A Systematic Review to Compare Three Injection Modalities in the Management of Pain and Function for Patients with Chronic Lateral Epicondylalgia

Mohammed Elmajee, Lynne Gaskell, Adam Watts, Munir Khan, Mostafa Elmajee* and Housameldin Raslan
Salford Royal NHS Foundation Trust, United Kingdom

*Corresponding author: Mostafa Elmajee, Salford Royal NHS Foundation Trust, United Kingdom, Tel: 00218928208802; E-mail: m.elmajee@edu.salford.ac.uk
Received date: May 07, 2016; Accepted date: May 25, 2016; Published date: May 31, 2016

Abstract

Aim: To provide an evidence-based scientific report on the efficacy of three common injection treatment modalities for Lateral Epicondylalgia (LE). These injections are contemporary and frequently used in clinical practice.

Objective: To systematically locate and appraise RCTs (Randomised Controlled Trials) of three comparative injection modalities (Corticosteroid Injection (CSI), Platelets Rich Plasma (PRP), and Autologous Blood Injection (ABI)) and to review their efficacy in the management of pain and dysfunction associated with LE.

Search strategy: RCTs that compare at least two of the three injections modalities and published from January 2005 to September 2015 were systematically searched. The following online search engines were utilised: The Cochrane Central Register of Controlled Trials (Central), Web of Sciences, PubMed, CINAHL, MEDLINE, and Academic Search Premier. The following search terms were used: “tennis elbow”, “lateral epicondylitis”, “corticosteroid injection”, “autologous blood injection”, “platelets rich plasma” and “randomised controlled trial”. The terms “tennis elbow” or “lateral epicondylitis” or “lateral epicondylalgia” were combined with each one of the injection modalities and the term “randomised controlled trial”. Methodological assessment was conducted by applying Sign 50 tool and The Cochrane Collaboration’s tool for assessing risk of bias. This systematic review protocol was conducted according to the standards presented in the Cochrane Handbook and recommendations in the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement.

Results: Seven RCTs were included within this review. Overall methodological quality was high, mostly level I studies. Three RCTs compared the effects of PRP and ABI, three studies concerned the comparison between PRP and CSI, and one RCT related to the effectiveness of ABI and CSI.

Conclusion: Corticosteroid injections failed to demonstrate long-lasting significant clinical effects in chronic LE. However, PRP and ABI were shown to have a progressive and increasing effect from 6 months to one year following the injections. PRP and ABI demonstrated comparable effects in terms of pain and function. Further studies are warranted to justify the higher costs associated with the use of PRP.

Keywords: Tennis; Elbow; Lateral epicondylitis; Epicondylalgia; Corticosteroid; Autologous blood; Randomized controlled trial; Platelet rich plasma

Introduction

The main aim of this review is to systematically locate and appraise published Randomised Controlled Trials (RCTs) that compare the three injection modalities Corticosteroid Injection (CSI), Platelet Rich Plasma (PRP) and Autologous Blood Injection (ABI)) for the treatment of lateral epicondylalgia (LE). The intention was to provide a robust scientific report of evidence-based knowledge to inform healthcare providers. LE affects 1 to 3% of adults in the general population each year [1-3]. The burden on the economic system is substantial, with 5% of the affected working-age subjects reporting work absence because of elbow symptoms in the past 12 months in 2012 [2,4].

This updated systematic review is justified on the basis of further quality evidence being published since the review conducted in 2013 [5] to discern if there are any advances on current best practice guidelines. They compared eight different treatments, including the three injections in this review. They concluded that there were a limited number of unbiased RCTs as evidence for the injection therapies’ effectiveness in the treatment of LE and advocated the need for more large-size and good quality RCTs. Furthermore, they only included RCTs that were conducted up to June 20, 2011.

Methods and Materials

The eligibility criteria for this review is illustrated in Table 1.

| Inclusion Criteria | Exclusion Criteria |
|--------------------|--------------------|
| Randomised controlled trials | Participants with Rheumatoid Arthritis, history of elbow trauma and suspicion of nerve involvement |
Comparative injection modalities of (CSI, PRP and ABI)  

| Comparative injection modalities of (CSI, PRP and ABI) | Studies published before 2005 |
|-------------------------------------------------------|-----------------------------|
| Published between January 2005 and September 2015     | Studies not published in the English language |
| Published in the English language                     | Involving subject with symptoms manifesting for less than 3 months |
| Involving humans above the age of 18                  | Involving humans above the age of 18 |

Table 1: Eligibility criteria list.

The following online search engines: The Cochrane Central Register of Controlled Trials (Central), Web of Sciences, PubMed, CINAHL, MEDLINE, and Academic Search Premier, using different combination of the terms “tennis elbow” or “lateral epicondylitis” and “randomised controlled trial”. The search began in June 2015 and was regularly updated up to September 2015. Finally, seven trials were included as illustrated in Figure 1.

Although local injections CSI, PRP, ABI, botulinum toxin, hyaluronic acid, polidocanol, glycosaminoglycan, bone marrow injection and prolotherapy can be utilised for LE [6]. In this review only CSI, PRP, ABI will be discussed in details since they are increasingly commonly utilised and contemporary injections [7]. CSI is one of the most common injections used to manage cases of LE [4]. However, the exact mechanism of action of CSI in LE is still undefined completely and further studies are warranted to assess why CSI can lead to pain improvements in some chronic cases of LE [8].

Blood-based injections can deliver platelets-derived and blood-derived mediators that can promote normal tendon healing [1]. These mediators seem to enhance vascularity of the relatively hypo vascular zones in the common extensor origin that have been described in a previous study [9]. Formulating a robust and up-to-date comparative review of these three injections will assist healthcare providers to provide the best possible injection therapy and can delay the need for surgical intervention.

Results

504 participants were included in the seven RCTs included in this review. The majority (52%) of the participants were female.

Three trials compared CSI and PRP. They include one study in 2011 [10] who demonstrated that PRP had better outcomes at 6 and 12 months (P<0.001), and CSI better at 4 weeks. However, this was not significant statistically (P = 0.206). Furthermore, PRP demonstrated better outcomes at 2 years (P<0.0001). In another trial in 2013 [11-13], CSI resulted in better outcomes at 1 month (P<0.003), with no difference between PRP and CSI groups at 3 months (P = 0.717). In the study in 2015 [12], PRP had better outcomes in comparison with CSI at 6 months (P<0.001).

Three trials compared PRP and ABI. They include one trial in 2011 [13] who reported no significant differences up to 6 months (p = 0.59). Furthermore, in another trial in 2011 [13], PRP resulted in better outcomes at 6 weeks (P<0.05), but no significant differences at 3 or 6 months (P = 0.32). However, the trial in 2014 reported no significant differences between ABI and PRP at 52 weeks (P = 0.662) [14,15].

Finally, one trial compared the effects of CSI in comparison with ABI and ECSW [15]. They showed that CSI had better outcomes at 4 weeks (P<0.001), but ABI showed improved outcomes at 1 year (P<0.001).

Discussion

Four trials including 250 participants received either PRP or CSI [10,13] and were regarded as one trial as they are one follow up study. The three trials differed in their inclusion criteria. Two trials used clinical criteria only to include participants, except one trial [11] who used Ultrasound (US) imaging as a criterion to diagnose and include participants, as well as using US imaging an outcome measure. The differences in the findings of the individual studies could have been biased by the baseline differences in the treatment arms with respect to underlying histopathological changes. In order to ensure homogeneity of the future study population, modern imaging techniques such as US imaging should be incorporated with pain and functional scores when recruiting patients.

Formulations differed in these three trials for example 1 ml of 40 mg triamcinolone acetonide was utilised in two studies [10,11], while the other study [11] used 2 ml of methylprednisolone of 40 mg/ml.

Other formulations of CSI that have been described in the literature are betamethasone (6 mg), dexamethasone (4-10 mg), and

Citation: Elmajee M, Gaskell L, Watts A, Khan M, Elmajee M, et al. (2016) A Systematic Review to Compare Three Injection Modalities in the Management of Pain and Function for Patients with Chronic Lateral Epicondylalgia. Orthop Muscular Syst 5: 215. doi: 10.4172/2161-0533.1000215
Difficulties in the definition of growth factors in PRP preparations have been observed previously [25]. All three trials compared PRP and ABI, and stated that they did not use an activating agent prior to the PRP injections [10]. Application of activating agents, such as calcium chloride or thrombin, stimulate complete release of growth factors from platelets [23]. Furthermore, it has been showed that with the use of thrombin with different isolation devices in PRP preparations there were discrepancies in the amount of platelet growth factors released, which are crucial for tissue healing [23]. Therefore, as the studies [11,12] did not mention the use of activating agents, it is difficult to ensure that all PRP treatment arms of the three trials utilised a similar technique [1].

In the trials that compared PRP and ABI, all participants were given scan-guided injections except by one trial [15]. However, there is no strong evidence in the literature to recommend one technique over the other [8]. All participants in PRP and ABI trials had an unknown number of penetrations by peppering technique except in one trial [29], whereby no peppering was performed. Applying a peppering technique might have confounded results achieved by the researchers who applied it.

In the trial conducted in 2011 did not specify the amount of ABI given to their participants, who received 2 injections of ABI at 0 and 1 months [14]. However, one injection of 2 ml and 3 ml of ABI were given in the trial in 2014 and the trial in 2011 respectively [14,15]. In addition to the platelets-derived growth factors present in ABI, there are also other plasma-derived biologically active substances that can effectively stimulate tendon healing [29].

With the exception of one trial, all trials that compared PRP and ABI used local anaesthetics with the ABI [14]. This could be regarded as another confounding variable, since the use of local anaesthetics have been shown to inhibit proliferation of tenocytes in an in vitro...
Complications of injections reviewed

Overall, CSI, ABI, and PRP were safe injections and no serious events such as hospitalization were reported. Temporary pain at the injection site was the most common side effect reported in these trials. Skin atrophy and depigmentation was reported following CSI use in the one study [11], but patients with atrophy and depigmentation had CSI before. Another trial [16] also reported that 5% of their CSI group had skin discolouration.

Furthermore, CSI is not effective in the long-term. This reported in two trials [10,13].

Limitations of this review

The conclusion drawn from this review should be interpreted in respect of some limitations. The review was conducted by one author, including searches and inclusion process, data extraction, quality assessment and critical appraisal, and the reporting.

This might have induced bias, particularly with regard to quality assessment of the trials included. However, the author has tried to adopt an impartial and fair method of scoring and grading. Furthermore, the second author, Lynne Gaskell has closely reviewed all the steps during conducting this review at Salford University. Ideally, systematic reviews should be conducted by the synergistic action of a team of experts working together.

Heterogeneity of included trials in terms of different outcomes and different methodologies did not allow quantitative synthesis of data into a meta-analysis but led to a broad-based narrative review.

Another limitation of this review was the inclusion of studies that were published in English language only. To conduct a comprehensive review, studies published in other languages should have been included.

Conclusion

CSI have been widely used in LE management, and are frequently requested by patients. However, this review presents an argument against their use for chronic LE, since no long-term benefits were found. This concurs with other reviews. While CSI have a well-documented short-term benefit, they appear to have a detrimental effect with longer follow up, such as an increase in recurrence rate when compared with PRP and ABI.

With regard to PRP and ABI, the available high-quality literature in this review has shown mixed results. The majority of trials found that although CSI may provide better temporary relief of symptoms in short-term, both PRP and ABI demonstrate improved outcomes from 6 months to 1 year. Therefore, current evidence supports that once injection therapy is considered, blood-based preparations should be considered over CSI. However, there was only one placebo-controlled trial among all trials in this review to support this recommendation, and they demonstrated no significant benefit in PRP in comparison to CSI.

In this review, comparative trials that investigated PRP and ABI efficacy have failed to show any significant difference between both injections on different outcomes. The available data in this review are limited by quality and size of study, and are currently insufficient to recommend PRP over ABI. Therefore, in the light of the current evidence, the use of PRP instead of ABI may be unjustified given the higher cost associated with the preparations of PRP.

Implications for future research

Future larger controlled studies on blood-based preparations could further enlighten aspects of these promising treatments in chronic LE. Information regarding indications; the effects of presence and absence of WBCs; number, time and frequency of injections required; and the efficacy of platelets-rich and platelets-poor concentrations of PRP, will clarify the different parameters of injections in the treatment of chronic LE.

References

1. Judson C, Wolf JM (2015) Tennis Elbow: Blood and Platelet-Rich Plasma (PRP) Injections. In Tennis Elbow. Springer US: 73-83.
2. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P (2010) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. International Journal of Surgery 8: 336-341.
3. Winston J, Wolf JM (2015) Tennis Elbow: Definition, Causes, Epidemiology. In Tennis Elbow. Springer US: 1-6.
4. Walker-Bone K, Palmer KT, Reading I, Coggon D, Cooper C (2012) Occupation and epicondylitis: a population-based study. Rheumatology (Oxford) 51: 305-310.
5. Krogh TP, Bartels EM, Ellingsen T, Stengaard-Pedersen K, Buchbinder R, et al. (2013) Comparative effectiveness of injection therapies in lateral epicondylitis: a systematic review and network meta-analysis of randomized controlled trials. American Journal of Sports Medicine 41: 1435-1446.
6. Stenhousse G, Sookur P, Watson M (2013) Do blood growth factors offer additional benefit in refractory lateral epicondylitis? A prospective, randomized pilot trial of dry needling as a stand-alone procedure versus dry needling and autologous conditioned plasma. Skeletal Radiology 42: 1515-1520.
7. Ring D (2015) Natural History and Common Misconceptions: Treatment with Education and Empathy. In Tennis Elbow. Springer US: 17-22.
8. Immernern I, Szabo RM (2015) Steroid Injections. In Tennis Elbow. Springer US: 61-72.
9. Bales CP, Placzek JD, Malone KJ, Vaupel Z, Arnoczy SP (2007) Microvascular supply of the lateral epicondylo and common extensor origin. Journal of Shoulder and Elbow Surgery 16: 497-501.
10. Gosens T, Peerbooms JC, van Laar W, den Oudsten BL (2011) Ongoing positive effect of platelet-rich plasma versus corticosteroid injection in lateral epicondylitis: a double-blind randomized controlled trial with 2-year follow-up. American Journal of Sports Medicine 39: 1200-1208.
11. Krogh TP, Fredberg U, Stengaard-Pedersen K, Christensen R, Jensen P, et al. (2013) Treatment of lateral epicondylitis with platelet-rich plasma,
glucocorticoid, or saline: a randomized, double-blind, placebo-controlled trial. Am J Sports Med 41: 625-635.

12. Gautam VK, Verma S, Batra S, Bhatnagar N, Arora S (2015) Platelet-rich plasma versus corticosteroid injection for calcific lateral epicondylitis: clinical and ultrasonographic evaluation. Journal of Orthopaedic Surgery (Hong Kong) 23: 1-5.

13. Creaney L, Wallace A, Curtiss M, Connell D (2010) 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. British Journal of Sports Medicine 45: 966-971.

14. Thanassas C, Papadimitriou G, Charalambidis C, Paraskevopoulos I, Papanikolaou A (2011) Platelet-rich plasma versus autologous whole blood for the treatment of chronic lateral elbow epicondylitis: a randomized controlled clinical trial. American Journal of Sports Medicine 39: 2130-2134.

15. Raeesadat SA, Rayegani SM, Hassanabadi H, Rahimi R, Sedighipour L, et al. (2014) Is Platelet-rich plasma superior to whole blood in the management of chronic tennis elbow: one year randomized clinical trial? BMC Sports Science, Medicine and Rehabilitation 6: 12.

16. Inklebarger J, Clarke T (2015) Corticosteroid injections for tennis elbow–A hard habit to break. International Musculoskeletal Medicine 37: 108-110.

17. MacMahon PJ, Eastace SJ, Kavanagh EC (2009) Injectable corticosteroid and local anaesthetic preparations: a review for radiologists. Radiology 252: 647-661.

18. Mazzocca AD, McCarthy MB, Chowaniec DM, Cote MP, Romeo AA, et al. (2012) Platelet-rich plasma differs according to preparation method and human variability. J Bone Joint Surg Am 94: 308-316.

19. Foster TE, Puukas BL, Mandelbaum BR, Gerhardt MR, Rodeo SA (2009) Platelet-rich plasma: from basic science to clinical applications. The American journal of sports medicine 37: 2259-2272.

20. Zimmermann R, Reske S, Metzler P, Schlegel A, Ringwald J, et al. (2008) Preparation of highly concentrated and white cell-poor platelet-rich plasma by platelethpheresis. Vox Sang 95: 20-25.

21. Bellapianta J, Swartz F, Lisella J, Czajka J, Neff R, et al. (2011a) Randomized prospective evaluation of injection techniques for the treatment of lateral epicondylitis. Orthopedics 34: 708-712.

22. Okçu G, Erkan S, Sencürtük M, Ozalp RT, Yercan HS (2012) Evaluation of injection techniques in the treatment of lateral epicondylitis: a prospective randomized clinical trial. Acta Orthop Traumatol Turc 46: 26-29.

23. Mazzocca AD, McCarthy MB, Chowaniec DM, Cote MP, Romeo AA, et al. (2012) Platelet-rich plasma differs according to preparation method and human variability. J Bone Joint Surg Am 94: 308-316.

24. Foster TE, Puukas BL, Mandelbaum BR, Gerhardt MR, Rodeo SA (2009) Platelet-rich plasma: from basic science to clinical applications. The American journal of sports medicine 37: 2259-2272.

25. Castillo TN, Pouliot MA, Kim HJ, Dragoo JL (2011) Comparison of growth factor and platelet concentration from commercial platelet-rich plasma separation systems. The American journal of sports medicine 39: 266-271.

26. Zimmermann R, Reske S, Metzler P, Schlegel A, Ringwald J, et al. (2008) Preparation of highly concentrated and white cell-poor platelet-rich plasma by platelethpheresis. Vox Sang 95: 20-25.

27. Mazzucco L, Balbo V, Cattana E, Guaschino R, Borzini P (2009) Not every PRP-gel is born equal. Evaluation of growth factor availability for tissues through four PRP-gel preparations: Fibrinet, RegenPRP-Kit, Platelex and one manual procedure. Vox Sanguinis 97: 110-118.

28. Mishra A, Pavelko T (2006) Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. Am J Sports Med 34: 1774-1778.

29. Anitua E, Andia I, Ardanza B, Nordén P, Nordén AT (2004) Autologous platelets as a source of proteins for healing and tissue regeneration. Thromb Haemost 91: 4-15.

30. Stergioulias A, Sotiropoulos D, Stasinopoulos D (2014) The Influence of Dexamethasone with Lidocaine Hydrochloride Iontophoresis in Recreational Tennis Players Suffering from Lateral Elbow Tendinopathy. J Mov Physiother Phys Rehabil 1: 114-01.

31. Cullinan FL, Boocock MG, Trevelyan FC (2014) Is eccentric exercise an effective treatment for lateral epicondylitis? A systematic review. Clinical Rehabilitation 28: 3-19.