Chapter 8
Tennis Elbow: Blood and Platelet-Rich Plasma (PRP) Injections

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Introduction

Lateral elbow epicondylitis, or tennis elbow, is a common musculoskeletal condition affecting 1–3 % of the adult population [1, 2]. The ailment affects men and women equally and presentation most often occurs between ages 35 and 50 [3]. Pain in the lateral elbow and weakened grip, especially with wrist extension, are the most common complaints. Symptoms tend to present between 6 months and 2 years [2, 4].

Lateral epicondylitis was originally described as an inflammatory condition, but no inflammatory cells have been demonstrated in pathologic specimens [3, 5, 6]. Alfredson et al. found normal levels of the inflammatory marker PGE-2 in postoperative tissue specimens from patients with lateral epicondylitis [6]. Instead, the pathologic findings have been described as angiofibroblastic tendinosis. Therefore, lateral epicondylitis is likely better characterized as a tendinopathy. The origin of the extensor carpi radialis brevis, or less commonly the extensor digitorum communis, are most commonly affected [5]. The extensor muscle origin at the lateral humeral epicondyle is thought to be at risk for multiple reasons. It may be susceptible to microtrauma from overuse and eccentric loading, and it may have impaired healing due to an inadequate vascular supply. Two relatively hypovascular zones in the common extensor origin have been described, one at the origin of the lateral epicondyle and the other 2–3 cm distal along the tendinous insertion [7].

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Treatment

Despite the multiple treatment methods that have been described, there is no unanimously supported algorithm for the treatment of lateral epicondylitis. An observational approach is the most conservative, and many patients will report improvement of symptoms by 1 year after initial onset [8]. However, the choice to passively allow the disease to run its course can be unacceptable for many patients, as it can entail decreased functional ability and consistent pain. Patients who are unable to work can face economic hardships. Symptomatic treatment consists of activity modification and nonsteroidal anti-inflammatory medications. Other conservative treatment modalities include various types of physiotherapy, including exercises, bracing, and ultrasound.

For the cohort of patients who do not respond to these treatments, injections have been utilized prior to any surgical treatment. Historical injections included lidocaine, alcohol, and carbolic acid [3]. Currently, the combination of corticosteroids with a local anesthetic is most widely used. However, in recent literature a number of alternative injections have been described in randomized controlled trials. These include autologous blood, platelet-rich plasma (PRP), botulinum toxin, hyaluronic acid, polidocanol, glycosaminoglycan, and prolotherapy. Beyond injections, approximately 4–11 % of patients with refractory cases will progress to requiring operative intervention [4].

Blood-Based Injections

There has been increasing interest in orthopedics in the use of autologous and platelet-rich preparations to stimulate bone, tendon, muscle, and cartilage healing. These preparations have been applied for chronic tendinopathies, acute muscle and ligamentous injuries, and intraoperative augmentation [9]. Growth factors such as transforming growth factor-beta, fibroblast growth factor-2, platelet-derived growth factors, insulin-like growth factor-1, epidermal growth factor, and vascular endothelial growth factor can be found in the alpha granules of platelets [9]. These growth factors have a number of functions, including cellular proliferation, cell migration, collagen synthesis, and angiogenesis [10]. Blood-based preparations also have a number of proteins, such as cell-adhesion molecules, that may participate in promoting inflammatory cell migration to the site of injury. Delivery of these bioactive factors has been achieved in various injection forms, including whole autologous blood, leukocyte-depleted moderate-yield PRP, and leukocyte-rich high-yield PRP [11].

In chronic tendinopathies, such as lateral epicondylitis, it has been theorized that relative hypovascularity of the tendon combined with repetitive overuse can lead to tendinopathy. Autologous blood preparations can ideally bring the body's own growth factors to the hypovascular site of injury. This could result in increased healing potential by the body's own means. Based on this hypothesis, preparations of autologous blood or PRP have been used in the treatment of lateral epicondylitis, Achilles tendinopathy, patellar tendinopathy, and plantar fasciitis. In the following

sections, the evidence for use of autologous blood and PRP injections in patients with lateral epicondylitis is reviewed.

Autologous Whole Blood

Autologous blood injection for the treatment of lateral epicondylitis was first described by Edwards and Calandruccio [12]. The authors noted that techniques such as forceful closed manipulation, traumatic injection, and percutaneous release resulted in improved outcomes for patients, and theorized that this was due to bleeding at the extensor origin following the trauma. This bleeding would then stimulate an inflammatory cascade to begin a healing response for the tendinopathy. They proposed that autologous blood injection, specifically composed of 2–3 ml of autologous blood combined with lidocaine, would deliver the cellular and humoral mediators to the elbow for a similar healing process.

In a case series of 28 patients with lateral epicondylitis symptoms present for 6 or more months who had failed conservative therapy, Edwards and Calandruccio found that after receiving one to three autologous blood injections, pain scores and Nirschl stages decreased at an average follow up of 9.5 months [12]. Overall, they found 79% relief of pain following autologous blood injections.

Preparation of autologous blood is relatively standard among various studies. A volume of 2–3 ml of blood is typically collected. Some studies advocate injecting a local anesthetic such as lidocaine or 2 ml bupivacaine a few minutes prior to blood injection to allow the anesthetic time to take effect. Others support combination of autologous blood with 1 ml local anesthesia in the same preparation in order to only perform one injection (Fig. 8.1). A single-shot or peppering injection technique can be used (Fig. 8.2).

There have been a number of randomized controlled trials evaluating autologous blood injections for lateral epicondylitis, although only one with comparison to a

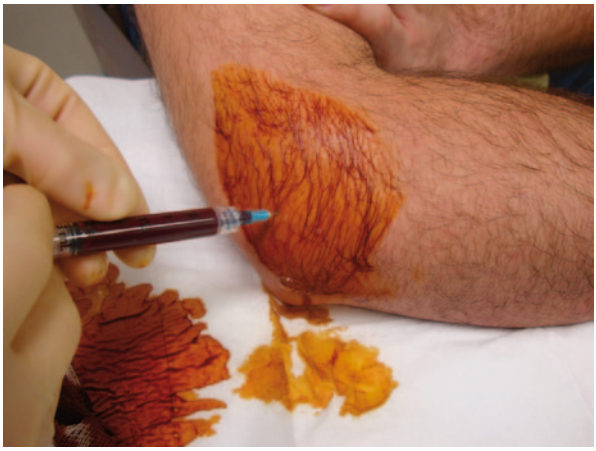

Fig. 8.1 Combination injection: autologous blood and 1 ml local anesthesia in one injection

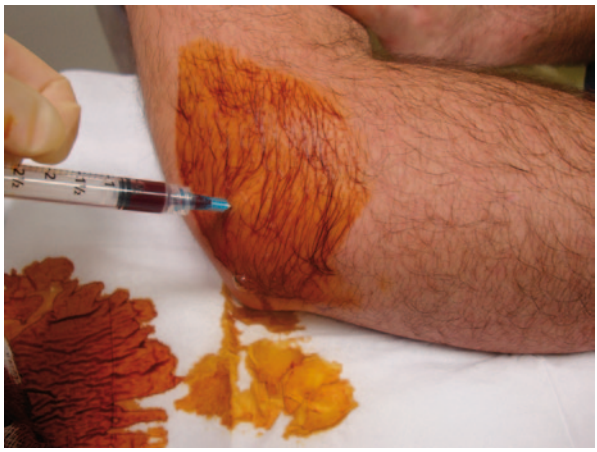

Fig. 8.2 Single-shot or peppering technique

placebo injection. Wolf et al. performed a randomized controlled trial (RCT) of 28 patients comparing autologous blood, corticosteroid, and a saline injection [13]. The study was double-blinded and patients were evaluated at 2 weeks, 2 months, and 6 months after injection with Visual Analog Scale (VAS), Disabilities of the Arm, Shoulder, and Hand (DASH), and the patient-related forearm evaluation. Although all of these outcomes demonstrated improvement from baseline in each group, there were no significant differences in any of the groups. However, the authors point out that the small number of patients in the study may limit their power to detect a difference between groups.

In 2010, Ozturan compared autologous blood injection to both corticosteroid injection and extracorporeal shock wave therapy in a three-armed randomized trial of 60 patients [14]. Although corticosteroid treatment showed the best outcomes at 4 weeks, success rates at 1 year were greatest for the autologous blood (83 %) and extracorporeal shock wave therapy (90 %) compared to only 50 % for corticosteroids. This study concluded that while corticosteroid injections provided better short-term relief of symptoms, autologous blood injections showed significantly better long-term results with decreased recurrence.

Kazemi directly compared autologous blood to corticosteroid injections in a short-term RCT of 60 patients [15]. As opposed to Ozturan et al.'s study, the authors found improved outcomes measures in the short-term for autologous blood. At 4 weeks, autologous blood was significantly more effective at decreasing pain scores at rest and with grip, as well as increasing QuickDASH scores ($p > 0.001$, $p = 0.002$, $p = 0.004$). These results persisted at 8 weeks ($p < 0.001$ for all measures).

Dojode performed a randomized study with 60 patients comparing autologous blood with local corticosteroid injection in a labor-intensive population [16] with 6 month follow up. Patients receiving corticosteroid injections had significantly decreased pain and Nirschl stage at 1 week ($p < 0.001$, both) and 4 weeks ($p = 0.002$, $p = 0.018$). However, outcomes were reversed as time went on. At 12 weeks and 6 months, patients who had received autologous blood had significantly lower pain and Nirschl stage scores ($p = 0.013$, $p = 0.018$ at 12 weeks, $p = 0.006$, $p = 0.006$ at

6 months, respectively). At the 6 month time follow up, 90% of patients who had received autologous blood injection reported complete relief of pain, compared to 47% of patients receiving steroid injection. This study concluded that autologous blood injections provide improved long-term relief of symptoms compared to corticosteroid injections.

There have been few side effects demonstrated from autologous blood injections. Most commonly authors cite the pain after injection as the most difficult side effect for patients. Ozturan describes 89% of patients having cessation of pain within 2 days, and the remaining 11% of patients had pain from 4 to 6 days[14]. In addition, 21% had elbow erythema, 16% had swelling, and 21% had nausea. Wolf et al. and Kazemi et al. described no side effects [13, 15]. Dojode reported 60% of patients having pain after the injection that resolved within a few days after injection [16].

In summary, autologous blood injections offer numerous factors to stimulate a healing cascade in the degenerative tendinous origin. Studies have shown beneficial effects for patients receiving these injections in the short- and long-term, predominantly compared to steroid injections. However, in the only placebo-controlled study, no significant benefit was observed for autologous blood injection. Additionally, one study showed no difference between autologous blood injections and extracorporeal shock wave therapy. Further investigation comparing autologous blood injections to placebo injections or conservative treatment with larger patient groups will shed more light on their efficacy.

Platelet Rich Plasma (PRP)

Autologous PRP is a concentrated source of platelets and platelet-derived growth factors that has been used for numerous musculoskeletal diagnoses. PRP is theorized to enhance the healing of wounds, bone, and tendons through release of specific growth factors upon platelet activation [17]. PRP has the theoretical advantage of increased concentration of platelets and therefore platelet-derived growth factors [17].

PRP is prepared by drawing 20–60 cc of blood from the patient. An FDA-approved blood separation device is used to centrifuge the blood for 15 min to isolate PRP [17]. This produces 3–6 mL of PRP (Fig. 8.3), which can be combined with or given after injection of 1–2 mL of local anesthetic (Fig. 8.4). Carofino et al. reported that lidocaine can cause inhibitory effects on tenocyte proliferation after exposure to PRP in vitro [18]. However, as the most common side effect from this injection is pain, it is standard to inject at least a small amount of local anesthetic into the skin with or prior to the injection.

Mishra et al. were the first to study the efficacy of PRP for lateral epicondylitis treatment [19]. In an unblinded prospective study, the authors treated 20 patients with chronic lateral epicondylitis using PRP in 15 and control bupivacaine in 5 [19]. At 8 weeks, patients who received PRP injections had significantly better VAS scores than the bupivacaine group. At final follow up of 1–3 years, 93% had reduction in VAS pain scores.

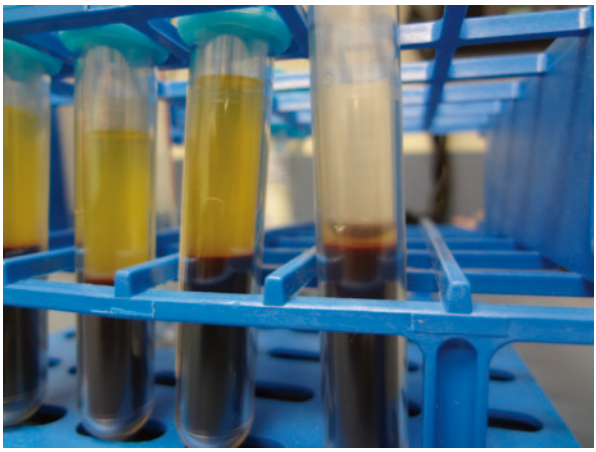

Fig. 8.3 Platelet-rich plasma (*PRP*). 20–60 cc of blood will, after 15 min centrifuge, produce 3–6 mL PRP

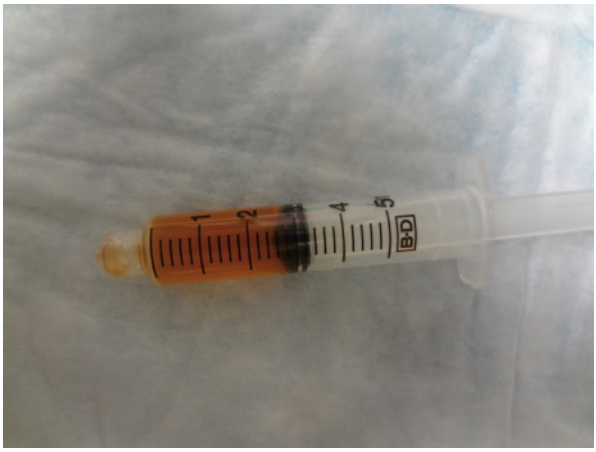

Fig. 8.4 Platelet-rich plasma (*PRP*) can be administered after local anesthetic, or be combined with it

There have been a number of randomized controlled trials evaluating PRP in the treatment of tennis elbow. Peerbooms et al. compared PRP with corticosteroid injection in a double-blind randomized trial of 100 patients [20]. Successful treatment was defined as >25% reduction in VAS score with no reintervention. The authors found that at the early 4-week time point, patients in the corticosteroid group showed slightly more improvement. However, at 26 and 52 weeks, VAS and DASH scores were significantly better for the PRP group ($p<0.001$ and $p=0.005$), with resolution in 73% of the PRP group vs. 49% the corticosteroid group. At 2 years, 81% of PRP patients reported successful outcomes compared to 40% of the corticosteroid group [21].

Krogh et al. compared PRP to corticosteroid and placebo injections with 60 patients in a short-term, randomized, double-blind trial [22]. Similar to the results of Peerbooms et al., improved pain relief was demonstrated at 1 month in the corticosteroid group compared to PRP and placebo. However, at 3 months follow up, there were no significant differences between the three groups using the patient-related tennis elbow evaluation (PRTEE).

Stenhouse et al. performed a randomized trial comparing 2 ml PRP injection with dry needling in 28 patients with refractory tennis elbow, with a mean duration of symptoms of 19 months [23]. The authors found that there was a trend towards greater clinical improvement, as measured by reduction in VAS scores, at 2 and 6 months for the PRP group compared to dry needling, but the differences were not significant. However, the small cohort sizes may have impacted power to determine a difference.

Mishra et al. recently reported the largest randomized controlled study to date, in which 230 patients were blinded and randomized to either needling the extensor origin with either PRP or nothing, after injection of lidocaine in both groups [24]. At 12 weeks with 83% follow up, the groups were not significantly different with regards to improvement in pain scores. However, for the 119 patients who had data available at 24 weeks, those receiving PRP had a 71% improvement in their pain scores compared to 56% for the control group ($p=0.027$). The percentage with remaining significant elbow tenderness was 29% for the PRP group vs. 54% for the control group ($p<0.001$).

The safety of PRP is similar to autologous blood, with minimal concern for immunogenic reactions. A number of patients report some magnitude of postinjection pain that can last up to 3–4 weeks [20]. Thanasas et al. found that patients who received PRP had more postinjection pain as compared to autologous blood injections [25]. Mishra et al. found no difference in the number of adverse events between the PRP and control needling groups, both causing pain in just under 20% of patients [24]. However, 2/116 patients did report severe pain that lasted 2–4 days.

It is important to note that the components of PRP can differ considerably depending on preparation methods. Mazzocca et al. demonstrated significantly different platelet and white-blood cell concentrations among different single-spin and double-spin separation techniques [26]. The literature on PRP in lateral epicondylitis includes different preparation methods that may lead to variable concentrations of platelets and growth factors, and therefore variable results. Additionally, Mazzocca et al. determined that each individual had varying concentrations of platelets and growth factors following different blood draws. These results suggest that differing concentrations of platelets and growth factors may contribute to the variable results seen among patients and in the literature.

PRP injection has demonstrated benefits in a difficult cohort of patients with chronic lateral epicondylitis who have failed other therapies. Research thus far has not supported any superiority for PRP over corticosteroids or placebo in the short-term, however, its superiority to corticosteroids in long-term (>3 months) follow up was demonstrated in two large double-blinded RCT with 2 years follow up [21, 24]. As compared to placebo injections, PRP has shown some long-term superiority in one study [24], but no significant differences in two smaller RCT's [22, 23].

Literature Comparisons of Autologous Blood and PRP Injections

Creaney et al. and Thanasas et al. both compared PRP with autologous blood injections in RCTs of 150 and 28 patients, respectively, who had failed first-line therapy for lateral epicondylitis [11, 25]. Creaney et al. defined success as a 25-point

reduction in the PRTEE [11]. In their trial, all patients were given two injections under ultrasound guidance. They found 66% success for the PRP group and 72% success for the autologous blood group, which was not significantly different. Twice as many patients in the autologous blood group (20% vs. 10%) sought eventual surgery. The study achieved 90% power to detect a difference of 10 points on the PRTEE scale but was limited by lacking a control group.

Thanasas et al. randomized patients to one injection of autologous blood or PRP in their single-blind study. They found their PRP group to have significantly better pain improvement than autologous blood at 6 weeks ($p<0.05$), but that the differences were not significant beyond this time point [25]. There were no significant differences in Liverpool elbow scores at any time points. A higher proportion of patients in the PRP group (64% vs. 29%) reported postinjection pain that gradually decreased. The authors theorized that this may result from the higher white blood cell concentration in PRP.

These studies suggest no definitive long-term difference in outcomes between PRP and autologous blood injections. Creaney et al. hypothesized that the reason for no difference in outcomes between PRP and autologous blood injections may be due to saturation of the beneficial capabilities of the growth-factors [11]. For instance, if the maximum collagen-producing capability has been reached with the platelets and growth factors in autologous blood, the higher concentration of these components in PRP may be unnecessary. Thanasas et al. described better short-term (6-week) pain scores for the PRP group with the caveat of more immediate postinjection pain, however, both injections show similar benefits in the long-term [25]. Therefore, with the current body of evidence, it is difficult to justify the additional expense of preparing PRP compared to autologous blood injections for lateral epicondylitis.

Conclusion

In reviewing the evidence for both of these treatments, the high-quality literature has shown mixed results. Both PRP and autologous blood injections have been compared with corticosteroid injection, which had long been considered the standard injection therapy for lateral epicondylitis. The majority of studies have found that although corticosteroids may provide better temporary relief of symptoms in the first month, both PRP and autologous blood demonstrate improved outcomes from 6 months to 1 year. Therefore, current evidence supports that once injection therapy is considered, autologous preparations should be considered over corticosteroids.

PRP and autologous blood injections have not been shown to have significantly different effects in comparative trials. In RCT's comparing autologous blood injection or PRP to placebo, no significant differences were appreciated in the majority of randomized trials [13, 14, 22, 23]. The largest randomized study of 230 patients demonstrated a benefit for PRP over placebo at 24 weeks, however, it was biased by a 48% loss-to follow up by that time point. Krogh et al. performed a systematic review and meta-analysis of 17 trials with 1381 patients comparing injection therapies in lateral epicondylitis, although only five of these trials looked at autologous blood

Table 8.1 Summary of Level I and II evidence

Study	Subject	Number of participants	Findings	Level of evidence
Wolf et al. [13]	ABI vs. Corticosteroid vs. Saline	28	No significant differences	Level II
Ozturan et al. [14]	ABI vs. Corticosteroid vs. Extracorporeal Shock Wave Therapy	60	Corticosteroids had better outcomes at 4 weeks, but ABI showed improved outcomes at 1 year	Level I
Kazemi et al. [15]	ABI vs. Corticosteroid	60	ABI with better outcomes at 4 and 8 weeks	Level I
Dojode et al. [16]	ABI vs. Corticosteroid	60	ABI provides better outcomes at 3 and 6 months, while results are better for corticosteroids at 1 and 4 weeks	Level I
Peerbooms et al. [20]	PRP vs. Corticosteroid	100	PRP better outcomes at 6 and 12 months, steroids better at 4 weeks	Level I
Gosens et al.* [21]	PRP vs. Corticosteroid	100	PRP better outcomes at 2 years	Level I
Krogh et al. [22]	PRP vs. Corticosteroid vs. Saline	60	Corticosteroids better outcomes at 1 month, no difference at 3 months	Level I
Stenhouse et al. [23]	PRP vs. Dry needling	28	No significant differences at 2 or 6 months	Level II
Mishra et al. [24]	PRP vs. Dry needling	230	No significant differences at 12 weeks, PRP with better outcomes at 24 weeks	Level I
Creaney et al. [11]	ABI vs. PRP	150	No significant differences up to 6 months	Level I
Thanasas et al. [25]	PRP vs. ABI	28	PRP better outcomes at 6 weeks, but no significant differences at 3 or 6 months	Level I

ABI Autologous blood injection, *PRP* Platelet-rich Plasma injection
*[21] was a follow-up study of [20]

or PRP injections [27]. Autologous blood and PRP were both shown to be superior to placebo with effect sizes of 1.43 (2.15–0.71) and 1.13 (1.77–0.49), respectively.

It is possible that the smaller randomized trials have lacked power to determine an advantage for autologous injections, or even that placebo injections that cause microtrauma at the site of injury may have a clinical benefit as opposed to conservative treatment. Nonetheless, at best there is a limited amount of evidence supporting the beneficial effect of these injections over placebo. Future large, randomized trials will be of importance to determine if these injections prove beneficial and cost-effective compared to conservative therapies (Table 8.1).

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