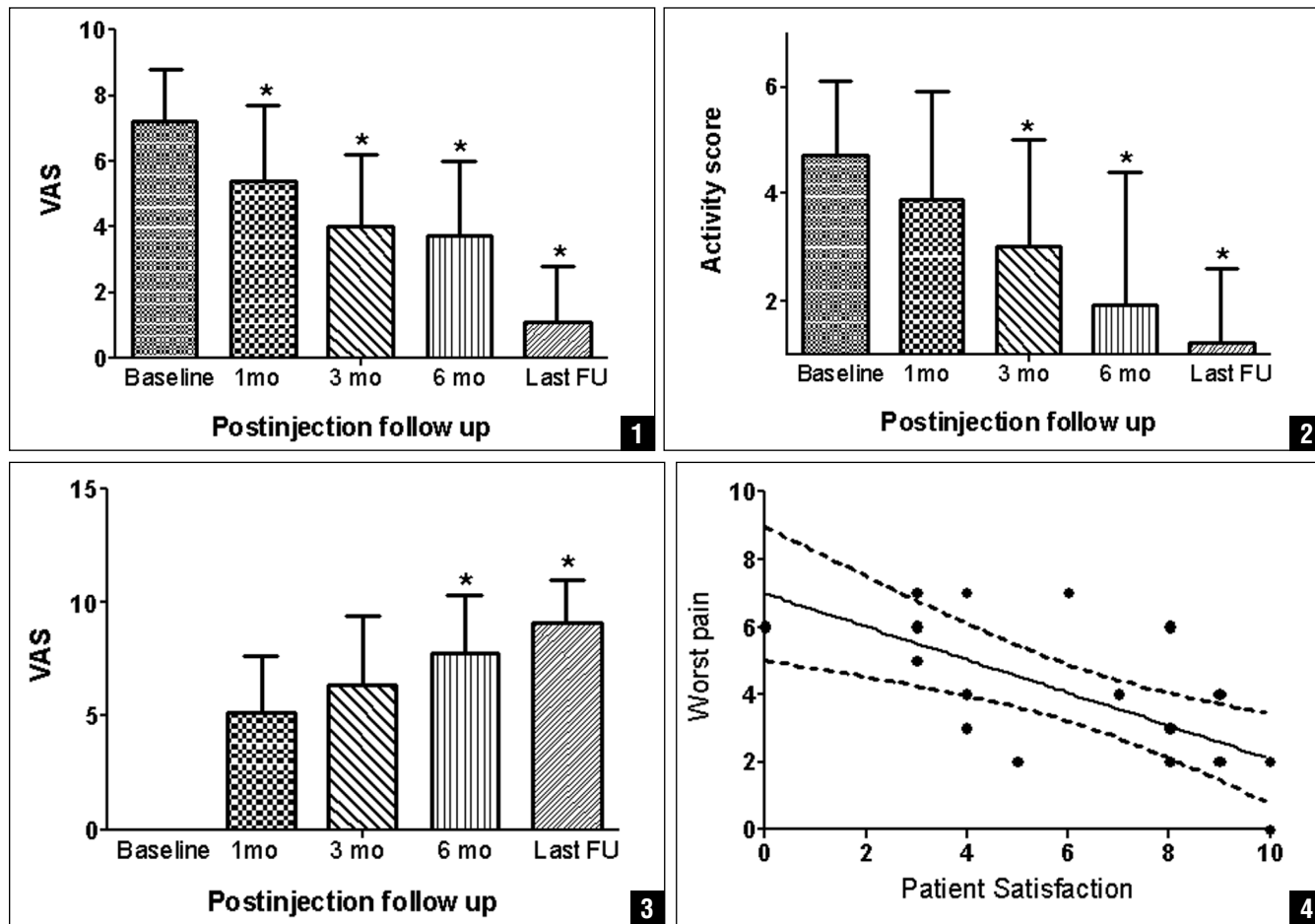


Figure 1: VAS subcategory rating pain at its worst from 0 (no pain) to 10 (worst pain). Data are mean±SD. Sample size was n=30, 27, 23, 17, and 26 for baseline; 1-, 3-, and 6-month; and last follow-up (FU), respectively (last follow-up range, 6-48 months; mean, 25±14 months). * denotes statistical significance of $P < .01$ or less comparing results for patients at each follow-up time to their own baseline scores. **Figure 2:** Nirschl activity score range from 1 (mild pain with exercise) to 7 (constant pain at rest). Data are mean±SD. Sample size was n=30, 27, 23, 17, and 26 for baseline; 1-, 3-, and 6-month; and last follow-up (FU) respectively (last follow-up range, 6-48 months; mean, 25±14 months). * denotes statistical significance of $P < .01$ or less comparing results for patients at each follow-up time to their own baseline scores. **Figure 3:** Satisfaction with platelet-rich plasma injection from 0 (not at all satisfied) to 10 (very satisfied). Data are mean±SD. Sample size was n=30, 27, 23, 17, and 26 for baseline; 1-, 3-, and 6-month; and last follow-up (FU), respectively (last follow-up range, 6-48 months; mean, 25±14 months). * denotes statistical significance of $P < .01$ or less comparing results for patients at each follow-up time to their own baseline scores. **Figure 4:** Correlation ($r = -0.66$; $P = .002$) between worst pain scores and patient satisfaction scores at 3-month follow-up (FU).

were not sensitive measures of change after treatment (data not shown). That is, changes over time after injection did not correlate well with improvements in worst pain or patient satisfaction scores. The 1 notable exception was the composite ordinal scale for tenderness (0, no tenderness; 18, severe tenderness) improved from cohort baseline of 3.5 ± 1.8 to 0.8 ± 0.9 ($P < .01$) at 3-month follow-up, and did not change further for the duration of follow-up.

Patient satisfaction with the injection increased progressively with time in step

with the improvements in elbow pain (Figure 3). In fact, patient satisfaction and worst pain scores were significantly inversely correlated at 3- (Figure 4) and 6-month follow-up: $r = -0.66$ ($P = .002$) and $r = -0.77$ ($P = .0009$), respectively. Worst pain scores were also significantly correlated with the improvement in Nirschl scores ($r = .54$; $P = .017$) as early as 3-month follow-up.

DISCUSSION

The results of this study suggest that a single platelet-rich plasma injection

can relieve pain and improve function in patients with long-term medial or lateral epicondylitis who had failed steroid treatment. Ninety percent of patients and elbows met the criterion of successful treatment: a 25% reduction in worst pain score for at least 1 follow-up visit with no further intervention at 12 months. As results show, even if this somewhat arbitrary criteria was more stringent, eg, 50% reduction in worst pain, we would have seen successful treatment in most patients (although the time course would

be shifted to longer follow-up times to see 50% reduction in worst pain). Worst pain scores were significantly better as early as 1-month follow-up, suggesting a rapid healing response after injection of platelet-rich plasma. This is notable because all patients had long-term symptoms of epicondylitis and at least 6 months of pain refractory to other treatments, including a steroid injection.

Two patients had no pain relief at 1-month follow-up and underwent surgery; it is possible that they could have had pain relief had they waited, as 70% of patients had >25% pain relief 3 months postoperatively, and none of the 28 patients who stayed the course of the platelet-rich plasma injection elected for subsequent surgery. It is estimated that 5% to 10% of patients with epicondylitis will seek operative treatment.⁵ Surgical repair of epicondylitis is generally associated with high success rates.⁵ However, the surgical morbidity and costs of surgery argue against the surgical option if other options are available.

The time course of change in VAS pain scores in the platelet-rich plasma-treated patients in our study was similar to what was observed by Peerbooms et al.¹⁹ In a randomized controlled trial, Peerbooms et al¹⁹ compared a single injection of platelet-rich plasma (n=51) with a single injection of corticosteroid (n=49). A successful treatment was defined as >25% reduction in the VAS for pain without re-intervention after 1 year. Results showed that 49% of patients receiving corticosteroid had relief of pain vs 73% in the platelet-rich plasma group ($P<.001$) at 1 year. Platelet-rich plasma-treated patients had a mean improvement in pain score of 64% compared to 24% of the corticosteroid-treated patients ($P<.001$). Of interest, the improvement in pain score was initially more rapid in the corticosteroid-treated patients than the platelet-rich plasma-treated patients, but over time, the effect attenuated in the corticosteroid group, whereas it continued to improve for the platelet-rich plasma group.

Other studies have evaluated the effect of platelet-rich plasma in various orthopedic conditions.¹¹⁻¹⁹ Unfortunately, results have varied, and few randomized controlled studies have been performed. For epicondylitis, no studies have compared platelet-rich plasma injection with a true control, such as patients who are randomized to placebo injection. Further, the types of platelet-rich plasma preparations vary not only with respect to the manner in which the platelets are harvested, but also to the concentration of the final injectable product, presence of leukocytes, and whether the platelets are activated prior to injection.²³ However, reports to date have generated interest in pursuing the concept of using naturally occurring growth factors to treat common orthopedic conditions.

A limitation of our study is that it was not a randomized trial with a formal control group. However, it is legitimate for patients to serve as their own control given they had failed to be relieved of pain after steroid injection and other forms of conservative treatment. Further, given their chronic pain, it is unlikely that their rapid improvement could be the result of a factor other than the platelet-rich plasma injection. Regarding the relatively small sample size, we note that a post hoc analysis showed adequate power given the large effect of platelet-rich plasma injections on worst pain scores. For example, for the comparison of matched baseline and 3-month follow-up worst pain scores observed (7.1 ± 1.5 vs 4.0 ± 2.2 ; SD of the differences, 2.6; n=23), there was 90% power to detect a smallest average difference between pairs of 2 with a significance level (alpha) of 0.01 (two-tailed).

We observed a significant correlation between changes in pain scores and patient satisfaction and Nirschl scores, substantiating use of the worst pain scores as the primary outcome variable (pain was the major symptom in all patients, and relief of pain was the primary goal of treatment). However, in the course of this

study we realized that the typical outcome tools used (VAS for pain, ASES shoulder and elbow survey, and Nirschl scale) may not be specific or sensitive enough to truly monitor progress after treatment of epicondylitis. Although nearly all patients reported little or no tenderness or functional limitations at last follow-up, there was no correlation between improvement in VAS pain scores and physician physical assessments and patient responses to questions about elbow tenderness. We also observed that the physical function component of the ASES tool did not uniformly address the types of disability associated with our patients. The limitation of the Nirschl scale was lack of a 0 score indicating no physical function disabilities whatsoever. The VAS for pain is somewhat problematic in that little information is available to interpret the scores; that is, we have no information as to what a given score (eg, a score of 1) relates to compared to other orthopedic conditions, or how it is affected by age and general health status.

CONCLUSION

A single injection of platelet-rich plasma at the site of the elbow pain resulted in relief of pain in patients with long-term epicondylitis refractory to other conservative treatments. Further study is necessary with randomized trials using peppering injections alone vs peppering injections with platelet-rich plasma to confirm the positive effect of platelet-rich plasma and elaborate the possible mechanism of action. A placebo group would be necessary since all patients would have already failed 6 months of conservative treatment. ●

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