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

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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; Autologus 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)	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	

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.

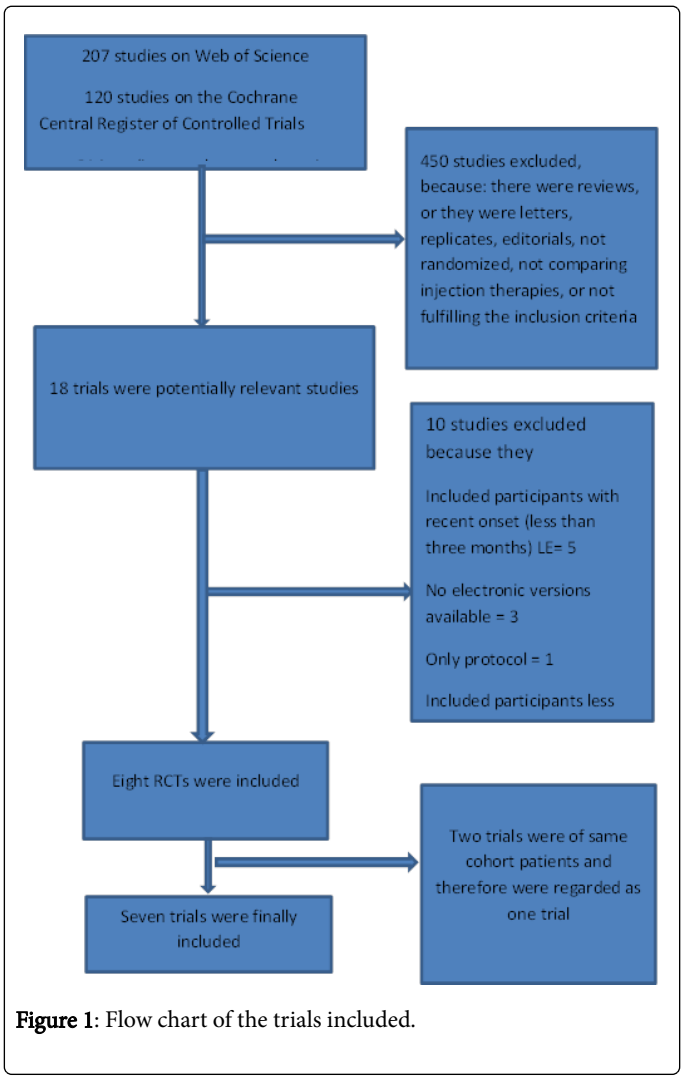

Figure 1: Flow chart of the trials included.

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

hydrocortisone (25 mg) [16,17]. These formulations not only differ in their duration of action, but also differ in their water solubility and their propensity to form particulate aggregates [18]. However, clinical outcomes may be unaffected by different formulations [19].

Different concentrations and forms of local anaesthetics have been described in the literature, but lidocaine (1–2%, without epinephrine) is utilised most commonly [17]. Nevertheless, researchers have not noticed any considerable difference in outcomes based on the concentration or type of local anaesthetic used [17]. In addition, lidocaine has been shown to have inhibitory effects on the proliferation of tenocytes in an in vitro study [20].

A peppering technique was used in all of the three trials which applied PRP and CSI, but two trials [11,12] did not specify the number of penetrations performed in the CSI arms. Most researchers in these four trials performed a single skin entry with 5 to 7 peppering penetrations. In 2011 a study was conducted comparing the single-injection with the peppering technique [21]. They concluded that the single-injection technique has a better outcome than the peppering technique. However, participants of this study were not blinded to the technique received and there was a high loss to follow up. It has been suggested that the peppering technique will lead to bleeding and create channels in the degenerative myxoid tissue of LE which could stimulate healing [22].

The number of CSI treatments to be given to an LE patient is another topic debated in the literature. Most researchers allow the use of 2 to 3 injections at two week intervals. However, up to 20 injections have been reported, this can increase side effects such as skin atrophy and depigmentation [2].

Two trials prepared PRP for their participants using similar techniques [10,11], Approximately 3 mL PRP was obtained for each patient in these two trials, and then to achieve a physiologic pH, the prepared PRP was buffered using 8.4% sodium bicarbonate. The differences in the study conducted in 2015 from the other two trials are that: they collected 20 ml from the participants of PRP treatment arm, used acid citrate as an anticoagulant, the speed of the centrifuge was set at 1500, 2 ml was injected, and there was no mention of the use of local anaesthetic [12].

Methods of isolation or centrifugation, single-spin (one step) and double-spin (double step) separation techniques; type and operation of the collecting tube; speed of the centrifuge; and other processes of production, such as the use of activating agent, can result in different amounts of platelets, White Blood Cells (WBCs), and growth factors in PRP preparations [23,24]. Furthermore, the variations in WBCs and other growth factors were observed in the same individual with repetitive blood draws [23]. Inconsistency in the amount and concentration of WBCs, VEGFs, and PDGFs in PRP samples taken for different purposes have been observed previously [25]. All three trials did not mention the concentration and amount of WBCs, Vascular Endothelial Growth Factors (VEGFs) and Platelet-Derived Growth Factors (PDGFs) obtained from their participants. The function of WBCs depends on their concentration (it has been theorised that WBCs can initiate an inflammatory phase which will subsequently stimulate healing in chronic tendinopathies), and in order to achieve beneficial effects of WBCs in PRP preparations, it is critical to define the amount of WBCs in these preparations [26].

Defining PRP preparations according to platelet count can be difficult as there is no consensus on adequate concentration which is considered to be therapeutic for tissue healing [24]. In the literature, many researchers assume platelets concentrations from 200 × 103 platelets/mL up to 1000 × 103 platelets/mL are considered to have therapeutic effects, which means an increase from 2 to 8-fold from native blood [24,26]. Higher volumes could be biologically unfavourable [24].

A peppering technique was applied to all participants in the three trials, but one trial [12] did not specify the number of penetrations performed. Most researchers in these trials performed a single skin entry with 5 to 7 peppering penetrations according to the technique prescribed in 2006 [27]. A peppering technique will lead to bleeding and create channels in the degenerative myxoid tissue of LE, which could stimulate healing [22].

This microtrauma created by peppering at the site of injury may have a clinical benefit, and hence it could be difficult to prove that the observed results in the PRP treatment arms are due to the PRP injections and not from the bleeding caused by the peppering technique [1].

In order to ascertain the effects of dry needling and its possible confounding effect with PRP injections, a study conducted an RCT, comparing dry needling with PRP injections in 28 patients for around 19 months [28]. The difference in VAS scores at 2 and 6 months between both groups was not significant, with slightly higher scores in the PRP group. However, the small number of participants might have impacted the power to determine a difference. Future large RCTs will be of importance in determining any differences.

Only one trial, out of three trials that applied PRP and CSI 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 amount of growth factors. Moreover, the amount of growth factors that can released from PRP preparations varies considerably, from 1 to 25-fold that of native blood [12].

In the trails 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

study [30]. Furthermore, the use of blood-based preparations has produced increasing levels of post-injection pain in comparison to CSI [1]. Therefore, many clinicians still use local anaesthetics with different injections in LE including ABI [31].

In addition to heterogeneity with trials comparing PRP and ABI, differences in post-injection policies, particularly the physiotherapy management, for example physiotherapy rehabilitation may have confounded results. Physiotherapy modalities such as eccentric loading can improve clinical outcomes in resistant cases of LE, either in isolation or as an adjunct to other therapies including ABI [31].

The Cochrane Collaboration's tool for assessing risk of bias and the Sign 50 critical appraisal tool have been applied to all trials in this review (Appendix).

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 have 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.

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