PM R 8 (2016) 780-791
www.pmrjournal.org

Analytical Review: Meta-Analysis

Efficacy and Safety of Autologous Blood Products Compared With Corticosteroid Injections in the Treatment of Lateral Epicondylitis: A Meta-Analysis of Randomized Controlled Trials

Xuankun Qian, MD, Qiao Lin, MD, Kongkong Wei, MD, Bin Hu, MD, Pengju Jing, MD, Jianmin Wang, PhD

Abstract

Objective: To compare the efficacy and safety of autologous blood products (ABPs) and corticosteroid injections (CSIs) in the treatment of lateral epicondylitis.

Type of Study: Meta-analysis.

Literature Survey: We systematically searched EMBASE, PubMed, the Cochrane Library, and Web of Science to identify randomized controlled trials (RCTs) that compared ABPs with CSIs for the treatment of lateral epicondylitis without language and publication date restriction through April 2015.

Methodology: Two investigators independently included and assessed the quality of each eligible study according to the method recommended by the Cochrane Collaboration. Available data about the main outcomes were extracted from each study and heterogeneity was assessed using the Q statistic and the inconsistency index (I^2). We also evaluated the publication bias and conducted a subgroup analysis. Review Manager 5.2 software was used for data syntheses and analyses, and the standardized mean difference (SMD) or mean difference (MD) was estimated by using random effects models with a 95% confidence interval (CI). To investigate the efficacy among different trial durations, the follow-up times were divided into short periods (2-4 weeks), intermediate periods (6-24 weeks) and long-term periods ($\geq$24 weeks).

Synthesis: Ten RCTs (n = 509) were included in this meta-analysis. The pooled analysis showed that CSIs were more effective than ABPs for pain relief in the short term (SMD = 0.88; 95% CI = 0.31-1.46%; $P = .003$). However, in the intermediate term, ABPs exhibited a better therapeutic effect for pain relief (SMD = −0.38; 95% CI = −0.70 to −0.07%; $P = .02$), function (SMD = −0.60; 95% CI = −1.13 to −0.08%; $P = .03$), disabilities of the arm, shoulder, and hand (MD = −11.04; 95% CI = −21.72 to −0.36%; $P = .04$), and Nirschl stage (MD = −0.81; 95% CI = −1.11 to −0.51%; $P < .0001$). In the long term, ABPs were superior to CSIs for pain relief (SMD = −0.94; 95% CI = −1.32 to −0.57%; $P < .0001$) and Nirschl stage (MD = −1.04; 95% CI = −1.66 to −0.42%; $P = .001$). Moreover, for grip strength recovery, no significant difference was found between the 2 therapies ($P > .05$).

Conclusions: Limited evidence supports the conclusion that CSIs are superior to ABPs for pain relief in the short term; however, this result was reversed in the intermediate and long term. ABPs seemed to be more effective at restoring function in the intermediate term. Because of the small sample size and the limited number of high-quality RCTs, more high-quality RCTs with large sample sizes are required to validate this result.

Introduction

Lateral epicondylitis (LE), also known as tennis elbow, is one of the most common tendon disorders of the arm in adults aged 30 to 64 years. In tennis players and workers with overuse-related injuries, the peak is between ages 45 and 54 years. An epidemiologic study conducted in 2006 showed that the prevalence of LE is 1.3% in general, without a gender difference [1]. Indications were also found that repetitive movements, forceful activities, physical load factors, and even smoking were associated with LE [1,2]. The major clinical symptoms of LE are pain and loss of function at the elbow, which often results in reduced activity and absence from work. With increasing knowledge about tendinopathy, the concept of LE has changed. However, the physiopathology of LE remains elusive. Degenerative changes of the common extensor origin characterized

1934-1482/$ - see front matter
http://dx.doi.org/10.1016/j.pmrj.2016.02.008

2. Smithard DG, O'Neill PA, Park C, et al. Can bedside assessment reliably exclude aspiration following acute stroke? Age Ageing 1998;27:99-106.
3. Teasell RW, Bach D, McRae M. Prevalence and recovery of aspiration post stroke: A retrospective analysis. Dysphagia 1994; 9:35-39.
4. Veis SL, Logemann JA. Swallowing disorders in persons with cerebrovascular accident. Arch Phys Med Rehabil 1985;66:372-375.
5. Burkhead LM, Sapienza CM, Rosenbek JC. Strength-training exercise in dysphagia rehabilitation: Principles, procedures, and directions for future research. Dysphagia 2007;22:251-265.
6. Logemann JA. Management of the patient with oropharyngeal swallowing disorders. In: Logemann JA, ed. Evaluation and treatment of swallowing disorders. 2nd ed. Austin, TX: pro-ed; 1998, 191-250.
7. Ding R, Larson RC, Logemann JA, Rademaker AW. Surface electromyographic and electroglottographic studies in normal subjects under two swallow conditions: Normal and during the Mendelsohn manuever. Dysphagia 2002;17:1-12.
8. Huckabee ML, Cannito MP. Outcomes of swallowing rehabilitation in chronic brainstem dysphagia: A retrospective evaluation. Dysphagia 1999;14:93-109.
9. McKee MG. Biofeedback: An overview in the context of heart—brain medicine. Cleve Clin J Med 2008;75:S31-S34.
10. Bogaardt HCA, Grolman W, Fokkens WJ. The use of biofeedback in the treatment of chronic dysphagia in stroke patients. Folia Phoniatr Logop 2009;61:200-205.
11. Bryant M. Biofeedback in the treatment of a selected dysphagic patient. Dysphagia 1991;6:140-144.
12. Crary MA. A direct intervention program for chronic neurogenic dysphagia secondary to brainstem stroke. Dysphagia 1995;10:6-18.
13. Crary MA, Carnaby GD, Groher ME, Helseth E. Functional benefits of dysphagia therapy using adjunctive sEMG biofeedback. Dysphagia 2004;19:160-164.
14. Reddy NP, Simcox DL, Gupta V, et al. Biofeedback therapy using accelerometry for treating dysphagic patients with poor laryngeal elevation: Case studies. J Rehabil Res Dev 2000;37:361-372.
15. Romano D. Virtual reality therapy. Dev Med Child Neurol 2005;47: 580.
16. Saposnik G, Teasell R, Mamdani M, et al. Effectiveness of virtual reality using Wii gaming technology in stroke rehabilitation. Stroke 2010;41:1477-1484.
17. Laver K, George S, Thomas S, Deutsch JE, Crotty M. Virtual reality for stroke rehabilitation: An abridged version of a Cochrane review. Eur J Phys Rehabil Med 2015;51:497-506.
18. Hsiao MY, Chang YC, Chen WS, Chang HY, Wang TG. Application of ultrasonography in assessing oropharyngeal dysphagia in stroke patients. Ultrasound Med Biol 2012;38:1522-1528.
19. Crary MA, Carnaby GD, Groher ME. Initial psychometric assessment of a functional oral intake scale for dysphagia in stroke patients. Arch Phys Med Rehabil 2005;86:1516-1520.
20. Hind JA, Nicosia MA, Roecker EB, Carnes ML, Robbins J. Comparison of effortful and noneffortful swallows in healthy middle aged and older adults. Arch Phys Med Rehabil 2001;82:1661-1665.
21. Bodén K, Hallgren Å, Hedström H. Effects of three different swallow maneuvers analyzed by videomanometry. Acta Radiol 2006;47:628-633.
22. McCullough GH, Kim Y. Effects of the Mendelsohn maneuver on extent of hyoid movement and UES opening post-stroke. Dysphagia 2013;28:511-519.
23. Kahrilas PJ, Logemann JA, Krugler C, Flanagan E. Volitional augmentation of upper esophageal sphincter opening during swallowing. Am J Physiol 1991;260:450-456.
24. Daniels SK, Huckabee ML. Rehabilitation of oropharyngeal dysphagia. In: Daniels SK, Huckabee ML, eds. Dysphagia following stroke. San Diego, CA: Plural; 2014, 301-342.
25. Wolf SL. Biofeedback. In: Downey JA, Myers SJ, Gonzalez EG, Liberman JS, eds. The physiological basis of rehabilitation medicine. 2nd ed. Stoneham, MA: Butterworth-Heinemann; 1994, 563-572.
26. McKee MG. Contributions of psychophysiologic monitoring to diagnosis and treatment of chronic head pain: A case study. Headache Q 1991;11:327-330.
27. Bach-y-Rita P, Wood S, Leder R, et al. Computer-assisted motivating rehabilitation (CAMR) for institutional, home, and educational late stroke programs. Top Stroke Rehabil 2002;8:1-10.
28. Manor Y, Mootanah R, Freud D, Nir G, Cohen JT. Video-assisted swallowing therapy for patients with Parkinson's disease. Parkinsonism Relat Disord 2013;19:207-211.
29. Macrae P, Anderson C, Taylor-Kamara1 I, Humbert I. The effects of feedback on volitional manipulation of airway protection during swallowing. J Mot Behav 2014;46:133-139.
30. Burdea GC. Virtual rehabilitation—benefits and challenges. Methods Inf Med 2003;42:519-523.

Disclosure

C.-M.L. Department of Biomedical Engineering, National Cheng Kung University, Tainan City, Taiwan, Republic of China
Disclosure: nothing to disclose

T.-G.W. Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital, Taipei City, Taiwan, Republic of China
Disclosure: nothing to disclose

H.-Y.L. Department of Digital Media Design and Management, Far East University, Xinshi District, Tainan City, Taiwan, Republic of China
Disclosure: nothing to disclose

H.-P.W. Department of Speech and Hearing Disorder and Sciences, National Taipei University of Nursing and Health Sciences, Taipei City, Taiwan, Republic of China
Disclosure: nothing to disclose

S.-H.H. Department of Biomedical Engineering, National Cheng Kung University, Tainan City, Taiwan, Republic of China
Disclosure: nothing to disclose

M.C. Department of Electrical and Computer Engineering, University of Texas at Austin, Austin, TX
Disclosure: nothing to disclose

J.-J.J.C. Department of Biomedical Engineering, National Cheng Kung University, No.1, University Road, Tainan City 70101, Taiwan, Republic of China. Address correspondence to: J.-J.J.C.; e-mail: chenjj@mail.ncku.edu.tw
Disclosure: nothing to disclose

Supported by grant no. 10146 from Central & Southern Medical Alliance, Taiwan Ministry of Health and Welfare.

Submitted for publication August 23, 2015; accepted January 6, 2016.

by hypercellularity, angiofibroblastic hyperplasia, and neovascularization, rather than an inflammation, might be the pathophysiologic events in the tendon lesions. As a result of repetitive stress and overuse of the elbow and wrist, those changes could cause microtrauma and partial and even full-thickness tendon tearing as a result of an immature reparative response [3,4]. Zeisig et al [5] also indicated that pain was related to vasculoneural ingrowth found in the extensor origin.

Numerous treatments of LE such as local injections, exercise, bracing, physiotherapy, and surgery have been reported, but none of them is universally effective. Corticosteroid injections (CSIs) are extensively used in the treatment of tendinopathy because of their relative low cost and easy application. Several randomized controlled trials (RCTs) and systematic reviews on tendonitis have shown that CSIs are effective in the short term at reducing pain and improving function [6-9]. However, these effects are lost in the intermediate and long term. In recent years, emerging biologic therapeutics termed *autologous blood products* (ABPs), which include autologous blood (AB) and platelet-rich plasma (PRP), have been used for the management of orthopedic diseases such as tendinopathy, ligament, cartilage, or other soft tissue injuries [10]. PRP is separated and concentrated from AB, and both PRP and AB contain growth factors or other cellular and humoral mediators that might be beneficial for the healing of soft injuries [11]. The long-lasting effects of ABPs on pain relief and functional restoration for LE have been observed in many clinical studies. Moreover, they are safe, readily available, and have a low risk of adverse effects [12-14].

Recently, several clinical trials have been conducted to compare the efficacy between ABPs and CSIs in LE management. However, a consensus has yet to be reached. Two prior meta-analyses were performed, including a clinical trial [15] that indicated weak evidence supporting the use of ABPs [9,16]. Another systematic review comparing AB or PRP with CSIs or a placebo concluded that the ABPs were superior to the control group. However, the studies included were of somewhat low quality. Furthermore, prior reviews have focused on qualitative analysis of the existing studies, thus leaving a gap in the knowledge when attempting to translate such information into clinical use [17,18]. Therefore, this meta-analysis was conducted to quantitatively assess the available data and further elucidate a difference in the efficacy of ABPs compared with CSIs over the short term (2-4 weeks), intermediate term (6-24 weeks) and long term (≥24 weeks) in hopes of providing useful evidence for clinicians.

Methods

We performed this meta-analysis and reported it in accordance with the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements [19].

Literature Search Strategy

Related literature was systematically searched in PubMed, EMBASE, the Cochrane Library, and Web of Science up to May 2015 without publication date and language limitations. The following key words were used: lateral elbow pain, tennis elbow, lateral epicondylitis, autologous blood, autologous platelet, platelet-rich plasma, steroid, corticosteroid, and glucocorticoids. Both clinical controlled trials and RCTs comparing the efficacy between ABPs and corticosteroids were included. Two researchers independently screened the title and abstract of all identified studies in our initial search. Articles unrelated to the major outcome were excluded. "Related" articles with the full text available were further selected according to the inclusion and exclusion criteria. The reference lists of included studies were manually searched. Disagreements were discussed with a third researcher until a consensus was reached.

The flow chart of the literature selection is shown in Figure 1. Altogether, 231 relevant articles were initially identified. Among them, there were 95 duplicate publications, and 120 studies were further excluded after screening the title and abstract. Finally, 10 studies were included in this meta-analysis from the remaining 16 studies after carefully reading the full text. One of the 6 excluded studies proved to be a cost-effective analysis without any main outcome [20]. Four articles were abstracts of related studies [21-24]. Two articles [15,25] included the same clinical trial results over different time frames. As a result, the study by Gosens et al [15] was included in our analysis. The 10 included studies were judged to be RCTs that compared ABPs with CSIs for LE management.

Inclusion and Exclusion Criteria

Studies that met the following criteria were included in the present meta-analysis:

1. The study compared ABPs (either AB or PRP) or a similar product containing platelets with a control (such as a glucocorticoid, corticosteroid, or steroid) in adults (≥18 years) with LE.
2. The study was an RCT or prospective cohort study only.
3. The major outcome involved the efficacy of pain relief or functional restoration.

Exclusion criteria were as follows:

1. No outcomes of interest were reported.

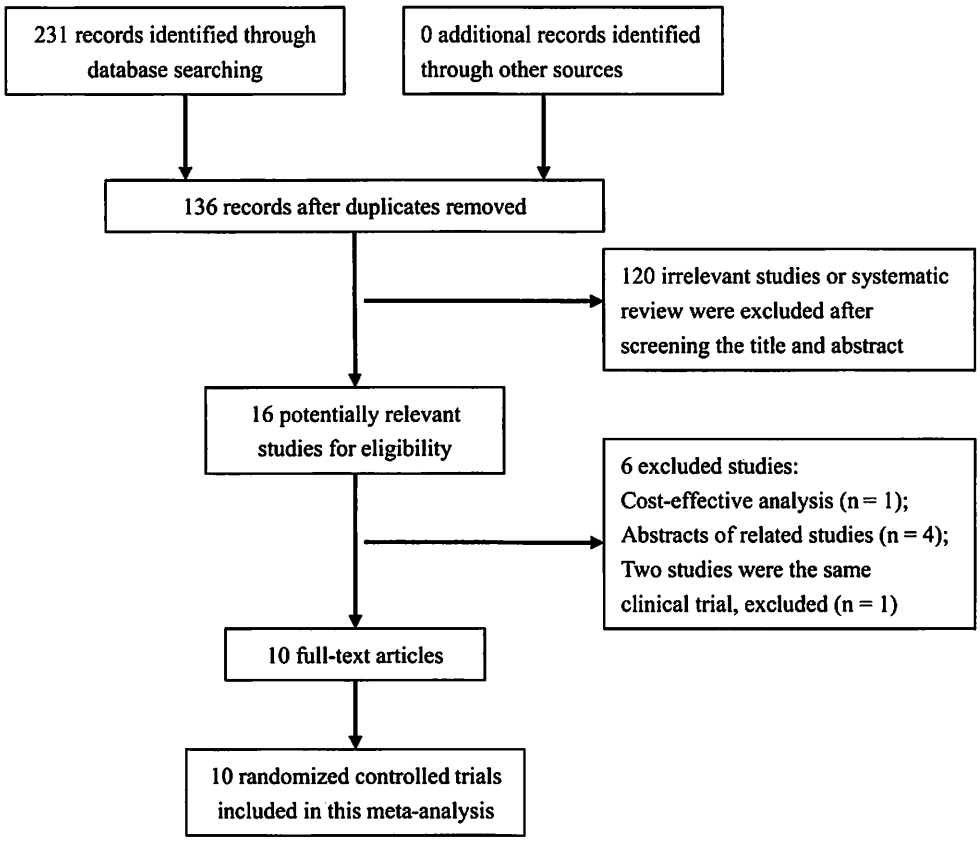

Figure 1. Flow diagram of the selection process of the included studies.

2. Articles were from the same institution or included the same data set.
3. Subjects had full-thickness tearing, traumatic disease, cervical radiculopathy, or systemic disorders such as rheumatoid arthritis.

The details of each study included in the meta-analysis are summarized in Table 1. The included studies were published between 2010 and 2015. A total of 509 subjects were included in this meta-analysis; 256 (50.3%) were treated with AB or PRP, and 253 (49.7%) were treated with CSIs. The mean number of subjects was 53, with a range of 19-100, and 282 (55.4%) were female. The mean follow-up time was 23 weeks (range, 6-52 weeks). The baseline characteristics of the experimental group and control group in each study were comparable.

Data Extraction

Two authors independently collected all related information from the included articles regarding study design, demographic characteristics (ie, the number of subjects in the intention-to-treat [ITT] population, age, and gender), interventions, control, primary outcomes (including pain scores, function scores, Disabilities of the Arm, Shoulder and Hand [DASH] scores, Nirschl stage, and grip strength), methodologic quality, and duration of follow-up. Pain score outcomes were extracted from the studies, including the visual analogue scale (VAS) and the Patient-rated Forearm Evaluation Questionnaire (PREFQ)—pain or other pain scores. Functional score outcomes were collected from the studies, including disabilities of the arm, limb function, and PREFQ—function. Further information including the main characteristics of the intervention or control protocols was also extracted. We contacted the trial authors by e-mail if the required information was obscure or missing. Moreover, the numbers of all reported adverse events were recorded to assess the safety of the 2 therapies.

As described in Table 1, most injections were performed at tender point(s) over the humeral lateral epicondyle or deep to the extensor carpi radialis brevis tendon (ECRB). In 6 trials [26-28,30,32,33], subjects were treated with AB, and in 4 trials [15,29,31,34], subjects were treated with PRP in the experimental group. Therapies in the control group varied among the different studies; in 5 studies, control subjects were treated with methylprednisolone [26,27,32-34], in 2 studies they were treated with Kenacort (triamcinolone) [15,31], and in 3 studies they were treated with an undefined corticosteroid [28-30]. A combination with local anesthetics, such as lidocaine or prilocaine, was

Table 1
Characteristics and interventions of the studies included in the meta-analysis

Authors, Year, Reference No.	Study Design	Subjects (No.)		Interventions		Age, Mean ± SD or Mean (Range)		Ratio of Gender		Follow-up, wk	Outcomes Measure
		ABP	CSI	ABP	CSI	ABP	CSI	ABP	CSI		
Kazemi et al, 2010 [26]	Single-blinded RCT	30	30	2 mL of autologous blood + 1 mL of 2% lidocaine	20 mg methylprednisolone mixed with 1 mL of 2% lidocaine	47.2 ± 10.6	47.0 ± 10.3	7:23	4:26	8	Pain score, limb function, grip strength, DASH, Nirschl stage
Ozturan et al, 2010 [27]	RCT	20	20	2 mL of autologous blood + 1 mL of prilocaine	1 mL of methylprednisolone + 1 mL of prilocaine	44 ± 8.5	45.8 ± 8.1	9:11	10:10	52	VAS, upper function score, grip strength
Peerbooms et al, 2010 [15]	Double-blinded RCT	51	49	3 mL of PRP collected from 27 mL of whole blood + bupivacaine hydrochloride 0.5% with epinephrine (1:200000)	40 mg/mL Kenacort (triamcinolone acetonide) with bupivacaine hydrochloride 0.5% with epinephrine (1:200000)	46.9 ± 8.4	47.3 ± 7.6	23:26	25:26	52	VAS, DASH
Wolf et al, 2011 [28]	Double-blinded RCT	10	9	2 mL of autologous blood + 1 mL of lidocaine	2 mL of corticosteroid + 1 mL of lidocaine	49 (34-64)	49 (34-64)	4:3	4:3	24	VAS, DASH, PRFE pain score, PRFE function score
Omar et al, 2012 [29]	RCT	15	15	Concentrated platelet	Corticosteroid	40.5 ± 15.5	37.5 ± 17.5	6:9	5:10	6	VAS, DASH
Dojode et al, 2012 [30]	RCT	30	30	2 mL of autologous blood + 1 mL of 0.5% bupivacaine	2 mL of local corticosteroid + 1 mL of 0.5% bupivacaine	42.9 (22-67)	42.2 (17-62)	13:17	12:18	24	Pain score, Nirschl stage
Krogh et al, 2013 [31]	Double-blinded RCT	20	20	3-3.5 mL of PRP collected from 27 mL of whole blood	1 mL of triamcinolone 40 mg/mL + 12 mL of lidocaine 10 mg/mL	47.6 ± 7.1	43.9 ± 8.7	9:11	11:9	12	Pain score, PRTEE score
Jindal et al, 2013 [32]	Single-blinded RCT	25	25	2 mL of venous blood + 1 mL of 2% lignocaine solution	40 mg of methyl prednisolone acetate + 1 mL of 2% lignocaine solution	39.04 ± 6.67	37.32 ± 7.52	14:11	17:8	6	VAS, Nirschl stage
Arik et al, 2014 [33]	RCT	40	40	2 mL of autologous venous blood +1 mL of 2% prilocaine hydrochloride	1 mL of 40 mg methylprednisolone acetate + 1 mL of 2% prilocaine hydrochloride	43.7 ± 7.8	46.7 ± 8.4	11:29	10:30	24	VAS, PRTEE score
Gautam et al, 2015 [34]	RCT	15	15	2 mL of PRP collected from 20 mL of whole blood	2 mL of methylprednisolone (40 mg/mL)	18-60	18-60	NA	NA	24	VAS, DASH score

ABP = autologous blood product; CSI = corticosteroid injection; SD = standard deviation; RCT = randomized controlled trial; DASH = disabilities of the arm, shoulder and hand; VAS = visual analogue scale; PRP = platelet-rich plasma; PRFE = patient-rated forearm evaluation; PRTEE = patient-rated tennis elbow evaluation; NA = not available.

applied in 8 trials, whereas the remaining 2 studies [29,34] made no mention of such a combination. Epinephrine was also co-injected in one trial [15]. Three trials [15,29,31] described the detailed process of PRP production. The studies by Wolf et al [28] also contained a control group. Only Peerbooms et al [15] reported that no activating agent was used to activate the platelets. An ultrasonography-guided injection was used in the study conducted by Krogh et al [31]. Most studies reported the use of anticoagulants during the production of ABPs.

Assessment of the Risk of Bias

The risk of bias of each included study was assessed according to the *Cochrane Handbook for Systematic Reviews of Interventions* guideline [35]. Two researchers assessed each of the following domains independently: allocation sequence generation; allocation concealment; blinding of subjects, treating doctors, and outcome assessors; appropriate use of the ITT population; selective outcome reporting; and other bias. Each of these key terms of risk of bias was marked as high risk of bias (HRB), unclear, or low risk of bias (LRB). A study was considered to be of LRB only when concealed allocation, blinded participants, outcome assessors, incomplete outcome data, and selective reporting were judged as LRB [35].

Table 2 shows the summary of methodologic quality for each RCT. Sequence generation and allocation concealment were judged as LRB in 5 trials [14,15,26,28,30] and 3 trials [15,28,31], respectively. Other studies mentioned that the clinical trial was randomized but did not report further details. Blinding of subjects, treating doctors, and outcome assessors were judged as LRB in 3 trials [15,28,31], 2 trials [28,33], and 5 trials [15,26,28,31,32], respectively. ITT analysis was found as LRB in 6 trials [14,15,26,30,32,33]. Four trials [15,26,29,31] provided detailed registration information without selective reporting of preestablished outcomes. We could not find other obvious bias in all RCTs. Overall, 2 studies had LRB [15,31], and the remaining 8 studies had unclear or high risk of bias.

Data Synthesis

Data Analysis

Review Manager (RevMan) statistical software (version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to calculate the effect sizes of the included studies. To investigate the effect of the trial follow-up duration on LE, a stratified analysis was performed by dividing the follow-up times into short term (range, 2-4 weeks), intermediate term (range, 6-24 weeks), and long term ($\geq$24 weeks). Changes from baseline were pooled to compare clinical outcomes between groups. All continuous data were presented as the mean and standard deviation (SD). Relative risk was calculated for dichotomous data, and mean difference (MD) was calculated for continuous data. Standardized mean difference (SMD) was used if different trials reported an outcome using different scales. Corresponding 95% confidence intervals (CIs) were also calculated. Clinical heterogeneity was assessed before we calculated the results. *Q* tests were therefore performed [36], with an I^2 value <25% considered low heterogeneity and an I^2 value >75% considered high heterogeneity [37]. Pooled analyses were performed with the application of a random-effects model in case of significant statistical heterogeneity. A subgroup analysis was carried out to compare the efficacy of AB and PRP with CSIs. A *P* value <.05 was considered statistically significant. Included studies were weighted according to their precision; the usual statistical method is to calculate study weights by the amount of information they contribute (more specifically, by the inverse variances of their effect estimates). This technique gives studies with more precise results (ie, narrower confidence intervals) more weight; it is a recognized and preferred method recommended by the Cochrane group for meta-analysis [35]. The

Table 2
Assessment of the methodologic quality of the studies included in the meta-analysis

Authors, Year, Reference No.	Sequence Generation	Allocation Concealment	Patient Blinding	Treating Doctor Blinding	Outcomes Assessor Blinding	Incomplete Outcome Data	Selective Reporting	Other Bias
Kazemi et al, 2010 [26]	LRB	HRB	HRB	HRB	LRB	LRB	LRB	LRB
Ozturan et al, 2010 [27]	Unclear	Unclear	HRB	HRB	HRB	HRB	Unclear	LRB
Peerbooms et al, 2010 [15]	LRB	LRB	LRB	HRB	LRB	LRB	LRB	LRB
Wolf et al, 2011 [28]	LRB	LRB	LRB	LRB	LRB	HRB	Unclear	LRB
Omar et al, 2012 [29]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	LRB	LRB
Dojode et al, 2012 [30]	LRB	Unclear	HRB	Unclear	Unclear	LRB	Unclear	LRB
Krogh et al, 2013 [31]	LRB	LRB	LRB	HRB	LRB	LRB	LRB	LRB
Jindal et al, 2013 [32]	Unclear	HRB	HRB	HRB	LRB	LRB	Unclear	LRB
Arik et al, 2014 [33]	Unclear	HRB	HRB	LRB	HRB	LRB	Unclear	LRB
Gautam et al, 2015 [34]	Unclear	HRB	HRB	HRB	HRB	Unclear	Unclear	LRB

LRB = low risk of bias; HRB = high risk of bias.

possibility of publication bias was explored by creating funnel plots if ≥10 studies were available in each pooled analysis [38], or it was evaluated by searching the clinical trial registries.

Results

Pain Intensity

All pooled analyses were conducted with a random-effects model because of significant statistical heterogeneity. Altogether, 10 trials (n = 509) provided the available data to compare the efficacy on pain intensity. As shown in Figure 2, CSIs were more effective than ABPs in providing pain relief in the short term (SMD = 0.88 [0.31-1.46]; $P = .003$; $I^2 = 88\%$). However, ABPs exhibited a better efficacy than did CSIs in the intermediate (SMD = −0.38, [−0.70 to −0.07]; $P = .02$; $I^2 = 66\%$) and long term (SMD = −0.94, [−1.32 to −0.57]; $P < .0001$; $I^2 = 57\%$).

Functional Restoration

Six trials (n = 269) reported functional scores as the major outcome. The results showed that there were no significant differences in functional scores between the 2 groups in the short term (SMD = 0.51 [−0.06 to 1.08]; $P = .08$; $I^2 = 80\%$) and long term (SMD = −0.65 [−2.10 to 0.81]; $P = .38$; $I^2 = 89\%$); however, significant differences in the intermediate term (SMD = −0.60 [−1.13 to −0.08]; $P = .03$; $I^2 = 76\%$) were observed (Table 3).

DASH Scores

Five trials (n = 239) reported DASH scores. A statistically significant result in favor of ABPs was found in the intermediate term (MD = −11.04 [−21.72 to −0.36]; $P = .04$; $I^2 = 89\%$). However, the difference could not be observed in the short term (MD = 2.04 [−8.18 to 12.26];

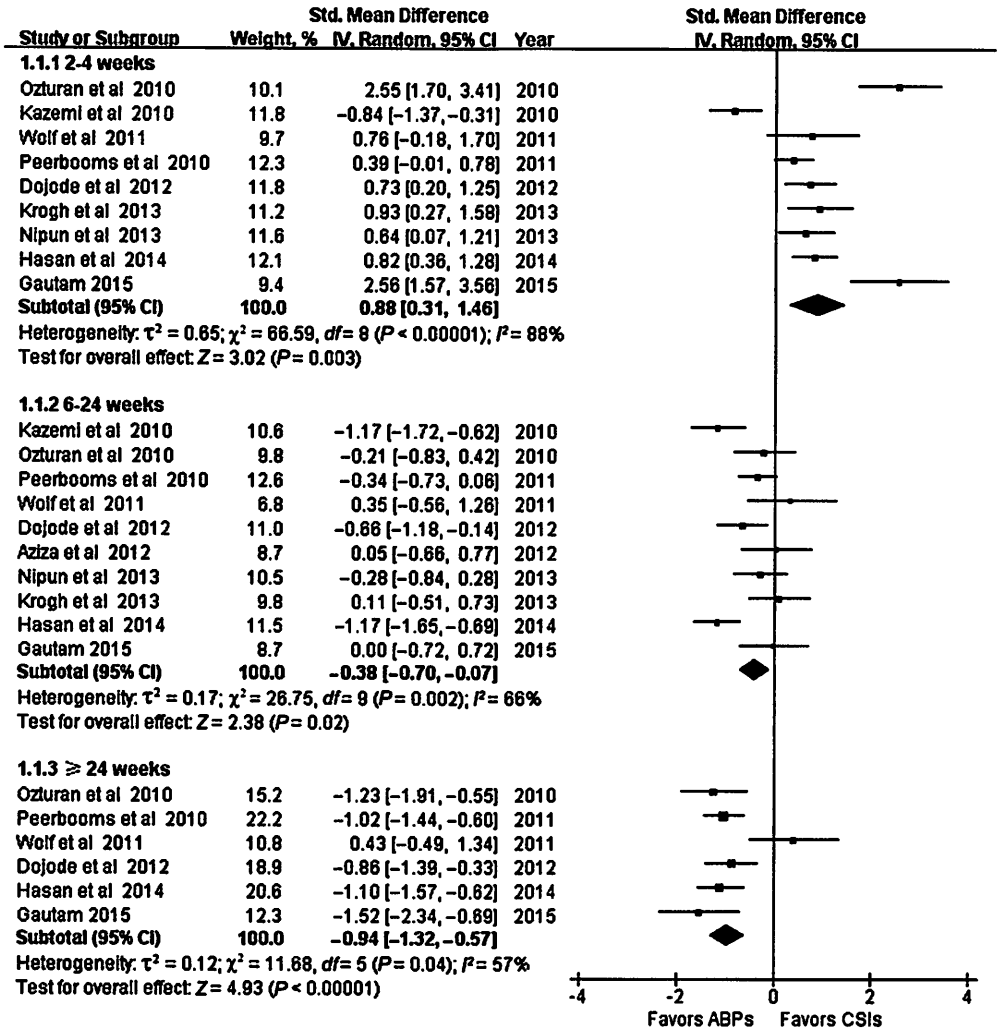

Figure 2. Forest plot of comparison of pain scores between autologous blood products (ABPs) and corticosteroid injections (CSIs) in the short, intermediate, and long term. Std = standard; IV = inverse variance; CI = confidence interval.

Table 3
Results of meta-analysis comparing autologous blood products and corticosteroid injections

Main Outcomes	No. of Studies	No. of Subjects	Heterogeneity						Effects Model	MD/SMD [95% CI]					
			Short Term		Mid Term		Long Term			Short Term		Mid Term		Long Term	
			P	I^2 (%)	P	I^2 (%)	P	I^2 (%)		SMD/MD [CI]	P	SMD/MD [CI]	P	SMD/MD [CI]	P
Pain score*	10	509	<.0001	88	.002	66	.04	57	Random	0.88 [0.31, 1.46]	.003	−0.38 [−0.70, −0.07]	.02	−0.94 [−1.32, −0.57]	<.0001
Function*	6	269	.0002	80	.0008	76	<.0001	89	Random	0.51 [−0.06, 1.08]	.08	−0.60 [−1.13, −0.08]	.03	−0.65 [−2.10, 0.81]	.38
DASH	5	239	.0003	84	<.0001	89	<.0001	91	Random	2.04 [−8.18, 12.26]	.70	−11.04 [−21.72, −0.36]	.04	−11.19 [−26.60, 4.22]	.15
Nirschl staging	3	170	.010	77	.97	0	–	–	Random	0.45 [−0.23, 1.13]	.20	−0.81 [−1.11, −0.51]	<.0001	−1.04 [−1.66, −0.42]	.001
Grip strength	4	210	.008	75	<.0001	87	.84	0	Random	−0.67 [−6.90, 5.57]	.83	6.81 [−2.07, 15.70]	.13	3.03 [−0.17, 6.23]	.06

MD = mean difference; SMD = standardized mean difference; CI = confidence interval; DASH = disabilities of the arm, shoulder and hand.
* Because the outcomes of pain score and function in the included trails were reported using different scales, SMD was calculated as the effect size.

$P = .70$; $I^2 = 84\%$) and long term (MD = −11.19 [−26.60 to 4.22]; $P = .15$; $I^2 = 91\%$; Table 3).

Nirschl Stage

Three trials (n = 170) reported the Nirschl stage. ABPs showed a beneficial effect in both the intermediate term (MD = −0.81 [−1.11 to −0.51]; $P < .0001$; $I^2 = 0\%$) and long term (MD = −1.04 [−1.66 to −0.42]; $P = .001$), but not in the short term (MD = 0.45 [−0.23 to 1.13]; $P = .20$; $I^2 = 77\%$; Table 3).

Grip Strength

Four trials (n = 210) reported grip strength as a major outcome. No significant difference was found between the 2 groups in the short term (MD = −0.67 [−6.90 to 5.57]; $P = .83$; $I^2 = 75\%$), intermediate term (MD = 6.81 [−2.07 to 15.70]; $P = .13$; $I^2 = 87\%$) and long term (MD = 3.03 [−0.17 to 6.23]; $P = .06$; $I^2 = 0\%$; Table 3).

Safety Assessment

Outcomes of adverse effects could not be pooled because of inconsistent reporting in each study. Therefore, a qualitative description of the adverse events reported in the included studies is summarized in Table 4. No noticeable or systemic adverse effects were reported in all included studies. Ozturan et al [27] reported temporary postinjection pain in most subjects that subsided within 2 days. Moreover, discoloration at the injection site was found in one subject in the CSI group. Dojode et al [30] also reported a high rate of postinjection pain at the injection site in the ABPs group (60%) versus the CSI group (26%), with some even lasting for several days. Two subjects (6.6%) also had local skin atrophy in the CSI group. In the study by Krogh et al [31], one subject experienced a minor rash, 3 had skin atrophy, and 1 had discoloration in the CSI group. Among them, 2 subjects had received previous glucocorticoid injections. However, 4 subjects in the ABPs group and one in the CSI group reported persistent pain. Arik et al [33] reported that 10 subjects (25%) had increased pain for up to 2 days after administration of ABPs. Other studies did not mention the details of adverse effects.

Stratified Analysis and Subgroup Analysis

Because follow-up duration could have an impact on the efficacy outcome, a stratified analysis was conducted and the follow-up times were divided into short, intermediate, and long term in this meta-analysis. To investigate which therapy is more effective for LE management, a subgroup analysis was performed to compare the efficacy of AB with PRP. As shown in Table 5, a better efficacy for PRP was displayed in the short term. However, there was no significant difference between PRP and AB in the long term.

Table 4
Adverse events of autologous blood products and corticosteroid injections

Study	Reinterventions		Postinjection Pain		Discoloration		Skin Atrophy		Minor Rash	
	ABP	CSI	ABP	CSI	ABP	CSI	ABP	CSI	ABP	CSI
Ozturan et al, 2010 [27]	14/20	2/20	20/20	20/20	1/20	–	–	–	–	–
Peerbooms et al, 2010 [15]	5/51	13/49	–	–	–	–	–	–	–	–
Wolf et al, 2011 [28]	3/10	3/9	–	–	–	–	–	–	–	–
Dojode et al, 2012 [30]	–	–	18/30	8/30	–	–	–	2/30	–	–
Krogh et al, 2013 [31]	–	–	4/20	1/20	–	1/20	–	3/20	–	1/20
Arik et al, 2014 [33]	–	–	10/40	–	–	–	–	–	–	–

ABPs = autologous blood products; CSI = corticosteroid injection; – = not reported.

Publication Bias

Because fewer than 10 studies were included in the pooled analysis, we did not create funnel plots. To address the issue of publication bias, we searched 2 clinical trial registries: ClinicalTrial.gov (http://www.clinicaltrials.gov) and Iranian Registry of Clinical Trials (http://www.irct.ir/). We found 2 completed but unpublished studies; one was completed in 2011, and the other was completed in 2012. We found no published articles about these studies. Negative trials are often unpublished and some older studies may have been conducted without registration in a clinical trial registry, which not only may result in potential publication bias but can also make it difficult to comprehensively assess publication bias.

Discussion

LE is common in general populations, especially among workers and tennis athletes who overuse their hands, and can have a serious effect on a person's work and life. Numerous therapies have been reported, but the available evidence to support a preferable treatment is inadequate or even conflicting. Thus we conducted this meta-analysis of 10 RCTs to compare the efficacy of ABPs and CSIs for LE management. Pooled pain scores showed that CSIs were superior to ABPs in the short term ($P = .003$), whereas ABPs were more effective than CSIs in the intermediate term ($P = .02$) and long term ($P < .0001$), which is consistent with a previous systematic review conducted by Coombes et al [9]. However, because of their specific exclusion criterion, only one RCT [15] was included. In contrast, another longitudinal study carried out by Krogh et al [14], in which the researchers compared all conservative interventions including both AB and PRP, concluded that ABPs were more effective when compared with CSIs for pain relief and functional restoration. However, their conclusions were limited because this systematic review did not take into consideration the influence of follow-up time on efficacy and only included data at the end point of each trial. We also assessed the effect on functional restoration. Both ABPs and corticosteroids showed improvement in limb function, with a slight advantage toward ABPs in the intermediate term ($P = .03$). Grip strength, an important indicator of arm function, was not compared in the previous study. In our study, the pooled analysis showed that no significant difference existed between the 2 groups ($P > .05$). From all of the pooled analysis results, ABPs exhibited a significant therapeutic effect on pain relief, but not on functional restoration and grip strength. One possible reason for the pain relief is that the cytokines present in ABPs, mainly hepatocyte growth factor, could inhibit the production of pain-associated molecules such as prostaglandin E2, cyclo-oxygenase (COX)-1, and COX-2 [39]. For functional restoration and grip strength, a single or acute injection may not change a long-standing chronic condition and reverse the degeneration of the tendon [40]. It was reported that local anesthetics were somewhat effective for LE because of their analgesic effects, which can relieve the painful condition immediately [41]. However, some studies also indicated that when using local anesthetics with PRP, some of the biologic actions of local anesthetics may interfere with the efficacy of PRP [42]. In vitro studies have shown that the addition of anesthetics to PRP can not only reduce

Table 5
Subgroup analysis of comparison of autologous blood and platelet-rich plasma

Duration	Pain Scores				Function			
	AB		PRP		AB		PRP	
	SMD [CI]	P	SMD [CI]	P	SMD [CI]	P	SMD [CI]	P
Short term	0.74 [−0.03, 1.52]	.06	1.20 [0.14, 2.27]	.03	0.49 [−0.34, 1.33]	.25	0.60 [0.05, 1.14]	.03
Mid term	−0.59 [−1.02, −0.16]	.007	−0.14 [−0.42, 0.14]	.33	−0.07 [−1.46, −0.07]	.03	−0.24 [−0.71, 0.23]	.31
Long term	−0.78 [−1.34, −0.22]	.006	−1.14 [−1.55, −0.72]	<.0001	−0.03 [−1.85, 1.79]	.97	−1.90 [−2.78, −1.02]	<.0001

AB = autologous blood; PRP = platelet-rich plasma; SMD = standardized mean difference; CI = confidence interval.

tenocyte proliferation and viability but also decrease the reactions of PRP [43,44]. Thus, although local anesthetics are effective for LE, they also may slow down or suppress the repair of the damaged tendon. In this meta-analysis, 8 of 10 studies used a combination of local anesthetics with ABPs or CSIs, which may have an effect on the evaluation of the efficacy of ABPs. To eliminate the interference of local anesthetics and to further verify the efficacy of ABPs, clinical studies without the use of local anesthetics are required.

CSIs, a standard but controversial treatment for LE, have been used extensively in the past. The present study indicated that CSIs had a better short-term outcome on pain relief than did ABPs but held no significant advantage in the long term. One possible reason for this finding is that LE is a degenerative disorder of the extensor tendon origin as a result of repetitive stress or overuse of the wrist rather than an inflammatory condition [45,46], in which the ECRB plays an important role. In recent years, an increasing number of studies have supported this theory. Histologic study of surgical specimens showed angiofibroblastic hyperplasia within the tendon, because the tendon was invaded by fibroblasts and vascular granulation, but no inflammatory cells were observed [47]. Moreover, an anatomic study by Bunata et al [48] of 85 cadaveric elbows showed that the ECRB tendon has a unique anatomic location that makes its undersurface vulnerable to contact and abrasion against the lateral edge of the capitellum during elbow motion, which further accelerates the degenerative process.

ABPs, an emerging biologic treatment, increasingly are being used to treat tendinopathy. However, their underlying mechanism has not yet been elucidated. Recently, scholars have reached the consensus that growth factors released by platelets together with other cytokines or cellular and humoral mediators in ABPs are helpful for stimulating repair mechanisms, thus promoting tenocyte proliferation and aiding in tendon healing. Moreover, several bioactive proteins within ABPs attract osteoblasts and macrophages to remove the necrotic tissue [11,49-51]. However, the question of whether AB or PRP is more effective for LE management has been debated in the literature. Currently, there is a paucity of evidence to support the idea that PRP is better than AB for tendinosis or other soft tissue injuries. Few severe adverse events are currently associated with PRP, and some clinicians may consider PRP more effective because it contains more platelets. However, the International Cellular Medical Society recommended a maximum 2.5-fold concentration of platelets above the baseline level because a higher concentration may inhibit tenocyte and fibroblast proliferation [52]. To investigate this issue, a subgroup analysis between the AB and PRP group was performed. The results showed that PRP had a better therapeutic effect than AB in terms of pain relief and functional restoration in the short term, although no significant difference between PRP and AB was found in the long term. Similarly, Thanasas et al [53] conducted am RCT to compare the efficacy of AB with PRP for LE management. A slight advantage for PRP over AB in terms of pain relief was observed after 6 weeks; however, no significant difference was observed at 6-month follow-up, which was similar to findings of another RCT [54]. Creaney et al [55] compared PRP to AB and showed a slight improvement with AB at 6 months, but a higher proportion of the AB group went on to have surgery in a trial of 150 subjects. Creaney et al [55] also indicated that increased stimulation with a higher concentration of growth factors may not be that beneficial because it may limit the collagen expression of fibroblast-tenocyte lineage cells, as evidenced by an in vitro cell culture assay [56]. Furthermore, many other factors such as white blood cells might have a potential influence on healing [57], thus having an impact on the results. In view of these unresolved questions, more research is needed to further explore the potential effects of other components of the blood on LE and to determine whether AB or PRP is more effective for LE management.

Adverse events should be taken into account when assessing safety. Several adverse effects of CSIs have already been reported; subcutaneous necrosis and tendon rupture are the most severe, whereas postinjection pain is the most common [14]. A previous meta-analysis reported a 10.7% rate of transient pain after CSIs [8]. In the studies included in our meta-analysis, a higher rate of postinjection pain was reported in both the ABP and CSI groups [27,30,31]. Fortunately, it subsided within 1-2 days without special intervention. Sölveborn et al [58] believed that postinjection pain was caused by the volume effect of the injection and the medication itself. Other adverse events including discoloration, local skin atrophy, minor rash, and loss of pigmentation were reported in the CSI group. No systemic or severe adverse events such as tendon rupture and infections after injections were reported in the studies included in our meta-analysis. Finally, a high recurrence rate of CSIs was also an important factor that should be taken into consideration. A previous randomized trial reported a 72% recurrence rate 6 weeks after the injection [59]. One study included in the present meta-analysis described a 37% recurrence of pain at 6 months [30]. Several explanations for the high recurrence rate exist. First, although CSIs could diminish short-term pain intensity by inhibiting neuropeptides and cytokines, they also may damage the tenocytes and suppress their viability [60,61]. Second, it is possible that some subjects did not strictly follow the doctor's advice and continued to overuse their elbows because of the temporary pain relief experienced after the corticosteroid injection [62]. Despite the fewer reported adverse effects, ABPs

also have some shortcomings. The major limitation is the lack of a significant short-term effect, because the regeneration of tendon tissue might take more than 3 months [31]. The high cost of PRP should also be considered.

Although this meta-analysis was conducted strictly according to the guidelines recommended by the *Cochrane Handbook for Systematic Reviews of Interventions*, some limitations could not be avoided. The primary limitation is the small number of subjects and the low quality of the studies in general. The inability to blind subjects and assessors to treatment allocation may lead to a strong placebo effect and an overestimation of the therapeutic effects. A lack of uniformity among trials related to the production of PRP and the concentration of platelets makes it difficult to compare trials. Because of these clinical inconsistencies, it is difficult to draw a solid conclusion about which therapy is more suitable for LE management. In addition, some unpublished studies were not included, which may result in potential publication bias. Given all of the aforementioned limitations, these results must be interpreted with caution. More high-quality studies with consistent standards are warranted to reassess the efficacy of these 2 therapies. Furthermore, correct blinding and allocation concealment, objective evaluation of outcomes, and accurate diagnosis of LE with not only clinical symptoms but also imaging techniques such as magnetic resonance imaging and ultrasound are indispensable. We also suggest that comprehensive comparisons with other conservative therapies should be performed, which would help clinicians make more informed decisions.

Conclusion

Our meta-analysis found limited evidence that CSIs were superior to ABPs in terms of pain relief in the short term, whereas ABPs were more beneficial in the intermediate term and long term. The study also found that the ABPs were more effective than CSIs in terms of functional restoration in the intermediate term. However, no sustained effectiveness could be observed in the long term. Because of a lack of uniformity among trials, the small sample size, and the limited number of high-quality RCTs, we could not draw a definitive conclusion to support the widespread use of ABPs for the management of LE. Further high-quality research is required, with a greater emphasis on increasing the sample size of the studies and standardization of study protocols and outcome measures.

References

1. Shiri R, Viikari-Juntura E, Varonen H, et al. Prevalence and determinants of lateral and medial epicondylitis: A population study. Am J Epidemiol 2006;164:1065-1074.
2. Walker-Bone K, Palmer KT, Reading I, et al. Occupation and epicondylitis: A population-based study. Rheumatology (Oxford) 2012; 51:305-310.
3. Connell D, Burke F, Coombes P, et al. Sonographic examination of lateral epicondylitis. AJR Am J Roentgenol 2001;176:777-782.
4. Walz DM, Newman JS, Konin GP, et al. Epicondylitis: Pathogenesis, imaging, and treatment. Radiographics 2010;30:167-184.
5. Zeisig E, Ohberg L, Alfredson H. Extensor origin vascularity related to pain in patients with tennis elbow. Knee Surg Sports Traumatol Arthrosc 2006;14:659-663.
6. Tonks JH, Pai SK, Murali SR. Steroid injection therapy is the best conservative treatment for lateral epicondylitis: A prospective randomised controlled trial. Int J Clin Pract 2007;61: 240-246.
7. Lewis M, Hay EM, Paterson SM, et al. Local steroid injections for tennis elbow: Does the pain get worse before it gets better? Results from a randomized controlled trial. Clin J Pain 2005;21: 330-334.
8. Gaujoux-Viala C, Dougados M, Gossec L. Efficacy and safety of steroid injections for shoulder and elbow tendonitis: A meta-analysis of randomised controlled trials. Ann Rheum Dis 2009;68: 1843-1849.
9. 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;376:1751-1767.
10. Wang-Saegusa A, Cugat R, Ares O, et al. Infiltration of plasma rich in growth factors for osteoarthritis of the knee short-term effects on function and quality of life. Arch Orthop Trauma Surg 2011;131: 311-317.
11. Anitua E, Andia I, Sanchez M, et al. Autologous preparations rich in growth factors promote proliferation and induce VEGF and HGF production by human tendon cells in culture. J Orthop Res 2005; 23:281-286.
12. Raeissadat SA, Sedighipour L, Rayegani SM, et al. Effect of platelet-rich plasma (PRP) versus autologous whole blood on pain and function improvement in tennis elbow: A randomized clinical trial. Pain Res Treat 2014;2014:191525.
13. Karimi Mobarakeh M, Nemati A, Fazli A, et al. Autologous blood injection for treatment of tennis elbow. Trauma Mon 2013;17: 393-395.
14. Krogh TP, Bartels EM, Ellingsen T, et al. Comparative effectiveness of injection therapies in lateral epicondylitis: A systematic review and network meta-analysis of randomized controlled trials. Am J Sports Med 2013;41:1435-1446.
15. Peerbooms JC, Sluimer J, Bruijn DJ, et al. 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;38:255-262.
16. Sheth U, Simunovic N, Klein G, et al. Efficacy of autologous platelet-rich plasma use for orthopaedic indications: A meta-analysis. J Bone Joint Surg 2012;94:298-307.
17. Sims SE, Miller K, Elfar JC, et al. Non-surgical treatment of lateral epicondylitis: A systematic review of randomized controlled trials. Hand (N Y) 2014;9:419-446.
18. Rodriguez JA. Corticosteroid versus platelet-rich plasma injection in epicondylitis. Orthop Nurs 2014;33:257-265; quiz 266-257.
19. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. Ann Intern Med 2009;151:W65-W94.
20. Peerbooms JC, Gosens T, Poole C, et al. The cost effectiveness of platelet rich plasma versus corticosteroids in the treatment of lateral epicondylitis. Value Health 2012;15:A357.
21. Gosens T, Peerbooms J, Correspondence A, et al. PRP or steroids in lateral epicondylitis? RCT with two year follow up. Arthroscopy 2011;27:e185-e186.

22. Shiple BJ. How effective are injection treatments for lateral epicondylitis? Clin J Sport Med 2013;23:502-503.
23. Mandelbaum B. An injection of platelet-rich plasma, glucocorticoid, or saline solution produced similar pain and disability results in lateral epicondylitis. J Bone Joint Surg Am 2013;95:2059.
24. Nichols AW. Two-year follow-up of injection with platelet-rich plasma versus corticosteroid for lateral epicondylitis. Clin J Sport Med 2012;22:451-452.
25. Gosens T, Peerbooms JC, van Laar W, et al. 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;39:1200-1208.
26. Kazemi M, Azma K, Tavana B, et al. Autologous blood versus corticosteroid local injection in the short-term treatment of lateral elbow tendinopathy: A randomized clinical trial of efficacy. Am J Phys Med Rehabil 2010;89:660-667.
27. Ozturan KE, Yucel I, Cakici H, et al. Autologous blood and corticosteroid injection and extracoporeal shock wave therapy in the treatment of lateral epicondylitis. Orthopedics 2010;33: 84-91.
28. Wolf JM, Ozer K, Scott F, et al. Comparison of autologous blood, corticosteroid, and saline injection in the treatment of lateral epicondylitis: A prospective, randomized, controlled multicenter study. J Hand Surg Am 2011;36:1269-1272.
29. Omar AS, Ibrahim ME, Ahmed AS, et al. Local injection of autologous platelet rich plasma and corticosteroid in treatment of lateral epicondylitis and plantar fasciitis: Randomized clinical trial. Egypt Rheumatologist 2012;34:43-49.
30. Dojode CM. A randomised control trial to evaluate the efficacy of autologous blood injection versus local corticosteroid injection for treatment of lateral epicondylitis. Bone Joint Res 2012;1: 192-197.
31. Krogh TP, Fredberg U, Stengaard-Pedersen K, et al. Treatment of lateral epicondylitis with platelet-rich plasma, glucocorticoid, or saline: A randomized, double-blind, placebo-controlled trial. Am J Sports Med 2013;41:625-635.
32. Jindal N, Gaury Y, Banshiwal RC, et al. Comparison of short term results of single injection of autologous blood and steroid injection in tennis elbow: A prospective study. J Orthop Surg Res 2013;8:10.
33. Arik HO, Kose O, Guler F, et al. Injection of autologous blood versus corticosteroid for lateral epicondylitis: A randomised controlled study. J Orthop Surg (Hong Kong) 2014;22:333-337.
34. Gautam VK, Verma S, Batra S, et al. Platelet-rich plasma versus corticosteroid injection for recalcitrant lateral epicondylitis: Clinical and ultrasonographic evaluation. J Orthop Surg (Hong Kong) 2015;23:1-5.
35. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available at www.cochrane-handbook.org. Accessed March 7, 2016.
36. Higgins J, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-1558.
37. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-560.
38. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: Power of statistical tests and prevalence in the literature. J Clin Epidemiol 2000;53:1119-1129.
39. Zhang J, Middleton KK, Fu FH, et al. HGF mediates the anti-inflammatory effects of PRP on injured tendons. PLoS One 2013; 8:e67303.
40. Martin JI, Merino J, Atilano L, et al. Platelet-rich plasma (PRP) in chronic epicondylitis: Study protocol for a randomized controlled trial. Trials 2013;14:410.
41. Mardani-Kivi M, Karimi-Mobarakeh M, Karimi A, et al. The effects of corticosteroid injection versus local anesthetic injection in the treatment of lateral epicondylitis: A randomized single-blinded clinical trial. Arch Orthop Trauma Surg 2013;133:757-763.
42. Andia I, Latorre PM, Gomez MC, et al. Platelet-rich plasma in the conservative treatment of painful tendinopathy: A systematic review and meta-analysis of controlled studies. Br Med Bull 2014; 110:99-115.
43. Fedder C, Beck-Schimmer B, Aguirre J, et al. In vitro exposure of human fibroblasts to local anaesthetics impairs cell growth. Clin Exp Immunol 2010;162:280-288.
44. Carofino B, Chowaniec DM, McCarthy MB, et al. Corticosteroids and local anesthetics decrease positive effects of platelet-rich plasma: an in vitro study on human tendon cells. Arthroscopy 2012;28: 711-719.
45. Alfredson H, Ljung BO, Thorsen K, et al. In vivo investigation of ECRB tendons with microdialysis technique—no signs of inflammation but high amounts of glutamate in tennis elbow. Acta Orthop Scand 2000;71:475-479.
46. Tosti R, Jennings J, Sewards JM. Lateral epicondylitis of the elbow. Am J Med 2013;126:357.e1-357.e6.
47. Nirschel R, Pettrone F. The surgical treatment of lateral epicondylitis. J Bone Joint Surg Am 1997;61:832-839.
48. Bunata RE, Brown DS, Capelo R. Anatomic factors related to the cause of tennis elbow. J Bone Joint Surg Am 2007;89:1955-1963.
49. Sampson S, Gerhardt M, Mandelbaum B. Platelet rich plasma injection grafts for musculoskeletal injuries: A review. Curr Rev Musculoskelet Med 2008;1:165-174.
50. Mishra A, Woodall J, Vieira A. Treatment of tendon and muscle using platelet-rich plasma. Clin Sports Med 2009;28:113-125.
51. Tohidnezhad M, Varoga D, Wruck C, et al. Platelet-released growth factors can accelerate tenocyte proliferation and activate the anti-oxidant response element. Histochem Cell Biol 2011;135: 453-460.
52. Graziani F, Ivanovski S, Cei S, et al. The in vitro effect of different PRP concentrations on osteoblasts and fibroblasts. Clin Oral Implants Res 2006;17:212-219.
53. Thanasas C, Papadimitriou G, Charalambidis C, et al. 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;39:2130-2134.
54. Raeissadat SA, Rayegani SM, Hassanabadi H, et al. Is platelet-rich plasma superior to whole blood in the management of chronic tennis elbow: One year randomized clinical trial. BMC Sports Sci Med Rehabil 2014;6:12.
55. Creaney L, Wallace A, Curtis M, et al. 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;45:966-971.
56. Anitua E, Sanchez M, Zalduendo MM, et al. Fibroblastic response to treatment with different preparations rich in growth factors. Cell Prolif 2009;42:162-170.
57. Anitua E, Andia I, Ardanza B, et al. Autologous platelets as a source of proteins for healing and tissue regeneration. Thromb Haemost 2004;91:4-15.
58. Sölveborn SA, Buck F, Mallmin H, et al. Cortisone injection with anesthetic additives for radial epicondylalgia (tennis elbow). Clin Orthop Relat Res 1995;316:99-105.
59. Bisset L, Beller E, Jull G, et al. Mobilisation with movement and exercise, corticosteroid injection, or wait and see for tennis elbow: Randomised trial. BMJ 2006;333:939.
60. Wan Nar Wong M, Lui WT, Chuen Fu S, et al. The effect of glucocorticoids on tendon cell viability in human tendon explants. Acta Orthop 2009;80:363-367.
61. Han SH, An HJ, Song JY, et al. Effects of corticosteroid on the expressions of neuropeptide and cytokine mRNA and on tenocyte viability in lateral epicondylitis. J Inflamm (Lond) 2012;9:40.
62. Smidt N, van der Windt DA, Assendelft WJ, et al. Corticosteroid injections, physiotherapy, or a wait-and-see policy for lateral epicondylitis: A randomised controlled trial. Lancet 2002; 359:657-662.