Journal of Orthopaedics 16 (2019) 496–499

Contents lists available at ScienceDirect

Journal of Orthopaedics

journal homepage: www.elsevier.com/locate/jor

Long-term follow-up of platelet-rich plasma injections for refractory lateral epicondylitis

Milos Brkljac*, James Conville, Ulhas Sonar, Shyam Kumar

Department of Orthopaedics, Royal Lancaster Infirmary, Ashton Road, Lancaster, LA1 4RP, United Kingdom

ARTICLE INFO

Keywords:
Tennis elbow
Lateral epicondylitis
Platelet-rich plasma
Lateral tendinosis

ABSTRACT

Background: Lateral epicondylitis (LE)[1] affects between 1 and 3% of the population. Recently, platelet-rich plasma (PRP)[2] has gained popularity.
Aim: Assess the long-term outcomes of PRP for patients with refractory LE.
Methods: We assessed 31 patients who had failed conservative management using the Oxford Elbow Score (OES).[3]
Results: Mean follow-up: 5.2 years (range 4.2–6.1 years). 87.1% exhibited minimum clinically important difference (MCID)[4] in pain scores between pre-op and long-term. 90.3% displayed MCID in function and psychosocial domains. Two patients had a repeat injection and six underwent open release.
Discussion: PRP is successful in treating refractory LE in most patients and avoiding surgery.

1. Introduction

Originally described by Morris as “lawn tennis arm” in 1883, the term “tennis elbow” has now prevailed. It refers to a painful condition affecting the common extensor origin of the forearm and is said to have a prevalence of between 1% and 3%.[1] The majority of patients are in their 4th or 5th decade with an equal distribution across genders. Affecting up to 50% of tennis players the condition is often caused by excessive and repetitive use of the wrist extensors.[2,3] The most commonly affected muscle is the extensor carpi radialis brevis (ECRB). Clinically, there is tenderness over the lateral epicondyle with pain elicited on resisted wrist extension. These symptoms result from an underlying pathological process which was initially thought to be inflammatory.

The term “lateral epicondylitis” (LE) has been used to describe the condition which is now understood to be degenerative.[4] The lack of inflammatory cells found on histology point to a degenerative tendinosis. Repetitive stress causes the tendon to undergo multiple microtears leading to angiofibroblastic hyperplasia. This term describes pathological changes to the collagen microstructure, characterised by altered collagen synthesis caused by granulation tissue.[5] Further pathophysiological mechanisms have been proposed, however, great variability of symptoms and responses to treatment remain between individuals.

The majority of LE can be treated non-operatively, which commonly involves: physiotherapy, non-steroidal anti-inflammatory drugs (NSAIDs) and injections.[6] Steroid injections have been used frequently, resulting in short term improvement, although, their exact mechanism is poorly understood.[7] Associated complications are well known, hence, a reluctance by clinicians to administer an excess of three injections every 12 months. More recently, whole blood and platelet-rich plasma (PRP) injections have risen in popularity.

The beneficial effect of PRP is attributed to its high concentrations of growth factors.[8] These supraphysiological quantities induce a transient inflammatory response to stimulate tendon repair as shown in animal models.[9] Whole blood (WB) is the most common alternative to PRP, although, numerous randomized controlled trials (RCTs) are yet to demonstrate which is superior.[8,10–12] The use of blood products is not well defined; optimal timing, concentration, and number of injections are yet to be determined. Various combinations of conservative management including physiotherapy, steroid injections and NSAIDs can be clinically justified which result in a resolution of symptoms in 90% of cases.[13] For those who fail to improve, operative management is usually considered.

Nirschl and Pettrone described the most commonly performed, open release procedure in 1979.[5] Numerous mini-open and arthroscopic techniques have emerged since, which all involve the release of the

Abbreviations: LE, Lateral Epicondylitis; PRP, Platelet-Rich Plasma; OES, Oxford Elbow Score; MCID, Minimum clinically important difference

* Corresponding author. 12 Julian Court Julian Road Sneyd Park, Bristol, BS9 1LA, United Kingdom.
E-mail address: milos.brkljac@doctors.org.uk (M. Brkljac).

https://doi.org/10.1016/j.jor.2019.08.023
Received 20 July 2019; Accepted 12 August 2019
Available online 14 August 2019

common extensor tendon. Older literature concluded that all techniques including, open percutaneous and endoscopic have comparable outcomes which are successful, with a relatively low complication and failure rates.[14,15] More recently, however, Pierce et Al.[16] concluded "surgery for tennis elbow is no more effective than nonsurgical treatment".

With no current consensus on a treatment algorithm and current evidence insufficient to confirm the positive effect of one modality over another the treatment of refractory LE remains a significant challenge. Here we have collected long-term data on a patient group treated with PRP who had pain refractory to conservative management. This included a minimum of one steroid injection. Most patients were referred for an open surgical procedure. Our main outcome is progression to surgery with functional scores collected pre and post-injection as well as at long-term follow-up.

2. Methods

We prospectively evaluated 34 patients suffering from refractory LE who had received a PRP injection between November 2011 and May 2013. Local institutional approval was obtained for the study.

Patients included in the study were considered to have refractory LE due to a failed trail of conservative management. All patients were reviewed by the senior author or a member of his team in clinic where conservative management comprised: analgesia, physiotherapy and least one steroid injection. These patients were referred for operative treatment of their condition before being offered a PRP injection.

The Arthrex ACP system (Arthrex, Inc. Florida, USA) was used for platelet-rich plasma preparation. This is a closed system using a double syringe method along with 16 ml of autologous blood drawn from the patient's contralateral arm. The blood was centrifuged at 1500 rpm for 5 min and 4–7 mls of platelet-rich plasma was extracted. No anticoagulant was added, 3 ml of PRP was used for injections. A 22-gauge needle was inserted into the common extensor tendon on the lateral epicondyle using a single skin portal. No local anaesthetic was infiltrated. Injections into the affected tendon were made using a pepper pot technique. Following the injection the arm was immobilised for 30 min. The affected limb was then placed in a polysling for 48 h after which the patients were encouraged to carry out eccentric elbow exercises. Patients were prohibited from using NSAIDS for three months.

The Oxford Elbow Score (OES) was employed to evaluate outcomes following PRP.[17] The OES is a 12 item score which includes three domains: elbow pain, elbow function and psychological-social. Each domain has four items. The responses range from 0 to 4 where a 0 represents the least severity. The maximum score obtainable using the OES is 48.

We calculated the minimal clinically important difference (MCID) by converting scores for each domain into a metric score using the below equation:

$$\text{Metric Score} = (100 \div 16 \times \text{domain score})$$

Metric scores taken at different times were subtracted from one another to determine if there was clinically important change. A difference of 18 was deemed significant for pain and psycho-social domains and 10 for the pain domain.[18] Our secondary outcome measure was progression to surgery, namely: open release procedure.

We performed our statistical analyses using the Statistical Package for the Social Sciences (SPSS) version 21. The one-way repeated measures ANOVA test was employed to compare between pre-op, post-op and current OES. A Kaplan-Meier curve was plotted to demonstrate the survival outcomes for elbows treated with PRP, using progression to surgery or repeated injection as end-points.

3. Results

Thirty-four patients were included in the study (18 women and 16 men). The mean age of our cohort was 46 years (range 33–61 years). All patients completed pre and post-operative OES, however, three patients were uncontactable at long-term follow-up and thus excluded from the study. The mean follow-up time was 5.2 years (range 4.2–6.1 years).

All patients complied with the post-procedure protocol. There were no reported complications following PRP injection or open release procedures.

Thirty patients (96.8%) demonstrated an improvement in their overall OES at long-term follow-up compared to their pre-op score. One patient (3.2%) experienced no change in symptoms. Comparing post-op scores with long-term scores demonstrated 77.4% had improved, 12.9% had declined and 9.7% had remained the same.

A total of eight patients had a further procedure following their initial injection, this included: two patients who had a repeat injection and six patients who underwent open release.

3.1. MCID

As shown in Table 2, 87.1% of patients exhibited a clinically important change in pain symptoms between pre-op and long-term scores. 90.3% displayed clinically important change in function and psychosocial domains between these two time periods.

3.2. Statistical analysis

We found statistical significance comparing the means of OES scores taken pre-op, post-op and at long-term follow up using a repeated one-way ANOVA analysis. The findings are displayed in Table 1. A pairwise analysis at each time point was carried out for each domain and the overall OES which revealed statistical significance ($p = < 0.01$).

We plotted a Kaplan-Meier curve to demonstrate the re-intervention rate for 31 elbows, seen in graph 1. The 3.5 year survival free rate was 74.2% (95% CI = 4.1–5.6 years).

3.3. Removal of interventions

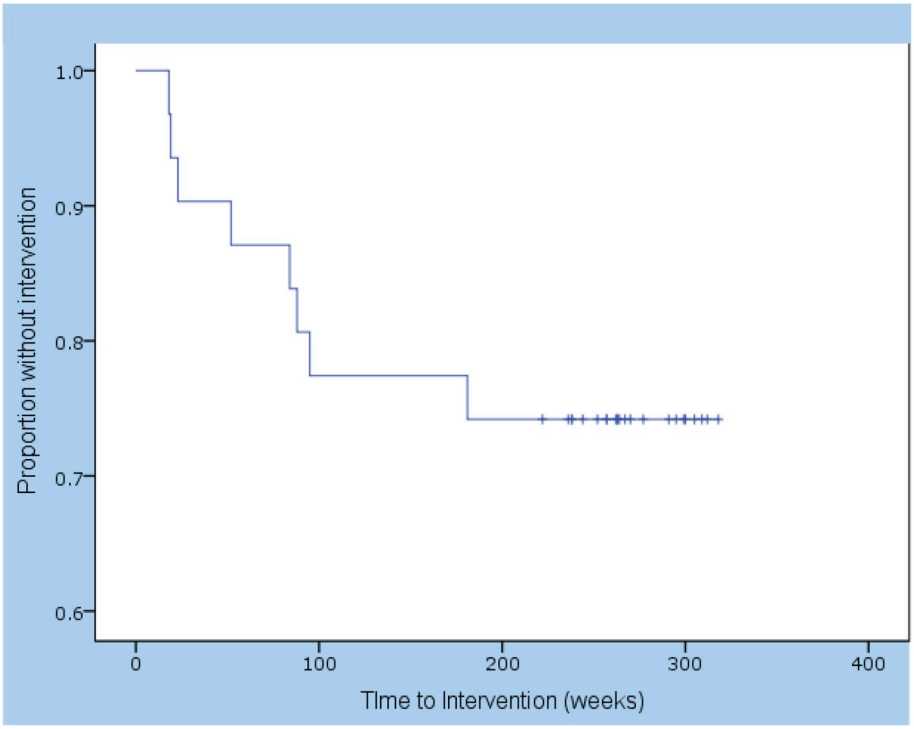
After removing those who underwent further intervention, 95.7% of patients saw a MCID when comparing overall pre-op and long-term OES. None of these patients saw a decrease in OES and only one patient had no change in OES between pre-op and long-term scores.

3.4. Interventions

All patients who underwent further intervention demonstrated an improvement in their overall OES comparing pre-op and post-op scores. All interventions occurred after post-op scoring. Five of these patients saw in improvement in overall OES following intervention, two saw no change and one had a deterioration of symptoms.

Table 1
Oxford Elbow Scores comparison repeated 1-way ANOVA analysis.

	Oxford Elbow Scores			P values
	Pre-Op mean (sd)	Post-Op mean (sd)	Long-term mean (sd)	
Overall	16.4 (6.7)	30.7 (12.4)	41.2 (9.3)	< 0.001
Pain	4.6 (2.8)	9.8 (4.2)	13.2 (3.5)	< 0.001
Elbow Function	7.7 (2.6)	11.9 (3.7)	14.5 (2.7)	< 0.001
Psycho-Social	4.1 (2.7)	8.9 (5.3)	13.6 (4.0)	< 0.001



Graph 1. Kaplan-Meier survival curve demonstrating time to further intervention in weeks following a single injection of PRP. Confidence intervals are not included.

4. Discussion

The treatment of refractory LE remains a significant challenge despite a wide range of available treatments. Corticosteroids have been the treatment of choice for some time. Patients commonly received multiple injections to alleviate their symptoms, however, their effect is usually temporary. The repeated use of corticosteroid injections is well documented to have negative effects on tendons, often leading to atrophy, and increased risk of rupture.[19] More recently, PRP has gained popularity with converse effects to that of corticosteroids, by stimulating proliferation and maturation of the healing process as well as suppressing inflammation.[20] This has been reported at a macroscopic level using ultrasonography.[21]

Patients included in our study were all exposed to a minimum of one corticosteroid injection, many had multiple injections which had ceased to have any beneficial effect. This refractory patient group had exhausted all conservative options.

4.1. Long-term improvement

Table 2 demonstrates that the positive of effects PRP continue many years after the initial injection. The mean difference between short-term and long-term follow up time was 56 months. Over half of patients achieved clinically important benefits in their OES from short to long-term. Such effects are corroborated by a large multicentre study by Mishra et al. which demonstrated the continued positive effect of PRP at 24 months when compared to needling only.[22] A recent systematic review by Ben-Nafa et al.[23] which included one study[24] with similar follow up to ours concluded that PRP has slower onset but longer lasting effect that corticosteroids, and importantly, no recurrence of symptoms.

Table 2
Minimal Clinically Important Difference (MCID) comparing Oxford Elbow Scores pre-operatively, post-operatively and at long-term follow up.

OES Domain	Positive MCID percentage (number)		
	Pre vs Post	*Post vs Long*	*Pre vs Long*
Pain	67.7% (21)	51.6% (16)	87.1% (27)
Function	74.2% (23)	58.1% (18)	90.3% (28)
Psycho-Social	58.1% (18)	58.1% (18)	90.3% (28)

4.2. Preparation

As interest in PRP has grown, more attention has been placed on how PRP in prepared. Initially discussed by Gosens et al.[25] and Moraes et al.[26] the concentration of leukocytes contained following different preparations methods may produce key differences in effect. Broadly speaking PRP can be classified into leukocyte-poor PRP (LP-PRP) or leukocyte-rich PRP (LR-PRP). The ACP Arthrex kit used in our study is considered a LP-PRP preparation. It contains 1.3 to 2.6 times the baseline platelet concentrations with low white cell counts.[27,28] LR-PRP contains between 3 and 8 times the baseline level of platelets along with high amounts of leukocytes due to the effects of concentration.[29,30] The first meta-analysis to compare preparation techniques concluded that there is strong evidence in support of LR-PRP over the LP-PRP, although it did include various tendon locations.[31]

4.3. Avoiding surgery

Most patients in this study had been referred for surgery before being offered PRP, with only six patients undergoing an open release at last follow up we believe that PRP is effective in avoiding surgery. A strength of this study is the length of follow-up time which has revealed the number of patients who eventually progress to surgery. Most studies currently available seek to compare various types injection such as corticosteroid, WB and PRP. A meta-analysis by Arirachakaran et al.[32] found 10 studies with a maximum of 12 month follow-up with no comment on progression to surgery as an outcome measure. Patients who successfully avoid surgery are not exposed to the risks of an open procedure usually performed under general anaesthesia. This has positive implications on health resource allocation and potentially incurs large cost savings.

4.4. Study limitations

Our study reports on a relatively small patient cohort who have failed conservative management, however, no consistent management protocol for this can be specified. This study does not benefit from a comparison arm using placebo or alternative therapy and thus conclusions cannot be made against other methods of treatment. We also acknowledge the variance in time to short-term follow up.

4.5. Controversy

There still remains considerable controversy regarding the true benefits of PRP with a highly critical review by Vos et al.[33] claiming that there is currently "strong evidence that PRP injections are not efficacious in the treatment of chronic lateral epicondylar tendinopathy". Their conclusions are based on a small number of studies which fulfilled the criteria for inclusion. Among these, four papers were deemed high quality with only one showing the positive effects of PRP.[8,12,21,34] Their main critique of study design stems from descriptions of blinding procedures and adequate "intention-to-treat" principle". Gosens et al.[25] dispute these conclusions in their letter to the editor and point to the opposing conclusions by Ahmed et al.[35]

4.6. Future studies

The design of future studies should consider the following to ensure meaningful conclusions can be made between PRP and other treatments: clear blinding and randomisation process, standard PRP preparation procedure, injection technique, post-procedure protocol and the addition of a saline control group. Adequate sample sizes calculated using power calculations along with long-term follow up using validated functional outcome scores.

5. Conclusions

We conclude that a single injection of PRP is successful in treating refractory LE in the majority of patients and preventing the need for surgery. PRP is safe and can improve function with positive effects continuing five years after the initial injection. There are considerable positive implications associated with avoiding surgery both in cost saving and the potential morbidity associated with undergoing an open procedure.

CRediT authorship contribution statement

Milos Brkljac: Methodology, Writing - original draft, Formal analysis, Writing - review & editing. **James Conville:** Writing - review & editing. **Ulhas Sonar:** Writing - review & editing. **Shyam Kumar:** Conceptualization, Methodology, Writing - review & editing.

References

1. Sanders Jr TL, Maradit Kremers H, Bryan AJ, Ransom JE, Smith J, Morrey BF. The epidemiology and health care burden of tennis elbow: a population-based study. *Am J Sports Med.* 2015;43(5):1066–1071.
2. Priest JD, Braden V, Gerberich SG. The elbow and tennis, Part 1: an analysis of players with and without pain. *Physician Sportsmed.* 1980;8(4):80–91.
3. Eygendaal D, Rahussen FT, Diercks RL. Biomechanics of the elbow joint in tennis players and relation to pathology. *Br J Sports Med.* 2007;41(11):820–823.
4. Doran A, Gresham GA, Rushton N, Watson C. Tennis elbow. A clinicopathologic study of 22 cases followed for 2 years. *Acta Orthop Scand.* 1990;61(6):535–538.
5. Nirschl RP, Pettrone FA. Tennis elbow. The surgical treatment of lateral epicondylitis. *J Bone Joint Surg Am Vol.* 1979;61(6A):832–839.
6. Kumar S, Stanley D, Burke NG, Mullett H. Tennis elbow. *Ann R Coll Surg Engl.* 2011;93(6):432–436.
7. Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: a systematic review of randomised controlled trials. *Lancet.* 2010;376(9754):1751–1767.
8. Creaney L, Wallace A, Curtis M, Connell D. Growth factor-based therapies provide additional benefit beyond physical therapy in resistant elbow tendinopathy: a prospective, single-blind, randomised trial of autologous blood injections versus platelet-rich plasma injections. *Br J Sports Med.* 2011;45(12):966–971.
9. Hudgens JL, Sugg KB, Grekin JA, Gumucio JP, Bedi A, Mendias CL. Platelet-rich plasma activates proinflammatory signaling pathways and induces oxidative stress in tendon fibroblasts. *Am J Sports Med.* 2016;44(8):1931–1940.
10. Raeissadat SA, Rayegani SM, Hassanabadi H, Rahimi R, Sedighipour L, Rostami K. Is Platelet-rich plasma superior to whole blood in the management of chronic tennis elbow: one year randomized clinical trial. *BMC Sport Sci Med Rehab.* 2014;6:12.
11. Raeissadat SA, Sedighipour L, Rayegani SM, Bahrami MH, Bayat M, Rahimi R. *Effect of Platelet-Rich Plasma (PRP) versus Autologous Whole Blood on Pain and Function Improvement in Tennis Elbow: A Randomized Clinical Trial. Pain Research and Treatment.* vol. 2014. 2014; 2014:191525.
12. Thanasas C, Papadimitriou G, Charalambidis C, Paraskevopoulos I, Papanikolaou A. Platelet-rich plasma versus autologous whole blood for the treatment of chronic lateral elbow epicondylitis: a randomized controlled clinical trial. *Am J Sports Med.* 2011;39(10):2130–2134.
13. Othman AM. Arthroscopic versus percutaneous release of common extensor origin for treatment of chronic tennis elbow. *Arch Orthop Trauma Surg.* 2011;131(3):383–388.
14. Lo MY, Safran MR. Surgical treatment of lateral epicondylitis: a systematic review. *Clin Orthop Relat Res.* 2007;463:98–106.
15. Karkhanis S, Frost A, Maffulli N. Operative management of tennis elbow: a quantitative review. *Br Med Bull.* 2008;88(1):171–188.
16. Pierce TP, Issa K, Gilbert BT, et al. A systematic review of tennis elbow surgery: open versus arthroscopic versus percutaneous release of the common extensor origin. *Arthroscopy : J Arthrosc Relat Surg Off Publ Arthrosc Assoc North Am Int Arthrosc Assoc.* 2017;33(6):1260–1268 e2.
17. Dawson J, Doll H, Boller I, et al. The development and validation of a patient-reported questionnaire to assess outcomes of elbow surgery. *J Bone Joint Surg Br Vol.* 2008;90(4):466–473.
18. Dawson J, Doll H, Boller I, et al. Comparative responsiveness and minimal change for the Oxford Elbow Score following surgery. *Qual Life Res : An Int J Qual Life Asp Treat Care Rehabil.* 2008;17(10):1257–1267.
19. Brinks A, Koes BW, Volkers AC, Verhaar JA, Bierma-Zeinstra SM. Adverse effects of extra-articular corticosteroid injections: a systematic review. *BMC Muscoskelet Disord.* 2010;11:206.
20. Lucarelli E, Beccheroni A, Donati D, et al. Platelet-derived growth factors enhance proliferation of human stromal stem cells. *Biomaterials.* 2003;24(18):3095–3100.
21. 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. *Am J Sports Med.* 2013;41(3):625–635.
22. Mishra AK, Skrepnik NV, Edwards SG, et al. Efficacy of platelet-rich plasma for chronic tennis elbow: a double-blind, prospective, multicenter, randomized controlled trial of 230 patients. *Am J Sports Med.* 2014;42(2):463–471.
23. Ben-Nafa W, Munro W. The effect of corticosteroid versus platelet-rich plasma injection therapies for the management of lateral epicondylitis: a systematic review. *Sicot-J.* 2018;4:11.
24. Gosens T, Peerbooms JC, van Laar W, den Oudsten 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.
25. Gosens T, Mishra AK. Editorial in response to the systematic review by de Vos et al: 'Strong evidence against platelet-rich plasma injections for chronic lateral epicondylar tendinopathy: a systematic review. *Br J Sports Med.* 2014;48(12):945–946.
26. Moraes VY, Lenza M, Tamaoki MJ, Faloppa F, Belloti JC. Platelet-rich therapies for musculoskeletal soft tissue injuries. *Cochrane Database Syst Rev.* 2014(4):CD010071.
27. Baksh N, Hannon CP, Murawski CD, Smyth NA, Kennedy JG. Platelet-rich plasma in tendon models: a systematic review of basic science literature. *Arthroscopy : J Arthrosc Relat Surg Off Publ Arthrosc Assoc North Am Int Arthrosc Assoc.* 2013;29(3):596–607.
28. Mazzocca AD, McCarthy MB, Chowaniec DM, et al. Platelet-rich plasma differs according to preparation method and human variability. *J Bone Joint Surg Am Vol.* 2012;94(4):308–316.
29. DeLong JM, Russell RP, Mazzocca AD. Platelet-rich plasma: the PAW classification system. *Arthroscopy : J Arthrosc Relat Surg Off Publ Arthrosc Assoc North Am Int Arthrosc Assoc.* 2012;28(7):998–1009.
30. U Carmona J, López C, Sandoval J A. Review of the currently available systems to obtain platelet related products to treat equine musculoskeletal injuries. *Recent Pat Regen Med.* 2013;3(2):148–159.
31. Fitzpatrick J, Bulsara M, Zheng MH. The effectiveness of platelet-rich plasma in the treatment of tendinopathy: a meta-analysis of randomized controlled clinical trials. *Am J Sports Med.* 2017;45(1):226–233.
32. Arirachakaran A, Sukthuayat A, Sisayanarane T, Laoratanavoraphong S, Kanchanatawan W, Kongtharvonskul J. Platelet-rich plasma versus autologous blood versus steroid injection in lateral epicondylitis: systematic review and network meta-analysis. *J Orthop Traumatol : Off J Ital Soc Orthop Traumatol.* 2016;17(2):101–112.
33. de Vos RJ, Windt J, Weir A. Strong evidence against platelet-rich plasma injections for chronic lateral epicondylar tendinopathy: a systematic review. *Br J Sports Med.* 2014;48(12):952–956.
34. Peerbooms JC, Sluimer J, Bruijn DJ, 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.
35. Ahmad Z, Brooks R, Kang SN, et al. The effect of platelet-rich plasma on clinical outcomes in lateral epicondylitis. *Arthroscopy : J Arthrosc Relat Surg Off Publ Arthrosc Assoc North Am Int Arthrosc Assoc.* 2013;29(11):1851–1862.