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REVIEW ARTICLE

Platelet—Rich—Plasma Injections in Treating Lateral Epicondylosis: a Review of the Recent Evidence

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Abstract Lateral epicondylosis is common, with various treatment modalities. Platelet—rich—plasma injections from autologous blood have recently been used in centres worldwide for the treatment of tennis elbow. We review and present the recent published evidence on the effectiveness of PRP injections for lateral epicondylosis. Nine studies met our inclusion criteria including 6 RCT's for the purpose of analysis. PRP injections have an important and effective role in the treatment of this debilitating pathology, in cases where physiotherapy has been unsuccessful.

Keywords PRP · Platelet—Rich—Plasma · Tennis elbow · Lateral epicondylosis · Lateral epicondylitis

Introduction

Lateral epicondylosis [1] affects 4 to 7 people per 1000 per year [2]. It is a painful and debilitating condition, caused by angiofibroblastic hyperplasia of the tendinous origin of extensor carpi radialis brevis (ERCB) muscle [3]. Multiple treatment modalities exist, including physiotherapy, bracing, injection therapy, extracorporeal shock wave therapy, ultrasound, acupuncture and open or arthroscopic surgery [4]. Varying degrees of evidence are available to support each treatment type.

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Corticosteroid injections have been the mainstay of treatment for chronic lateral epicondylosis for many years. However, despite short term effectiveness there are no studies proving significant long term resolution of symptoms [5]. Well recognised side effects of corticosteroid treatment are to be considered also, such as altered skin pigmentation and subcutaneous atrophy.

Other recognised injection treatments consist of autologous blood [6], platelet-rich plasma (PRP) [7], hyaluronan gel [8], and botulinum A injections [9]. The literature suggests that the use of PRP injections, to aid and expedite healing of tendons and ligaments, is increasing [10–12], especially in the treatment of lateral epicondylosis [13]. However, its use is not solely limited to this condition with positive results being reported in the literature for its use in chronic plantar fasciitis [14]. PRP has also been shown to improve osteochondral healing both macro and microscopically, including following mosaicplasty, albeit in rabbit models [15, 16]. Multiple PRP injections may have a role in chronic patellar tendinopathy, though its effect on those with a longer history is yet to be established [17].

Despite a study in 2006, showing a significant reduction in pain, following PRP injection in chronic lateral epicondylosis [7], a rating of "unknown effectiveness" was given to PRP in a Clinical Evidence Systematic Review published in 2011 [13]. At the time of the literature search for the review, in 2009, no Randomised Controlled Trial's (RCT) had been performed. Since this time multiple studies have been performed with promising results (see Table 1). Recent NICE guidelines in 2013 suggest the evidence remains inadequate, and that PRP and autologous blood injections should only be used in a research setting [18].

We review and present the recent published evidence on the effectiveness of PRP injections for lateral epicondylosis and discuss the findings.

Table 1 Previous RCT's comparing PRP with other treatment options

Author	Year	No	PRP Injection vs	Comments
Mishra A K	2013	225	Active control	Significant pain improvement at 24 weeks compared with control group
Gosens	2011	100	Cortico-steroid (CCS) Injection	Significant improvement VAS and DASH at 2 years
Krogh	2013	60	Glucocorticoid & Saline	No significant improvement in pain at 3 months compared to saline or CCS.
Thanasas	2011	28	Autologous whole blood Injection	Significant pain improvement at 6 weeks. No significant difference in function
Creaney	2011	150	Autologous blood injection	No significant difference at 6 months. Higher conversion rate to surgery in ABI group
Peerbooms	2010	100	Cortico-steroid (CCS) Injection	Significant decrease in pain and increase in function compared to CCS

Materials & Methods

The electronic databases Pubmed/Medline and Google Scholar were searched. Keywords and MeSH terms used were "PRP", "platelet-rich plasma", "lateral epicondylitis", "lateral epicondylosis" and "tennis elbow". Inclusion criteria included all English language human clinical trials published in the last 10 years. All study design types, apart from case reports, were included. Nine studies met our inclusion criteria, including 6 RCT's.

Results

A total of 6 RCT's were found comparing PRP injections with other treatment modalities (Table 1).

The largest RCT to date, published by Mishra et al. in 2013, compared PRP with an active control group and recruited 225 patients [19]. This followed a previous pilot study by the lead author in 2006, which showed a 93 % reduction in pain, at mean follow up of 25 months, when injecting PRP [7]. The original study however, was underpowered and not randomized.

Mishra's recent work is a well designed double blind, prospective, multicenter, controlled trial which followed strict inclusion and exclusion criteria. PRP was prepared using the GPS centrifuge system (Biomet Biologics, Warsaw, Indiana). 2–3 mls of type 1 PRP was injected into ECRB tendon in a peppered fashion with 5 penetrations through a single skin portal [19]. In the control group needling was performed using the same method, with bupivacaine instilled rather than PRP. VAS and The Patient-Related Tennis Elbow Evaluation (PRTEE) were recorded as primary outcome measures at 12 and 24 weeks. At 24 weeks follow up the PRP group had a 71.5 % improvement in VAS scores, compared with 56.1 % in the control group, which was a statistically significant difference. However, only 119 out of 225 patients had available data at 24 weeks, making the study underpowered and unreliable at this time point. There were no recorded significant differences between the two groups in PRTEE scores. Success was determined by a >25 % reduction in pain score, 83.9 % of the PRP group reached a successful outcome at 24 weeks compared with 68.3 % in the control group. Rehabilitation was not standardized across the trial centers, a weakness that the authors recognize.

Three RCT's have compared PRP with steroid injections. Gosens and Peerbooms followed 100 consecutive patients for 2 years and presented their findings in two separately published papers [20, 21]. The study was performed at two centres and was double blinded. VAS and DASH scores were used as outcome measures [22]. Patients who suffered symptoms for longer than 6 months, and experienced pain of at least 50 on VAS, were included. All patients in the trial had received previous treatment with either immobilization, steroid injection and/or physiotherapy. Power calculations were met in both treatment arms at both 1 and 2 year follow up. As in Mishra's study, the Biomet Bologics centrifuge and PRP collection system was used to collect 3 mls of PRP, bupivacaine hydrochloride 0.5 % with epinephrine (1:200000) was added to the mixture. 1 ml of type 1, unactivated PRP or corticosteroid (kenacort 40 mg/ml triamcinolone acetonide with bupivacaine/epinephrine) was injected to the most tender point along the lateral epicondyle. The remaining 2 mls of the solutions were injected in a peppered fashion 5 times to the common extensor tendon, through one skin penetration. Unlike Mishra's study, all subjects followed a standardized rehabilitation programme including an eccentric muscle and tendon stretching programme. At 4 weeks follow up PRP treated patients showed a mean improvement of 21 % in VAS scores, steroid treated patients showed a 33 % improvement. Steroid treated patients also showed greater improvement on the DASH score at 4 weeks. The findings at 8 weeks showed increased improvement on both VAS and DASH scores for steroid injections compared to PRP, however none of the findings, at 4 or 8 weeks, were statistically significant. At 12 weeks, PRP treated patients continued to progressively improve with regards to VAS and dash scores, whereas it was reported that steroid treated patients actually declined. This trend continued at both 6 months, 1 and 2 year follow up, with high levels of significance. Gosen's and Peerbooms studies are well designed, and statistically affirm PRP injections to be superior to steroid injections for the treatment of lateral epicondylosis at 2 year follow up. The study suggests superior short term pain relief with steroids, although this finding was

not significant. In this study the DASH scores in the corticosteroid group were on average no better at 26 weeks than at baseline when re-interventions were excluded.

A further RCT published by Krogh et al. in 2013 compared PRP with steroid, and saline injections in a randomized, double-blind, placebo-controlled trial [23]. The Biomet Biologics centrifuge system was again used to prepare the PRP solution. A peppering technique consisting of 7 perforations was used to insert 3–3.5 mls of type 1 PRP in an even distribution throughout the common tendon origin, through one skin perforation. The same technique was used for the saline injection. The steroid injection consisted of 1 ml triamcinolone 40 mg/ml+2 mls lignocaine 10 mg/ml. This was injected to the deepest aspects of the common tendon origin, there is no mention of peppering with regards to injecting the steroid. A standardized rehabilitation programme was advised, including a standard tennis elbow stretching and training programme for all patients. The primary outcome measure was a change in pain intensity after 3 months, using the pain section of the PRTEE questionnaire. Secondary outcome measures included changes in functional disability, ultrasound changes in colour Doppler and tendon thickness, adverse effects, and pain. A power calculation was based on an anticipated 12 month follow-up, however due to a high dropout rate 3 month data was chosen post hoc, as the primary outcome. Twenty patients were recruited in each arm of the study and all were available for 3 month data collection. At 3 months the study found no statistically significant difference between the groups in terms of reduction of pain or function. The results of the study indicate that the short term increase in pain (flare reaction) following injection was greater in the PRP group than the corticosteroid group. The median duration of post-injection pain was 2–3 weeks for PRP and <1 week for steroids. There was a significant difference in tendon thickness noted at 3 months between PRP and steroid, with steroid reducing the thickness more. It is noted that 20 % of PRP patients contacted the department in the first few days following injection complaining of pain, compared with just one patient treated with steroid. Skin atrophy was seen in 15 % of the steroid group. The authors conclude that if a treatment has a late onset then it would not have been recognized in this study, such as that effect of PRP found in Gosen's and Peerbooms work. Unlike the previously mentioned RCT's, Krogh's study included patients who had not failed any previous treatments and had only suffered 3 months of symptoms. Also, the full data set, published as an addendum, shows a high dropout rate in the steroid group after 3 months, with a high percentage of crossover. The pain scores also rebound in the steroid group after 3 months, which is a trend noticed in other studies. The authors conclusions that corticosteroid is superior to PRP may be misleading.

There are 2 published RCT's comparing PRP with autologous whole blood. The first of these, published in 2011 by Creaney et al., included 150 patients who had previously failed conservative physiotherapy [24]. Outcome was based on the PRTEE score and measured at 1,3 and 6 months. A reduction of >25 points on the scale was classed as a clinically significant improvement. A power analysis required 44 patients in each arm of the study. In this study, unlike the other RCT's, patients who had received previous treatment other than physiotherapy (steroid injections, dry needling or previous blood injections) were excluded. PRP was prepared using an LC6 centrifuge (Sarstedt, Numbrecht, Germany) spun at 2000 g for 15 min. This preparation gave a concentration of platelets at a mean of 2.8x higher than baseline. The affected area was infiltrated with 2 mls of bupivacaine and then injected with PRP or autologous blood. There is no mention in the methods section of the study if the PRP was activated or had WBC removed, we assume this was type 1 PRP. All injections were performed under ultrasound guidance and injected into hypoechoic clefts within the tendon. No dry needling was performed, the authors state this was done in an attempt to minimize trauma. Patients received 2 separate injections, with a 1-month interval. Patients in both groups were given general post-procedure advice but no standardized rehabilitation protocol. Results show a success rate of 72 % in the autologous blood group and 66 % in the PRP group, the difference between the two treatments was not statistically significant. The study reports that patients who had a successful outcome in the autologous blood group experienced a mean improvement of PRTEE score of 46.8 compared with 35.8 in the PRP group. It must be noted however, that 20 % of patients who received autologous blood went on to surgery before the end of the study compared to only 10 % in the PRP group. The authors suggest caution in concluding a true difference between the groups at 6 months. The study shows that both PRP and autologous blood produce a significant decrease in pain levels at 6 months in up to 70 % of cases. The lead investigator wasn't blinded in this study, which could introduce an element of bias. This study also stopped at 6 months follow-up, it would have been interesting to see results at 1 year.

Thanasas also compared PRP and AWB, with a smaller number of patients [25]. Twenty-eight patients were included in the study, 14 in each arm, and like Creaney's study, ultrasound was used to guide injection. A standardized rehabilitation program was followed. All patients had suffered with lateral epicondylosis symptoms for no less than 3 months, however the study does not report whether any previous conservative physiotherapy had been attempted. The GPS III centrifuge system from Biomet was used for PRP preparation. This gave a product of type 1A PRP. PRP extraction was tested for platelet count in two healthy individuals, and showed an average of 5.5x above baseline. This was a single blinded study with patients being informed of the treatment they received. Outcome measures were VAS and Liverpool Pain score, and were recorded at 6 weeks, 3 and 6 months. A power analysis required 13 patients in each group. All patients except 1 were available for follow up at 6 months. Nine out of

14 in the PRP group, complained of local pain and discomfort at the injection site in the first week, compared with 4 out of 14 in the AWB group. At 6 months both groups had significant reductions in pain scores, with an increased reduction in pain in the PRP group throughout treatment. However, the difference between the groups at 6 months was not statistically significant. Functional scores improved in both groups throughout the trial, however no significant difference was found between groups. The Liverpool elbow score was used to assess function, the authors conclude that due to components of the score measuring range of movement and ulna nerve symptoms (which should not be affected by tennis elbow), any significant change in symptoms due to tennis elbow may no be accurately shown.

Two non-randomized, prospective studies report the benefits of PRP. Hechtman et al. reported the results of 30 patients (31 elbows) treated with PRP, the cohort group consisted of a mixture of both medial and lateral epicondylitis, with lateral epicondylitis making up 23 of the cases [26]. All patients had suffered from symptoms for >6 months and had failed conservative treatment with both physiotherapy and steroid injections. The study reports that 90 % of patients experienced significant pain relief, measured as a>25 % decrease in pain scores. As reported in Mishra's study in 2013, pain scores continued to improve, up to a mean follow up of 25 months [27]. However, 38 % of patients did complain of some residual pain at last follow up despite an improvement overall. A statistically significant decrease in functional activity scores was shown at 3, 6 and 25 month follow up (mean). Patient satisfaction scores increased over the length of the study and were significant at 6 months and last follow-up. Two patients in the study opted for surgery at 1 month follow up, both were competitive sports players. Of the patients who remained in the study, none went on to surgery.

A further prospective study, by Chaudhury et al. used sonographic assessment as the outcome measure [28]. This was a pilot study and only included 6 patients. The aim of the study was to determine if PRP is associated with improved tendon morphology and increased vascularity. PRP was injected under ultrasound guidance to the origin of the common extensor tendon, targeted to the area of maximum tenderness and poorest sonographic appearance. A peppering technique was used. US appearance was compared with baseline findings (pre injection) at 1 and 6 months. A contrast agent was injected intravenously. Images were taken at rest and after a standardized set of wrist exercise to recruit increased blood supply to the area. Results showed 3 out of 6 patients had improved morphology compared to baseline at 3 months, and at 6 months all patients remaining in the study had improved morphology, however this finding was not statistically significant. The study suggests that PRP increases vascularity to the common extensor origin, which may precede improved tendon morphology. However, no definite conclusions can be made from such a small study.

Table 2 Platelet-rich plasma classification system

TYPE	WHITE BLOOD CELLS	ACTIVATED?
1	Increased over baseline	No
2	Increased over baseline	Yes
3	Minimal or no WBC's	No
4	Minimal or no WBC's A: Platelets >5x baseline B: Platelets <5x baseline	Yes

A retrospective study performed by Mautner et al. in 2013 reported on 30 patients following PRP [29]. In this study, 93 % of patients reported at least moderate improvements in symptoms with an 81 % decrease in VAS score at an average of 15 months follow up time. Ultrasound was used to guide the PRP injections. This study included other tendinopathies treated with PRP including patella, Achilles tendon, and rotator cuff, and reported good outcomes in these subgroups.

Discussion

The natural history of tennis elbow has been shown to be self-limiting in the majority of sufferers, with most recovering within 1 year with conservative management [30]. The most effective treatment for chronic lateral epicondylitis, however, is argued amongst experts.

It is our view, after review of the literature, that PRP injections have an important and effective role in the treatment of this debilitating pathology, in cases where physiotherapy has been unsuccessful.

There are numerous studies suggesting successful outcomes with physiotherapy for acute cases, with up to 90 % resolution. Previously, cases that persisted despite physiotherapy have been treated with corticosteroid injections. Steroid injections are reported to give short-term pain relief, however the proven recurrence rates and complications (including dermal depigmentation, subcutaneous atrophy, and a theoretical risk of increased tendon rupture) should limit their use.

PRP has been shown to provide a continuing long-term benefit in cases of chronic lateral epicondylosis, in the recent literature. It is superior to AWB injections and placebo/dry needling procedures. PRP has very few complications. The only consistent adverse effect reported is an increase in pain at the injection site compared to other injection types in the first few weeks following treatment. In our experience reducing the volume of injection from 3 to 1 ml of PRP reduces the pain of injection without compromising efficacy. An audit of our own practice with 1 ml PRP injection under local anaesthetic using a peppering technique (prepared with the Biomet Recover System) with post-injection physiotherapy including an eccentric loading regime has demonstrated an 85 % success

rate at 3 months post injection in a group of patients who had failed other treatments.

There remain, however, some unanswered questions. There are various preparation systems available commercially for PRP, a mixture being used in the studies reviewed. Each system comes with a manufacturer recommendation for rpm and time for which the whole blood is to be spun. These different preparation methods can give rise to various concentrations of platelets (from baseline). There is some evidence to suggest concentrations 2.5x baseline increase stimulation of fibroblasts, compared to higher concentrations [24]. The most frequent preparation system in our review was the Biomet Biologics system, which gives concentrations of approximately 5.5x baseline. All studies using this system reported good results. It would be interesting to directly compare different concentrations of PRP, although logistically a study of this nature would be difficult to set up.

Mishra, in an earlier study, devised a classification system for the different types of PRP [19]. This classification is based on the platelet concentration, the presence or absence of white blood cells, and whether or not the PRP has been activated with exogenous thrombin or calcium chloride [19]. Each type is then further divided into subtypes A or B based on platelet concentration (Table 2). Most of the studies reviewed injected type 1A PRP. There are no clinical studies to our knowledge comparing different classes of PRP and this may have important implications for the type of injury being treated. Thanasas et al. hypothesize that the increased presence of white blood cells in PRP concentrate, may lead to a more intense inflammation response than other injection types, accounting for reported effects of increased pain following PRP injection.

Post-procedure protocol may affect the outcome of the PRP treatment, again there are no studies comparing different protocols following PRP, with good results reported in both studies with standardized protocols and those without. Some studies do not mention whether patients were discouraged against NSAID's following injection, which also may affect outcome. Alpha granules in platelets contain growth factors (TGF-b, VEGF, PDGF, EGF) and these factors enhance the recruitment, proliferation, and differentiation of cells involved in tissue regeneration. Inflammatory mediators released by cells during the peppering technique activate these growth factors [25]. If NSAID's are taken by the patient prior to, or following injection, the activation of growth factors may be decreased.

Surgery offers good results for chronic lateral epicondylitis, with a recent study reporting over 90 % good to excellent outcomes at nearly 10-year follow-up. However surgery is not without risk, in terms of scar, infection and neurovascular problems. If PRP therapy could be used as an alternative, then we feel this option would present a safer option to patients and may offer a more cost effective alternative to the healthcare system. The level of evidence currently available for use of PRP differs considerably for the various studies performed. However, the recent RCT's we have discussed suggest a benefit of PRP versus steroid injections at level II evidence. Further, larger studies may consolidate these findings as PRP is more frequently used.

Compliance with ethical standards Conflict of Interest: The authors declare that they have no conflict of interest. This article does not contain any studies with human participants or animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study.

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