



Clinical effectiveness of Platelet Rich Plasma injections for Epicondylalgia

Evidence Review

A review of the clinical effectiveness of platelet rich plasma injections for epicondylalgia

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EXECUTIVE SUMMARY

Epicondylalgia, also known as epicondylitis or tennis or golfer's elbow, is a common debilitating condition. Epicondylalgia is pain in an epicondyle of the humerus or in the tendons or muscles originating from it. The condition usually arises from resisted use of either the extensor or flexor muscles of the wrist and can be associated with occupational tasks or sports such as tennis or golf, which require forceful and/or repetitive activity. Overall the economic burden of epicondylalgia is high resulting in significant loss of work days and reduced work capacity.

Recently, platelet rich plasma (PRP) has been the focus in the field of musculoskeletal medicine. PRP, an autologous blood product, has three-to-five fold higher platelet count and is postulated to promote tendinous healing through release of growth factors.

An Evidence Review on the clinical effectiveness of PRP injections for epicondylitis was conducted by the National Trauma Research Institute (NTRI) through ISCRR in 2014.¹ The review included two randomised controlled trials (RCTs) that evaluated the effectiveness of PRP injections compared with placebo and one RCT that compared the effectiveness of Autologous Whole Blood (AWB) with saline injection plus lidocaine. The Evidence Review concluded that there was insufficient evidence to validate the use of PRP or AWB in clinical practice in patients with epicondylitis.

WorkSafe Victoria (WSV) commissioned this current Evidence Review to provide an updated review of the clinical effectiveness of PRP injections on epicondylalgia.

The key questions, developed in consultation with WSV, were:

1. What is the effectiveness of autologous PRP injections on persistent pain, function, quality of life, return to work, medication use and healthcare utilisation in people suffering from epicondylalgia?
2. Are there any potential risks or harms from the use of autologous PRP injections when used in epicondylalgia?

Method

A systematic review of evaluation studies that investigated the effectiveness of PRP compared with placebo in patients with persistent epicondylalgia was conducted in October 2018. Another search was conducted in February 2019 to identify any new studies published since October 2018.

Key findings

The key findings from the published literature on the effectiveness of autologous PRP injections on persistent pain, function, quality of life, return to work, medication use and healthcare utilisation in people suffering from epicondylalgia are presented below.

Evidence from five RCTs investigating PRP was mixed and does not support the use of PRP for epicondylalgia with any confidence.

- Five primary studies that evaluated the clinical effectiveness of PRP compared to normal saline, dry needling or anaesthetic have been published since April 2014.
- No systematic reviews were identified that evaluated the clinical effectiveness of PRP compared to saline, dry needling or anaesthetic since April 2014.
- The two main outcome measures reported in the published studies were pain and functional status.
- Three studies compared PRP injections with normal saline and two studies compared PRP with anaesthetic.

- Evidence from three studies that compared PRP injections with normal saline reported mixed effects. One of the three primary studies that compared PRP injections with normal saline demonstrated that PRP injections were significantly more effective than normal saline injections in the intermediate-term (6 months). A longer term study found PRP treatment was not more effective in reducing pain at 12 months compared with normal saline. The differences in the outcome of the intermediate and long-term studies (6-12 months) varied possibly due to factors other than PRP injections. One study reported no significant difference in pain relief between the PRP interventions (leukocyte-rich PRP and leukocyte-poor PRP) compared with normal saline at 8 weeks.
- Evidence from two studies comparing PRP injections with anaesthetic reported mixed results. In one study, PRP injections significantly reduced pain and improved elbow function at 12 months. However, there was no statistically significant evidence of PRP effectiveness at 6 months after injection in another study. The difference in the outcomes of the interventions in two studies could possibly be due to factors other than PRP injections.
- Overall, although some research indicated that PRP had positive outcomes in the intermediate (6 months) to longer term (12 months), the evidence from three of the five RCTs indicated that PRP was not significantly better than saline or anaesthetic up to 6 months post-injection, thereby limiting its usefulness.
- There is lack of data about the effectiveness of PRP injections on quality of life, return to work, medication use and healthcare utilisation outcomes.

There were no serious risks or harms reported from the use of autologous PRP injections when used to treat epicondylalgia, indicating that PRP injections are safe to use in patients with epicondylalgia.

- Evidence indicated that PRP injections are safe to use in patients with lateral epicondylalgia.
- No serious adverse effects were reported in four of the five studies.
- Recurrence of pain symptoms was reported in one study.

Overall, there is insufficient evidence to confirm the effectiveness of PRP injections for epicondylalgia compared with placebo. More research is needed to demonstrate the effectiveness of PRP injections.

INTRODUCTION

Epicondylalgia, or epicondylitis, commonly known as tennis elbow (lateral epicondylitis) or golfer's elbow (medial epicondylitis), is a common debilitating condition.² The pain is either in the medial (inside) or lateral (outside) epicondyle (rounded projection at end of the bone) of the humerus or in the tendons or muscles originating from it.

Lateral epicondylalgia (LE) affects 1-3% of the population,³⁻⁶ affecting men and women equally, mainly in the age range 35 – 55 years.⁵ The condition usually arises from overuse of either the extensor or flexor muscles of the wrist. Lateral epicondylalgia can be associated with heavy physical work^{7,8} or sports such as tennis or golf, which require forceful and/or repetitive activity; whereas keyboard use, overhead work, and hand transmitted vibrations are also considered as risk factors.^{2,7} Medial epicondylitis affects 1.9% of the general population and is more common in women compared to men. It is significantly associated with forceful activities among men and with repetitive movements of arms among women.⁹

Overall the economic burden of epicondylalgia is high, resulting in significant loss of work days and reduced work capacity in 5% of affected working-age adults.¹⁰

Numerous treatment modalities such as non-steroidal anti-inflammatory drugs and corticosteroid injections have been used to treat epicondylalgia, but recently platelet rich plasma (PRP) has been the focus in the field of musculoskeletal medicine.¹¹ PRP injections involve taking blood from the patient and separating the plasma from the red blood cells using a centrifuge and then injecting the plasma component back into the patient. On average, PRP has a three-to-five fold higher platelet count compared with whole blood and is rich in leukocytes. PRP is postulated to promote tendinous healing through release of growth factors.¹² The growth factors released upon platelet activation stimulates tissue remodelling, wound healing and angiogenesis.¹³

An Evidence Review on the clinical effectiveness of PRP injection for epicondylitis was conducted by the National Trauma Research Institute (NTRI) through ISCRR in 2014.¹ The review included two randomised controlled trials (RCTs) that evaluated the effectiveness of PRP injections compared with placebo and one RCT that compared the effectiveness of Autologous Whole Blood (AWB) with saline injection plus lidocaine. The Evidence Review concluded that there was insufficient evidence to validate the use of PRP or AWB in clinical practice in patients with epicondylitis.

OBJECTIVES

The objective of this Evidence Review was to review the current scientific evidence on the clinical effectiveness of PRP injections for epicondylalgia.

Research Questions

The key research questions developed in consultation with WorkSafe Victoria were:

1. What is the effectiveness of autologous PRP injections on persistent pain, function, quality of life, return to work, medication use and healthcare utilisation in people suffering from epicondylalgia?
2. Are there any potential risks or harms from the use of autologous PRP injections when used in epicondylalgia?

METHODS

An updated systematic search of scientific literature to identify studies that investigated the effects of PRP on persistent epicondylalgia published since April 2014, was conducted in October 2018. Another search was conducted in February 2019 to identify new studies published since October 2018.

Literature search

The specific inclusion and exclusion criteria are described below.

Population

Studies were included for review if they described adults with persistent epicondylalgia. Studies were excluded for patients with tendon conditions for less than three months, or who had acute fractures, trauma, burns or cancer. Paediatric or pregnant patients were excluded.

Intervention

Studies were included if they compared the effectiveness of PRP administered by injection against placebo including saline injections, anaesthetic or dry needling. Studies that compared PRP with corticosteroids were excluded from review as current evidence suggests that corticosteroid injections for treating epicondylalgia may provide only short-term benefit.^{14, 15}

Study designs

Systematic reviews and randomised controlled studies were included for review. Quantitative studies without appropriate controls or low-level evidence studies were excluded.

Outcomes

Primary outcomes included pain (objective and subjective), physical function (objective and subjective), patient impression of change, quality of life, return to work, medication use, healthcare utilisation and/or adverse events.

Search process

The search process is summarised in Figure 1 and further described in Appendix 1.

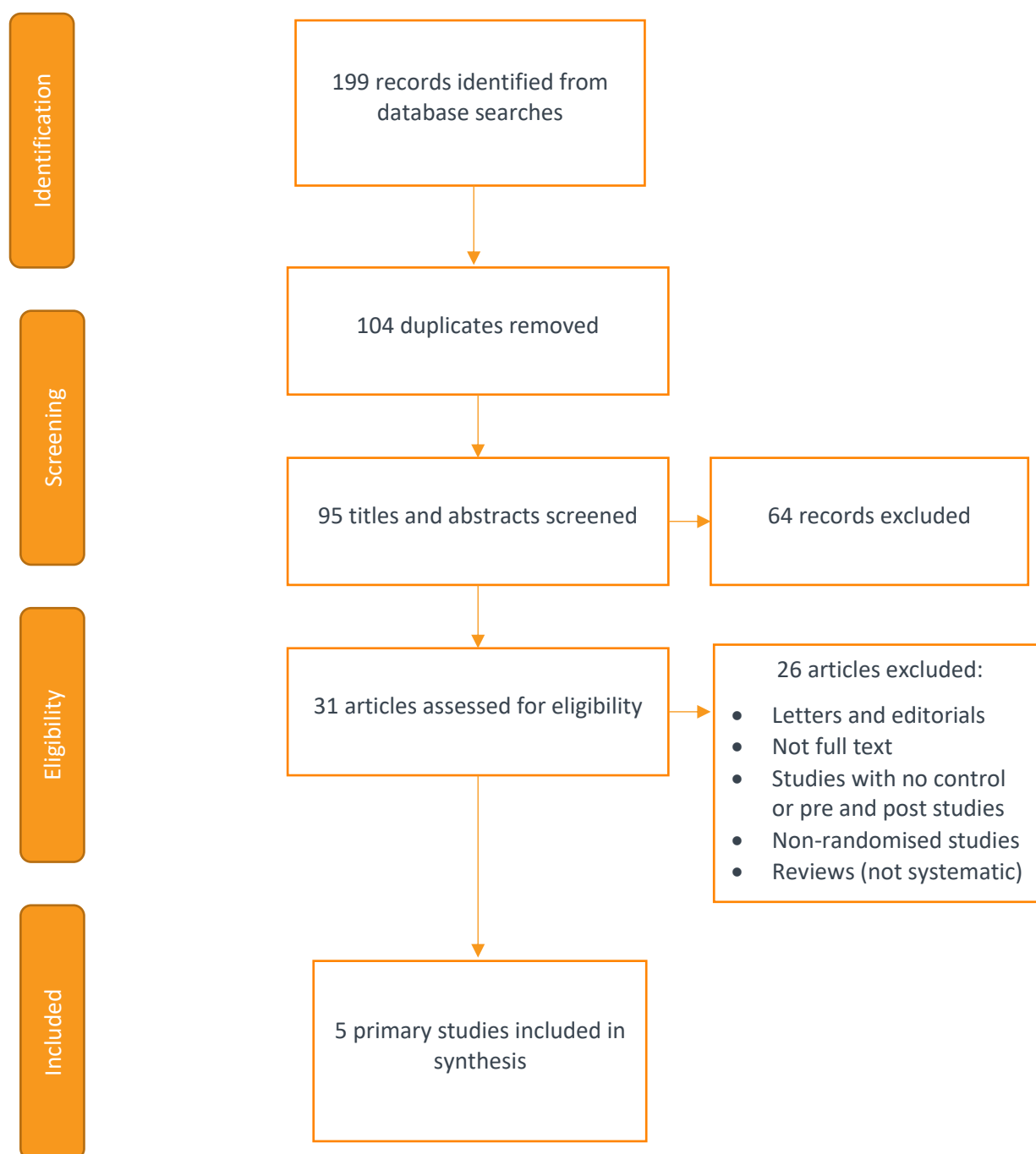


Figure 1. PRISMA diagram showing search process for identifying studies of autologous PRP in patients with epicondylalgia

QUESTION 1. WHAT IS THE EFFECTIVENESS OF AUTOLOGOUS PLATELET RICH PLASMA INJECTION ON PERSISTENT PAIN, FUNCTION, QUALITY OF LIFE, RETURN TO WORK, MEDICATION USE AND HEALTHCARE UTILISATION IN PEOPLE SUFFERING FROM EPICONDYLALGIA?

Key findings

- Evidence from five RCTs investigating the effectiveness of PRP was mixed and inconclusive.
- Three studies compared PRP injections with normal saline and two studies compared PRP with anaesthetic.
- Evidence from three studies that compared PRP injections with normal saline reported mixed effects. One of the three primary studies that compared PRP injections with normal saline demonstrated that PRP injections were significantly more effective than normal saline injections in the intermediate-term (6 months). A longer-term study found PRP treatment was not more effective in reducing pain at 12 months compared with normal saline. The differences in the outcome of the intermediate and long-term studies (6-12 months) varied possibly due to factors other than PRP injections. One study reported no significant difference in pain relief between the PRP interventions (leukocyte-rich PRP and leukocyte-poor PRP) compared with normal saline at 8 weeks.
- Evidence from two studies comparing PRP injections with anaesthetic reported mixed results. In one study PRP injections significantly reduced pain and improved elbow function at 12 months. However, there was no statistically significant evidence of PRP effectiveness at 6 months after injection in another study. The difference in the outcomes of the interventions in two studies could possibly be due to factors other than PRP injections.
- Overall, although some research indicated that PRP had positive outcomes in the intermediate (6 months) to longer term (12 months), the evidence from three of the five RCTs indicated that PRP was not significantly better than saline or anaesthetic up to 6 months post-injection, thereby limiting its usefulness.

Detailed findings

Study characteristics

Five primary studies that investigated the effects of autologous PRP injections compared with saline, dry needling or anaesthetic in patients with lateral epicondylalgia were identified. The five primary studies that assessed the effectiveness and safety of PRP injections for epicondylalgia were undertaken in India,^{3, 4} France,¹³ Brazil¹⁶ and Turkey¹². The study characteristics of the primary studies are shown in Table 1.

The quality of the primary studies were appraised using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for quantitative studies.¹⁷

Intervention characteristics

The treatment for epicondylalgia includes 'wait and see', non-steroidal anti-inflammatory medication, dry needling, physiotherapy, exercise therapy, and PRP injections. For PRP injections, a peppering technique is often used, which involves injecting the needle at one point, then penetrating the tendon at multiple points to achieve an even distribution of the solution.¹⁸

PRP injections varied across the research studies included in this review in terms of frequency, intensity and methodology. The volume of PRP ranged from 1 – 3ml per injection; and one study involved two injections delivered 4 weeks apart. Across studies, there was heterogeneity in PRP preparation methods, dosages, the mechanism of application of PRP injections, and scoring systems for assessment of the effectiveness of PRP injections.

Table 1. Study Characteristics

| Reference (Year) Country | Study design (Follow-up) | Level of Evidence | Cohort; N; % male | Intervention | Key characteristics of intervention | Control | Intensity | Primary (P) and secondary (S) outcome(s) | Quality rating ¹⁷ |
|---|--|----------------------|---|--|--|---|-----------|---|---------------------------------|
| Behera (2015) India ³ | Randomised controlled trial (12 m) | II | Patients with painful and recalcitrant lateral epicondylar tendinopathy of the humerus; 25, 28% | 3 ml of type-4B PRP and 0.5 ml of calcium chloride using peppering technique (n=15) | Injected into the maximum hypo-echoic area of the extensor carpi radialis brevis (ECRB) tendon | 3 ml of bupivacaine and 0.5 ml of normal saline injected in a similar fashion (n=10) | 1 x 3 ml | P: Pain; Elbow function; Activity- related pain | Strong |
| Montalvan (2016) France ¹³ | Single-centre randomized double-blind placebo- controlled study (12 m) | II | Patients suffering of tennis elbow for no more than 3 months; 50; 68% | 2 ml PRP injection guided by ultrasound. First at inclusion and second time at interval of 4 weeks (n=25) | First injected 2ml of 1% lidocaine s.c. followed by injection of PRP (intervention group) or saline (control group) US guided needle advanced into tendons, parallel to tendon fibres and injected into superficial, medium and deep tendon sites. | 2 ml saline solution guided by ultrasound (n=25) | 2 x 2 ml | P: Efficacy (Pain); Safety (side effects) | Strong |
| Palacio (2016) Brazil ¹⁶ | Prospective randomized study (Triple blinding) (6 m) | II | Patients with lateral epicondylitis; 60; NA | Infiltration of 3 ml of platelet- rich plasma (n=20) | Before placement of sterile ocular fields, asepsis and antisepsis procedures were performed using chlorhexidine and then patients received infiltration of 3 ml of platelet-rich plasma | Two control groups 3 ml of 0.5% neocaine (n=20) 3 ml dexamethasone* (n=20) | 1 x 3 ml | P: Pain; Function | Strong |

| Reference (Year) Country | Study design (Follow-up) | Level of Evidence | Cohort; N; % male | Intervention | Key characteristics of intervention | Control | Intensity | Primary (P) and secondary (S) outcome(s) | Quality rating ¹⁷ |
|---|--|----------------------|--|---|--|--|---------------|--|---------------------------------|
| Seetharamaiah (2017) India ⁴ | Randomised (6 m) | II | Patients with unilateral or bilateral tennis elbows for > 3 month; 80; 39% | 1 ml PRP with 0.1 ml of calcium chloride using peppering technique | 1 ml of 2% lignocaine with adrenaline injected at the injection site after giving test dose. After 10 min, proposed injection injected. Site of injection- 5mm distal to LE. Injection given on, and around the tendon, and not inside the tendon. | Two control groups - 1 ml of triamcinolone* 1 ml of normal saline | 1 x 1 ml | P: Pain (VAS and Facial Pain Scale (FPS)) | Moderate |
| Yerlikaya (2018) Turkey ¹² | Double- blinded, randomized, controlled study (8 wks) | II | Patients with LE related pain for > 3 months; 90; 28% | Two intervention groups - 1.5 ml leukocyte-poor- PRP using peppering technique 1.5 ml leukocyte-rich- PRP using peppering technique | Injected at the most sensitive point without ultrasound guidance | 1.5 ml normal saline | 1 x 1.5 ml | P: Pain (VAS); PRTEE; Grip strength; Extensor tendon thickness S: Paracetamol use and post-injection reaction (swelling/redness and/or soreness) | Strong |

Notes: FPS = Faces Pain Scale; LE = Lateral Epicondylitis; PRP = Platelet Rich Plasma; PRTEE = Patient-Related Tennis Elbow Evaluation; RCT = Randomised Controlled Trial; VAS = Visual Analogue Scale; ECRB = Extensor Carpi Radialis Brevis; * = control group not used in our analysis

Effectiveness of PRP interventions – pain relief and functional improvement

This section provides a synthesis of the evidence of effectiveness of PRP injections to relieve pain, improve function and quality of life, reduce medication and healthcare utilisation and assist people with epicondylalgia to return to work. Summary of the findings from primary studies are shown in Table 2.

The two main outcome measures reported in the studies were pain and functional status, which were assessed by several different tools (see Table 6 in Appendix 2, for description).

Five RCTs^{3, 4, 12, 13, 16} investigated the effectiveness of PRP injections compared with placebo. The findings from these studies were mixed and inconclusive.

Of the five good quality RCTs, three studies^{4, 12, 13} compared PRP injections with normal saline whereas two studies compared PRP with anaesthetic. Evidence from one¹³ of three primary studies that compared PRP injections with normal saline demonstrated that PRP injections were not more effective compared with normal saline injections over a long-term follow-up (12 months); whereas another study⁴ reported that PRP was significantly more effective in relieving pain related to lateral epicondylalgia compared with saline over an intermediate-term follow-up (6 months). The differences in the outcomes of the intermediate and long-term studies (6-12 months) varied possibly due to factors other than PRP injections. One study¹² that investigated whether a leukocyte-rich PRP preparation enhanced healing reported improvements in all three study groups (leukocyte-rich PRP, leukocyte-poor PRP and normal saline), with no significant differences between them at 8 weeks follow-up.

The findings from two studies^{3, 16} that compared PRP injections with anaesthetics were also mixed. One study³ showed that leukocyte-poor (type-4) PRP injections enabled significant improvement in pain and elbow function at 12 months compared with anaesthetic, demonstrating PRP injection to be an effective treatment of epicondylalgia. However, another intermediate term study¹⁶ (with 6 month follow-up) reported no statistically significant difference between PRP and local anaesthetic in treating lateral epicondylalgia. The difference in the outcomes of the interventions in two studies could possibly be due to factors other than PRP injections.

The limitations reported in the studies included possible selection bias, short follow-up period, difficulty in translating physical intensity of pain into a scale in millimetres, the exact quantification of the growth factors injected were unknown, and use of paracetamol (due to its analgesic effect) could lead to bias in the VAS assessment (see Table 7 in Appendix 3, for description).

There is a lack of data about the impact of PRP injections for epicondylalgia on quality of life, return to work, medication use and healthcare utilisation outcomes. None of the included primary studies evaluated these outcomes.

Table 2. Summary of key outcomes

| Reference | Intervention effects | Conclusions |
|---------------------------------------|---|---|
| Behera (2015) India ³ | <p>Pain (VAS Score): PRP group: mean VAS score (\pmSD) ↓ from baseline (75.3\pm6.4) to 12m FU (12.7\pm13.9); # Bupivacaine –mean VAS score (\pmSD) ↓ from baseline (75.6\pm7.3) to 12m FU (41.1\pm11.7); #</p> <p>Elbow Function – Modified Mayo clinic performance index for elbow function (MMCPIE): PRP – mean MMCPIE score (\pmSD) ↑ from baseline (63.2\pm10.2) to 12m FU (92.8\pm6.0); # Bupivacaine – mean MMCPIE score (\pmSD) ↑ from baseline (61.4\pm7.4) to 12 m FU (74.7\pm 7.5); #</p> <p>Activity-related pain – Nirschl score: PRP – mean Nirschl score (\pmSD) ↓ from baseline (5.1\pm0.6) to 12m FU (1.2\pm0.61); # Bupivacaine – mean Nirschl score (\pmSD) ↓ from baseline (5.3\pm0.7) to 12 m FU (2.3\pm 0.7); #</p> <p>Between group comparisons – (PRP vs Bupivacaine) Significant improvement in the scores in PRP vs Bupivacaine group</p> <p>VAS for pain - % change from baseline - 83.2% vs. 45.6%; p<0.001 MMCPIE score - % change from baseline - 47.0% vs. 21.7%; p<0.001 Nirschl score - % change from baseline - 76.6% vs. 56.3%; p<0.001</p> | Leukocyte-poor (type-4) PRP injection for recalcitrant lateral epicondylar tendinopathy (LET) enabled good improvement in pain and function. PRP injection is a minimally invasive yet effective treatment for LET. |
| Montalvan (2016) France ¹³ | <p>Global Pain score –VAS score: PRP group: mean VAS score (\pmSD) ↓ from baseline (6.8\pm0.8) to 12m FU (1.7\pm1.5); p<0.001 Saline –mean VAS score (\pmSD) ↓ from baseline (7.0\pm1.0) to 12m FU (1.8\pm2.1); p<0.001</p> <p>Pain - Roles-Maudsley score: PRP – mean R-M score (\pmSD) ↓ from baseline (3.3\pm0.7) to 12m FU (2.3\pm1.1); # Saline – mean R-M score (\pmSD) ↓ from baseline (3.4\pm0.5) to 12m FU (2.2\pm0.9); #</p> <p>Between group comparisons - PRP vs Saline: baseline – 12m FU VAS Score – p =0.63; ns Roles-Maudsley score – p=0.68; ns Pain on ECRB contraction – ↓ 66% vs 48% ; ns Pain on EDC contraction – ↓ 56% vs 36%; ns</p> | Two intra-tendinous ultrasound-guided PRP injections were not more effective than two injections of saline for the treatment of tennis elbow at 12 month follow-up. |

| Reference | Intervention effects | Conclusions |
|---|--|--|
| Palacio (2016) Brazil ¹⁶ | <p>DASH score: PRP: mean DASH score ↓ (45.7 to 10.7) from baseline to 3m FU; # Neocaine: mean DASH score ↓ (49.7 to 16.6) from baseline to 3m FU; #</p> <p>PRTEE score: PRP: mean DASH score ↓ (47.1 to 13.0) from baseline to 3m FU; # Neocaine: mean DASH score ↓ (51.7 to 15.5) from baseline to 3m FU; #</p> <p>Between group comparisons (PRP vs normal saline) DASH score – p=0.41; ns PRTEE score – p=0.66; ns In both groups - proportion of improvement of symptoms was the same. In both groups - improvement in 90% participants.</p> <p>No statistically significant difference between the treatments over 6m follow-up.</p> | No statistical evidence that PRP might provide better treatment compared to local anaesthetic, in treating lateral epicondylitis of the elbow. |
| Seetharamaiah (2017) India ⁴ | <p>Pain (VAS Score): PRP: mean VAS score ↓ significantly (47.7 to 24.5) from baseline to 6m FU (↓ 49%); p<0.001 Saline: mean VAS score ↑ (41.3 to 66.9) from baseline to 6m FU (↑ 62%); #</p> <p>Pain (FPS score): PRP group: mean FPS score ↓ significantly (45.8 to 22.9) from baseline to 6m FU (↓ 50%); p<0.001 Saline: mean FPS score ↑ (44.5 to 68.8) from baseline to 6m FU (↑ 55%); #</p> <p>Saline control group showed worsening of results in VAS and FPS scores 6m.</p> <p>Between group comparisons (PRP vs normal saline) VAS scores at 6m FU - p<0.001 FPS score at 6m FU - p<0.001 PRP showed statistically significant improvement in pain scores (VAS and FPS scores) than placebo at 6 months.</p> | A single injection of PRP to relieve the pain of LE was significantly better than placebo over a 6 month follow-up. |
| Yerlikaya (2018) Turkey ¹² | <p>Pain (VAS score - nocturnal) -LP-PRP: mean VAS score (±SD) ↓ significantly from baseline (7.4±2.1) to 8 wks FU (3.4±3), p<0.001 LR-PRP: mean VAS score (±SD) ↓ significantly from baseline (6.5±2.4) to 8 wks FU (3.2±3.4), p<0.001 Saline: mean VAS score (±SD) ↓ significantly from baseline (6.8±1.8) to 8 wks FU (3.5±3), p<0.001</p> | Significant improvements in pain scores were reported in all groups; but no significant differences were detected between groups |

| Reference | Intervention effects | Conclusions |
|-----------|---|-------------|
| | <p>Pain (VAS score - motion)</p> <p>-LP-PRP: mean VAS score (\pmSD) ↓ significantly from baseline (8.7\pm1.7) to 8 wks FU (5.2\pm2.9), p<0.001</p> <p>LR-PRP: mean VAS score (\pmSD) ↓ significantly from baseline (7.9\pm1.8) to 8 wks FU (4.3\pm3.2), p<0.001</p> <p>Saline: mean VAS score (\pmSD) ↓ significantly from baseline 8.2\pm1.7) to 8 wks FU (5.3\pm3.1), p<0.001</p> <p>Between group comparison:</p> <p>No significant difference in pain scores between LR-PRP vs LP-PRP vs normal saline groups</p> <p>No significant difference in function, grip, pinch measurement and extensor tendon thickness between LR-PRP vs LP-PRP vs normal saline groups</p> | |

Notes: FPS = Faces Pain Scale; LE = lateral epicondylitis; LP-PRP = leukocyte-poor PRP; LR-PRP = leukocyte-rich PRP; MRI = magnetic resonance imaging; NS = not significant; PRP = platelet-rich plasma; PRTEE = Patient-Related Tennis Elbow Evaluation; RCT = randomised controlled trial; TGF- β = transforming growth factor; VAS = Visual Analogue Scale * ECRB: extensor carpi radialis brevis; * EDC: extensor digitorum communis; # = not stated

QUESTION 2. ARE THERE ANY POTENTIAL RISKS OR HARMS FROM THE USE OF AUTOLOGOUS PRP INJECTIONS WHEN USED IN EPICONDYLALGIA?

Key findings

- Evidence indicated that PRP injections are safe to use in patients with lateral epicondylalgia.
- No serious adverse effects were reported in four of the five studies.
- Recurrence of pain symptoms was reported in one study.

Detailed findings

This section provides a synthesis of the evidence related to risks or harms of autologous PRP injections in patients with epicondylalgia. Table 3 provides a summary of the findings on the safety or adverse effects of PRP injections compared with other treatments.

Based on five primary studies, no serious adverse effects were reported with autologous PRP injections; and they were considered to be safe to use in patients with lateral epicondylalgia. Of the five studies, one study¹³ reported mild side effects in the PRP group including local cutaneous allergic reaction in 8% of participants; and pain during and after injection in 16% of participants, however the symptoms disappeared within 72 hours.

Seetharamaiah *et al.*⁴ reported recurrence of pain symptoms in 13% of participants at six months follow-up.

Table 3. Adverse effects associated with autologous PRP injections

| Reference (Year) Country | Follow-up | Post intervention treatment | Safety/adverse effects |
|-------------------------------------|-----------|---|---|
| Behera (2015) India ³ | 12m | Oral paracetamol (650mg) for pain allowed. After 2 days, standard wrist extensor stretching for 4 weeks under supervision of physiotherapist. After 4 weeks, wrist extensor muscle strengthening exercise. Full activity allowed after 4 months. | None of the patients who received a leukocyte PRP injection complained of increased post-injection pain. LP-PRP helped decrease the injection-related pain and made the recovery more comfortable. No patients had any complications except one patient who had vague giddiness after bupivacaine injection, which resolved within 30 minutes. |

| Reference (Year) Country | Follow-up | Post intervention treatment | Safety/adverse effects |
|---|-----------|--|---|
| Montalvan (2016) France ¹³ | 12m | 1g paracetamol and local ice application allowed. Rehabilitation or physical therapy not prescribed or allowed. | No tendon rupture detected in any group. Side effects did not occur often and were very mild. Commonly reported side effect was pain during and after injection which disappeared within 72 hours – reported by 16% (n=4) of patients in the PRP group and 8% (n=2) in the saline group. 8% (n=2) reported local cutaneous allergic reaction after first PRP injection. 4% (n=1) developed a haematoma after saline injection which disappeared within 3 days. |
| Palacio (2016) Brazil ¹⁶ | 6m | None reported. | None reported. |
| Seetharamaiah (2017) India ⁴ | 6m | Paracetamol was prescribed for pain relief. | Recurrence of pain symptoms at 6 m FU in 13.3% participants. |
| Yerlikaya (2018) Turkey ¹² | 8wks | Use of paracetamol up to 4g/day for pain before and after injection allowed. Exercise program was initiated on second day after injection. Exercise program included 3 sets/day of 10 repetitive range of motion, stretching strengthening and gripping exercise for 4 weeks. | No significant differences were detected between groups in terms of paracetamol use and post-injection reaction. |

SUMMARY AND IMPLICATIONS

This Evidence Review identified the current available evidence on the effectiveness of PRP injections compared with placebo in patients with persistent epicondylalgia. A summary of key findings according to the two guiding review questions is presented below.

Evidence from five RCTs investigating PRP was mixed and does not support the use of PRP for epicondylalgia with any confidence.

- Five primary studies that evaluated the clinical effectiveness of PRP compared to normal saline, dry needling or anaesthetic have been published since April 2014.
- No systematic reviews were identified that evaluated the clinical effectiveness of PRP compared to saline or dry needling since April 2014.
- The two main outcome measures reported in the published studies were pain and functional status.
- Three studies compared PRP injections with normal saline and two studies compared PRP with anaesthetics.
- Evidence from three studies that compared PRP injections with normal saline reported mixed effects. One of the three primary studies that compared PRP injections with normal saline demonstrated that PRP injections were significantly more effective than normal saline injections in the intermediate-term (6 months). A longer-term study found PRP treatment was not more effective in reducing pain at 12 months compared with normal saline. The differences in the outcome of the intermediate and long-term studies (6-12 months) varied possibly due to factors other than PRP injections. One study reported no significant difference in pain relief between the PRP interventions (leukocyte-rich PRP and leukocyte-poor PRP) compared with normal saline at 8 weeks.
- Evidence from two studies comparing PRP injections with anaesthetic reported mixed results. In one study PRP injections significantly reduced pain and improved elbow function at 12 months. However, there was no statistically significant evidence of PRP effectiveness at 6 months after injection in another study. The difference in the outcomes of the interventions in two studies could possibly be due to factors other than PRP injections.
- Overall, although some research indicated that PRP had positive outcomes in the intermediate (6 months) to longer term (12 months), the evidence from three of the five RCTs indicated that PRP was not significantly better than saline or anaesthetic up to 6 months post-injection, thereby limiting its usefulness.
- There is lack of data about the effectiveness of PRP injections on quality of life, return to work, medication use and healthcare utilisation outcomes.

There were no serious risks or harms reported from the use of autologous PRP injections when used to treat epicondylalgia indicating that PRP injections are safe to use in patients with epicondylalgia.

- Evidence indicated that PRP injections are safe to use in patients with lateral epicondylalgia.
- No serious adverse effects were reported in four of the five studies.
- Recurrence of pain symptoms were reported in one study.

Overall, there is insufficient evidence to confirm the effectiveness of PRP injections for epicondylalgia. More research is needed to demonstrate the effectiveness of PRP injections in

comparison to placebo, as much of the research has focused on comparison of PRP with corticosteroids.

APPENDIX

Appendix 1. Literature search process and study classification

Search process

Search strategy

1. Platelet rich plasma.mp.
2. Platelet rich therapy.mp.
3. Platelet.mp.
4. Inject*.mp.
5. Injections, Intra-Articular/ or Intra-articular.mp.
6. Epicondylopathy.mp.
7. Epicondylalgia.mp.
8. Epicondylitis.mp.
9. Epicondylosis.mp.
10. Tennis Elbow.mp.
11. Golfer elbow.mp.
12. Elbow epicondylar tendinitis.mp.
13. 1 or 2 or 3
14. 4 or 5
15. 6 or 7 or 8 or 9 or 10 or 11 or 12
16. 13 and 14
17. 15 and 16
18. limit 17 to (English language and humans and yr="2014 -Current")

One reviewer conducted a comprehensive database search of Medline, Embase, the Cochrane Library, All EBM, and CINAHL using search strategy as mentioned above. The number of outputs from each database are mentioned in Table 4 below.

Table 4. Databases accessed

| Database | Date searched | # of outputs |
|--------------|---------------|--------------|
| Ovid Medline | 11 Oct 2018 | 36 |
| Embase | 11 Oct 2018 | 75 |
| All EBM | 11 Oct 2018 | 25 |
| Cochrane | 11 Oct 2018 | 21 |
| CINHAL | 11 Oct 2018 | 42 |
| Total | | 199 |

Additionally, we searched the reference list of included studies to identify relevant references. We undertook an electronic search for Health Technology Assessments (HTA) and Evidence-based guidelines (EBGs).

Identified titles were retained if they described PRP intervention in adults with persistent lateral epicondylalgia. Following the initial screening process, full text articles were obtained and assessed for eligibility based on specific criteria developed a priori by the ISCRR project team in collaboration

with the WSV project sponsors. Only the RCTs that investigated the effects of PRP compared with placebo in patients with epicondylalgia were included. Specific inclusion and exclusion criteria are described below in Table 5.

Table 5. Specific inclusion and exclusion criteria

| Criteria | Inclusion | Exclusion |
|--------------------------------|--|--|
| Patient/ population | Adults with epicondylalgia/epicondylitis May also look at adults with other persistent tendon conditions and persistent joint conditions, depending on amount of publications for epicondylalgia. | Paediatrics; cancer; pregnancy; acute trauma/burns; tendon or joint conditions for less than 3 months; acute fractures |
| Intervention/ indicator | Platelet rich plasma (PRP) administered by injection | Interleukin-1; hyaluronic acids (because of the possibility of being non-autologous); autologous chondrocyte implantation; autologous chondrocyte implantation combined with hyaluronic acid (non-autologous); bone shaft fractures and fracture healing; plantar fasciitis; used as an exogenous gel; used in reconstructive orthopaedic surgery; dislocations; mesenchymal stem cells; facial rejuvenation therapy |
| Comparison/ control | Placebo (Injection of saline/anaesthetic etc.); Dry needling | Corticosteroid injections |
| Outcomes | Pain (objective and subjective); physical function (objective and subjective); patient impression of change; quality of life; return to work; medication use; healthcare utilisation; adverse events | N/A |
| Setting | Outpatient | Inpatient, Long term care |
| Study Design | SRs, HTA (health technology assessments) and EBGs (evidence-based guidelines), RCTs | Low level evidence |
| Publication details | English language studies on humans | Non English studies, animal studies |
| Time period | Research published since April 2014 for epicondylalgia | Research published earlier than April 2014 for epicondylalgia |

Study Classification

Initially 199 records were identified through database searches. Following removal of duplicates, the titles and abstracts of 95 papers were reviewed manually. After the initial title and abstract screen, 31 papers were identified as potentially relevant. Full text papers were obtained and assessed for eligibility. 26 records were excluded as they did not meet the inclusion criteria for this review.

Five papers that fit the inclusion criteria that investigated the clinical effectiveness of PRP for lateral epicondylalgia in adults were retained for data extraction and synthesis. Information on study

design, sample characteristics, intervention characteristics and study results was extracted for each included study. One reviewer systematically extracted information from all included papers.

Appendix 2. Scales and tools to measure outcomes

Table 6. Scales and tools to measure outcomes

| | |
|--|--|
| Faces Pain Scale (FPS) | Patients' subjective assessment of pain from smiling face image (no pain) to crying face image (worst pain) |
| Visual Analogue Scale (VAS) | Patients' subjective assessment of pain from 0 (no pain) to 10 (severe pain) ² |
| Patient Related Tennis Elbow Evaluation (PRTEE) | Questionnaire related to pain and function: 5 pain items; 10 activity items. Score 0 (best) to 100 (worst) ² |
| Disabilities of the Arm, Shoulder, and Hand (DASH) | Questionnaire related to pain and function: 6 pain items; 24 activity items. Score 0 (best) to 100 (worst) |
| Grip strength | Objective measure of function: Hand dynamometer measures isometric grip force (0-90kg). Grip strength value is average of 6 tests ² |
| Mayo Clinic performance index | Questionnaire related to elbow function: 4 parameters (pain, motion, stability, daily function). Score 0 (worst) to 100 (best) ¹¹ |
| MRI grade improvement | Objective measure of signal intensity within extensor tendon. Grade 0 (low intensity = worst tendon damage to generalised increased intensity = least tendon damage) |

Appendix 3. Strengths and limitations

Table 7. Limitations and strengths identified in studies

| Reference (Year) Country | Limitation/Strengths |
|--|--|
| Behera (2015) India ³ | L: Pre and post-injection MRI should have been performed to measure the affected area for quantification of improvement. The sample size was small and from a single centre and the follow-up period of one year wasn't long enough to demonstrate longer-term (>12m) effectiveness. The study lacked exact quantification of the growth factors being injected. |
| Montalvan (2016) France ¹³ | S: randomization and double-blind design; homogeneous characteristics of the patients who were selected by a single physician, had suffered recent epicondylitis and had never been infiltrated; the injection procedure that was guided by ultrasound and was performed by a unique operator; evaluations were all performed by the same physician. |
| Palacio (2016) Brazil ¹⁶ | L: VAS presents practical limitations in clinical scenarios, due to difficulty in translating the physical intensity of pain into a scale in millimetres. |
| Seetharamaiah (2017) India ⁴ | None reported |
| Yerlikaya (2018) Turkey ¹² | L: (i) Shorter follow-up period and being a single-centre study. As a result, the effect of PRP on tendon repair can alter over time. Therefore, there is a need for long-term studies comparing the effect of LR-PRP and LP-PRP with different preparation techniques. (ii) Use of paracetamol because its analgesic effect could lead to bias in the VAS assessment. |

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