Platelet-Rich Plasma Versus Autologous Whole Blood for the Treatment of Chronic Lateral Elbow Epicondylitis

A Randomized Controlled Clinical Trial

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Background: Chronic lateral elbow epicondylitis is a tendinosis with angiofibrolastic degeneration of the wrist extensors’ origin. Healing of this lesion is reported with the use of autologous blood as well as with platelet-rich plasma (PRP).

Purpose: A comparative study of these 2 treatments was conducted in an effort to investigate the possible advantages of PRP.

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

Methods: Twenty-eight patients were divided equally into 2 groups, after blocked randomization. Group A was treated with a single injection of 3 mL of autologous blood and group B with 3 mL of PRP under ultrasound guidance. A standardized program of eccentric muscle strengthening was followed by all patients in both groups. Evaluation using a pain visual analog scale (VAS) and Liverpool elbow score was performed at 6 weeks, 3 months, and 6 months.

Results: The VAS score improvement was larger in group B at every follow-up interval but the difference was statistically significant only at 6 weeks, when mean improvement was 3.8 points (95% confidence interval [CI], 3.1-4.5) in group B (61.47% improvement) and 2.5 points (95% CI, 1.9-3.1) in group A (41.6% improvement) (P < .05). No statistically significant difference was noted between groups regarding Liverpool elbow score.

Conclusion: Regarding pain reduction, PRP treatment seems to be an effective treatment for chronic lateral elbow epicondylitis and superior to autologous blood in the short term. Defining details of indications, best PRP concentration, number and time of injections, as well as rehabilitation protocol might increase the method’s effectiveness. Additionally, the possibility of cost reduction of the method might justify the use of PRP over autologous whole blood for chronic or refractory tennis elbow.

Keywords: lateral elbow epicondylitis; platelet-rich plasma; autologous whole blood; pain; function

Lateral elbow epicondylitis ("tennis elbow") is a common clinical entity affecting 1% to 3% of the population.13 The cause of the disease is a combination of mechanical overloading and abnormal microvascular responses.23,27,30 Nirschl and Pettrone24 attributed the cause to microscopic tearing with formation of reparative tissue (ie, angiofibroblastic hyperplasia) in the origin of the extensor carpi radialis brevis muscle. In some cases, symptoms do not resolve and lead to chronic disease.

The concept of delivering humoral mediators in an effort to promote normal tendon healing by locally injecting autologous blood was first reported in 2003.9 The cells responsible are platelets. In addition to their well-known role in hemostasis, platelets play an instrumental role in the normal healing response via the local secretion of growth factors and recruitment of reparative cells. Within platelets, the alpha granules are storage units, which contain prepackaged growth factors in an inactive form. The main growth factors contained in α-granules of platelets are transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and epithelial growth factor (EGF). These factors enhance the recruitment, proliferation, and differentiation of cells involved in tissue regeneration.19

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Platelet-rich plasma (PRP) is defined as autologous blood with a concentration of platelets above baseline values. Platelet-rich plasma contains a 2- to 8-fold increase in platelet concentration and 1- to 25-fold growth factor concentrations, depending on which factor is examined. A platelet concentration of at least 1 000 000 platelets/mL in 5 mL of plasma is associated with the enhancement of healing. The use of PRP for healing purposes was first popularized in maxillofacial and plastic surgery in the 1990s. Its use in orthopaedics started later and it is increasing. Laboratory and clinical studies of PRP use on tendons, ligaments, muscle, bone, and cartilage are already published.

We conducted a study to investigate the effectiveness of PRP compared with autologous blood on chronic lateral epicondylitis and the possible benefit of the first method over the second.

### METHODS

We conducted a randomized trial of 28 consecutive patients with chronic lateral epicondylitis (ie, duration of symptoms ≥3 months). Blocked randomization was used to achieve an equal number of cases in each group. Every eligible patient with an odd sequence number was randomly allocated to 1 group. The following patient was automatically placed in the opposite group. Randomization was performed using an Internet platform called "research randomizer form v4.0." Group A was treated with 1 injection of 3 mL of whole blood and group B with 1 injection of 3 mL of PRP. The GPS III system (Biomet Biologics, Inc, Warsaw, Indiana) was used for the extraction of the PRP.

Each group included 14 cases. Age, gender, occupation, dominance of the hand, and duration of the symptoms did not differ substantially between the 2 groups (Table 1).

Inclusion criteria were clinically diagnosed lateral epicondylitis (based on symptoms, site of tenderness, and pain elicited with resisted active extension of the wrist in pronation and elbow extension), no history of trauma, duration equal to or more than 3 months, no previous local injection treatment of any kind, no medical history of rheumatic disorder, and no signs of posterior interosseous nerve entrapment. Exclusion criteria were recent onset of symptoms (<3 months), history of trauma, medical comorbidities such as rheumatoid arthritis, previous local injections (eg, cortisone), and suspicion of nerve involvement.

The treatment protocol for group A was a single injection of 3 mL of autologous peripheral whole blood, deep at the origin of wrist extensors with a peppering technique (single skin insertion, deep peripheral multiple sites of injection) under aseptic technique with the assistance of ultrasound guidance. Group B treatment protocol included a single injection of 3 mL of autologous PRP under the same technique. For the PRP preparation, the Biomet GPS III was used. This system uses, under aseptic technique, 27 to 55 mL of autologous peripheral blood with 3 to 5 mL of anticoagulant, centrifuges it at 3200 rpm for 15 minutes, and finally extracts 3 to 6 mL of PRP. No activator was used. Activation takes place in vivo after contact of platelets to the collagen. To estimate the concentration of the PRP extraction, samples of 2 healthy volunteers were examined (blood test parameters within normal limits). Compared with whole blood, the concentration of platelets was found raised from 235 000/mL to 1292 500/mL (5.5 times on average). White blood cells are included in the concentrate with an average ratio of 11171 (platelets/leukocytes). This is a type IA PRP according to the recently presented Mishra classification. Growth factors using this procedure are reportedly raised as follows: BGF, 3.9X; VEGF, 6.2X; TGF-β1, 3.8X; insulin-like growth factor (IGF)-1, 1X; and PDGF, not applicable.

No cortisone or nonsteroidal anti-inflammatories were prescribed during follow-up. For pain relief only, oral paracetamol and ice therapy were used. Patients of both groups were requested to refrain from heavy labor activities for a week. A week after the injection, each patient was reassessed and given a simple program of stretching and eccentric loading exercises to be performed on an individual basis twice every day for 5 weeks.

This is a single-blind study. Patients were aware of the treatment because it was practically difficult to mask the process. The assessment was performed by 2 members of the study team. The 2 assessors had no participation in treatment so were unaware of which treatment each patient received. Reevaluation was done at 6 weeks, 3 months, and 6 months after the injection. Visual analog pain scale (VAS) (range, 0 [no pain] to 10 [agonizing pain]) and the Liverpool elbow score were used to evaluate patients before and after the treatment. The Liverpool score evaluates range of motion, daily activities, and ulnar nerve function and was selected as the most suitable score for the evaluation of the disease.

For the purposes of statistical analysis, the 2-sample Student t test was used to compare the results in VAS and Liverpool score between the 2 groups. Sample estimation was performed using Lehr formula, and power was fixed at 80%. According to these parameters, the minimum sufficient number of patients in each group was 13. The level of statistical significance was set at P < .05.

### TABLE 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (Range), y</th>
<th>Gender, M/F</th>
<th>Dominant/ Non-Dominant</th>
<th>Duration (Range), mo</th>
<th>Occupation: Office/Labor/Housekeeping</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (whole blood)</td>
<td>36.6 (29-52)</td>
<td>11/3</td>
<td>13/1</td>
<td>5.1 (3-14)</td>
<td>8/2/4</td>
</tr>
<tr>
<td>B (platelet-rich plasma)</td>
<td>35.9 (34-56)</td>
<td>10/5</td>
<td>11/3</td>
<td>4.7 (3-12)</td>
<td>7/1/6</td>
</tr>
</tbody>
</table>

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addition to measuring absolute numbers, relative improvement regarding time of the above-mentioned scores was calculated as well.

RESULTS

Follow-up was completed successfully at 6 months except for 1 patient from group A who was lost at 6 months’ reevaluation.

At the end of the first week, when patients came back for exercise instructions, most of the patients in group B (PRP) reported local pain and discomfort that started from the day of injection and gradually subsided (9 of 14 group B compared with 4 of 14 in group A). With the exception of the above, no other complication was noted.

Pretreatment VAS scores were 6.0 (95% confidence interval [CI], 5.32-6.68) for group A and 6.1 (95% CI, 5.43-6.77) for group B. Regarding relative improvement of VAS score, group B showed better outcome compared with group A at every reevaluation interval but the difference was statistically significant only at 6 weeks. At 6 weeks, mean improvement was 3.8 points (95% CI, 3.1-4.5) in group B (61.47% improvement) and 2.5 points (95% CI, 1.9-3.1) in group A (41.6% improvement; \( P < .05 \)). The absolute VAS score was 2.35 (95% CI, 1.83-2.87) for group B and 3.5 (95% CI, 2.82-4.18) for group A (Figure 1). Further improvement at 3 and 6 months was noted in both groups. Specifically, at 3 months the outcome was 4.2 (95% CI, 3.5-4.9; 68.5% improvement) for group B compared with 3.2 (95% CI, 2.3-4.1; 53.6% improvement) for group A (\( P = .11 \)). At 6 months it was 4.4 (95% CI, 3.4-5.4; 70.8% improvement) for group B compared with 3.4 (95% CI, 2.4-4.4; 67.8% improvement) for group A (\( P = .32 \)). As shown in Figure 1, absolute VAS scores at 3 months were 1.92 (95% CI, 1.41-2.43) for group B and 2.73 (95% CI, 2.28-3.28) for group A, while at 6 months they were 1.78 (95% CI, 1.14-2.42) and 2.53 (95% CI, 1.89-3.17), respectively.

When examining improvement in Liverpool score expressed as the relative difference between groups, no significance was noted at all follow-up intervals. Change scores were as follows (group B/group A): 2.02 points (95% CI, 1.62-2.42; 28.9% improvement)/1.85 (95% CI, 1.39-2.31; 24.5% improvement) at 6 weeks (\( P = .45 \)), 2.17 (95% CI, 1.73-2.61; 31% improvement)/1.86 (95% CI, 1.41-2.31; 25.5% improvement) at 3 months (\( P = .45 \)), and 2.3 (95% CI, 1.94-2.66; 33.9% improvement)/1.97 (95% CI, 1.44-2.5; 26.9% improvement) at 6 months (\( P = .58 \)).

Pretreatment scores were 6.97 (95% CI, 6.65-7.29) for group A and 6.99 (95% CI, 6.88-7.50) for group B. Results are as follows: 9.01 (95% CI, 8.59-9.43) at 6 weeks, 9.16 (95% CI, 8.73-9.59) at 3 months, and 9.32 (95% CI, 9.05-9.59) at 6 months for group B; and 8.68 (95% CI, 8.48-9.08) at 6 weeks, 8.72 (95% CI, 8.35-9.09) at 3 months, and 8.85 (95% CI, 8.4-9.3) at 6 months for group A (Figure 2).

DISCUSSION

There is enough laboratory evidence of PRP effect on tendon healing. Cell culture studies have provided evidence that PRP can stimulate processes associated with tendon healing. Several investigators have found increased collagen gene expression and increased production of VEGF and hepatocyte growth factor in human tenocytes treated with PRP. Recently, it was reported that PRP stimulates the mobilization of circulation-derived cells to the area of injection and stimulates type I collagen production. Several investigators have demonstrated greater cell proliferation and angiogenesis in animal tendon models treated with PRP. Other studies have found that PRP can enhance human stromal and mesenchymal stem cell proliferation.

The action of PRP is that it may be possible to initially inhibit excess inflammation while stimulating proliferation and maturation. This may be especially important in
preventing the fibrous scar tissue healing that occurs with macrophage-mediated tendon-to-bone healing. This is supported by the studies of Woodall et al. who found that PRP suppresses macrophage proliferation and interleukin (IL)-1 production within the first 72 hours after exposure. This differential induction of cells has important implications for tendon and muscle healing.

In the past few years, clinical studies of testing platelet-rich plasma and autologous blood have been published for the treatment of tennis elbow, both with promising results. Initially, it was considered that the use of autologous blood might provide the necessary cellular and humoral mediators to induce a healing cascade, given that the pathologic nature of refractory lateral epicondylitis is anginofibroblastic hyperplasia at the origin of extensor carpi radialis brevis. In this particular study of Edwards and Calandrucio, 28 patients with chronic lateral epicondylitis were injected with 2 mL of autologous blood under the extensor carpi radialis brevis. The average follow-up period was 2.6 months. Nine patients needed a second or third injection. Finally, 22 patients (79%) were relieved completely of pain even during strenuous activity. In another study, the injection of the autologous blood was performed under ultrasound guidance in 35 patients. Both VAS and Nirschl scores improved significantly at 4 weeks and further on at 6-month follow-up. Moreover, sonography demonstrated a reduction in the total number of interstitial cleft formations and anechoic foci and a significant reduction in tendon thickness and neovascularity, although sonographic abnormality remained in many asymptomatic patients.

With the positive outcome of autologous blood injections and the increasing interest in the potential of growth factors, PRP was used in a pilot study for chronic lateral epicondylitis by Mishra and Pavelko. Fifteen patients treated with PRP noted 81% improvement in their VAS scores at 6 months compared with before the treatment. At final follow-up (mean, 25.6 months), patients reported 93% reduction in pain. Two controlled trials of PRP and cortisone injections for tennis elbow have been published recently. In the study of Peerbooms et al., 1 year after the procedure, PRP-treated patients reported a mean improvement of 63.9% in their VAS scores compared with the initial values, whereas the corticosteroid-treated patients reported a 24.0% improvement. Also, after 1 year, Disabilities of the Arm, Shoulder and Hand (DASH) scores improved 66% in PRP patients versus a 17.4% improvement in corticosteroid-treated patients. Worth mentioning is that the corticosteroid group was better initially and then declined, whereas the PRP group progressively improved. In the second clinical study of Mishra et al., PRP had superior results compared with corticosteroid injection for chronic lateral elbow tendinosis.

In our study, we tried to focus on the potential benefits of PRP treatment on a common clinical entity such as chronic lateral elbow epicondylitis. The choice of a control group treated with an injection of autologous blood was made to investigate the superiority of PRP as a higher concentrate of growth factors. Early results (6-week interval) were better in the PRP group with regard to VAS, but not statistically significant thereafter. There is strong evidence to claim that PRP treatment leads to greater initial reduction in pain compared with autologous whole blood, but this difference declines at 3 and 6 months. In the functional score of Liverpool, there was not a statistically significant difference between groups. Similar improvement in both groups at every follow-up interval was noted but a comment must be made on this. This score evaluates ability in everyday activities like housekeeping, dressing, or sports but estimates as well the range of movement, which is not usually affected in tennis elbow, and the ulnar nerve, which is always normal. These last 2 components of the questionnaire affect total score and perhaps cover possible clinical and statistical significance. The choice of this functional score is justified, however, as being more appropriate for lateral epicondylitis than other scores such as the Mayo elbow score or Broberg-Morrey score.

Regarding the higher reported postinjection pain in patients of group B, we hypothesize that the increased presence of white blood cells in this PRP concentrate may have led to more intense inflammation response.

The rehabilitation program after the injection is perhaps an important element of the treatment success. We suggested early eccentric training for all the patients of the study as described. Other authors have also underlined this. In the laboratory study of Virchenko and Aspberg, the effect of PRP on rat Achilles tendon rupture with and without mechanical load was studied. At 14 days, unloading (with Botox) abolished any effect of the platelets and reduced the mechanical properties of the repair tissue to less than half of normal. The authors concluded that PRP may accelerate the initial inflammatory phase of tendon repair, thereby making cells more receptive to earlier mechanical loading. The type of exercise perhaps plays a role when trying for the best outcome. Eccentric muscle strengthening seems to be more beneficial in the rehabilitation of tennis elbow as shown in the study of Croisier et al. An isokinetically eccentrically trained group was compared with a control group that underwent a passive standardized rehabilitation program that excluded strengthening exercises. The first group showed a significantly more marked reduction of pain intensity, mainly after 1 month of treatment; an absence of strength deficit on the involved side; an improvement of the tendon image in ultrasound; and a more marked improvement in disability status during occupational, spare time, and sports activities.

The limitation of the study is the relatively small number of cases included but with the power of 80% and the level of significance at 5%, there is enough proof to support the superiority of PRP treatment over autologous blood, regarding pain, in the short term. It is useful to report that when an outcome reaches statistical significance, a bigger sample cannot change but only verify this finding. Regarding pain (in the long term) as well as Liverpool elbow score, a bigger sample would be required to verify the lack of statistical significance if a power greater than 80% was chosen.

More studies on this topic could further enlighten aspects of this promising treatment and give more information about specific indications; best PRP concentration and the presence or absence of white blood cells in it;
time, number, and frequency of injections needed; and possible adverse effects. Particularly interesting would be a comparative study between platelet-rich and platelet-poor concentration, with and without white blood cells, to determine the efficacy of the methods and the inflammatory response they produce. The cost of the treatment is an important issue to be considered. The use of PRP was initially expensive and no health system is covering its use to our knowledge but this cost is being reduced. The clarification of the above-mentioned topics for investigation will probably lead to a better understanding and more efficient use of PRP in lateral epicondylitis.

In conclusion, we showed that PRP led to pain relief earlier than autologous whole blood, and we believe its application will be increasingly widened in the near future because of the safety of the method and the possible reduction of the cost.

REFERENCES