Autologous platelet rich plasma or whole blood injections for epicondylitis

Plain language summary

Epicondylitis or epicondylalgia is commonly known as tennis or golfers elbow. It is a painful condition. The pain can extend from one or both sides of the elbow and into the forearm and wrist.

The condition is often easily fixed. When it does not get better, there are not many proven treatments. One treatment that has been suggested is platelet-rich plasma (PRP) injections and autologous whole blood (AWB) injections.

AWB injection means taking blood from the patient and re-injecting around the patient's sore elbow. PRP injection means taking blood from the patient and then using a special device to remove the red blood cells. The remainder is injected around the patient's sore elbow.

PRP and AWB injections are new and not yet funded by Transport Accident Commission (TAC) or Victorian WorkCover Authority. This review looked at whether the injections work. If they did work they could be offered to TAC clients or injured workers.

Three studies were found. Two compared PRP with fake injections; and one compared AWB with fake injections. These studies did not prove that PRP or AWB is better than fake injections.

None of the studies identified any serious side effects.

national trauma research institute

ISCRR
Institute for Safety, Compensation and Recovery Research

Autologous platelet rich plasma or whole blood injections for epicondylitis:

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MONASH University

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For Transport Accident Commission and Victorian WorkCover Authority

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EVIDENCE REVIEW SUMMARY

Autologous Platelet Rich Plasma or whole blood injections for epicondylitis

Key messages

This review identified two studies evaluating the effect of Platelet Rich Plasma (PRP) and one evaluating autologous whole blood (AWB) against placebo in patients with epicondylitis.

Although it would appear that at three months PRP and AWB is no more effective than placebo with regards to pain and functional outcomes, the evidence is insufficient to confirm this.

The evidence in support of the long-term effectiveness of PRP is low quality. No evidence has evaluated the long-term effectiveness of AWB.

No significant adverse events were associated with PRP or AWB.

Further high quality research is needed to demonstrate the effectiveness of PRP or AWB in epicondylitis.

Purpose

The Transport Accident Commission (TAC) and Victorian WorkCover Authority (VWA) requested a review of the evidence to determine whether PRP or AWB is an effective treatment compared to placebo in patients with epicondylitis. In this review placebo was thought to be the most appropriate comparator given that the effect and safety of other interventions such as corticosteroids is uncertain.

This report sought to answer the following questions:

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

Rationale

To ensure funding decisions made regarding PRP and AWB injections are evidence-based and in the best interests of injured Victorians.

New research relevant to PRP injections is regularly being published. This review is important for VWA/TAC as it provides an independent, thorough search and quality assessment of the peer-reviewed literature in this area. This can then be used to support

funding decisions regarding this treatment. It can also be repeated in the future to incorporate new evidence as it arises.

Methods

Systematic review methods were used. A comprehensive search of Medline, Embase, the Cochrane Library, All EBM, and CINAHL was undertaken in April 2014 to identify relevant research. Reference lists of included studies were also scanned to identify relevant references.

Studies identified by the searches were screened for inclusion. In this review studies were only included if they were systematic reviews, randomized controlled trails or controlled clinical trials that investigated the effects of PRP or AWB compared with placebo in patients with epicondylitis. Studies that met the selection criteria were reviewed to identify the most up-to-date and comprehensive source of evidence, which was then critically appraised to determine whether it was of high quality.

Research findings and implications

There is insufficient evidence to validate the use of PRP or AWB in clinical practice in patients with epicondylitis. Based on this evidence the TAC and VWA may need to consider whether it is feasible to fund these procedures.

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BACKGROUND

Condition

Epicondylitis is a musculoskeletal disorder caused by an inflammation of the lateral (outside) or medial (inside) elbow epicondyle. The condition usually arises from resisted use of either the extensor or flexor muscles of the wrist (1) and can be associated with occupational tasks or sports, such as tennis or golf, which require forceful and/or repetitive activity (2). The prevalence of epicondylitis is highest in people between 45–54 years (3) with lateral being more common (prevalence of 0.7 -1.3 percent) (3-5) than medial (prevalence of 0.3 -0.4 percent) (3, 4).

Overall the economic burden of epicondylitis is high resulting in significant loss of workdays and reduced work capacity (4). In a study conducted in the United States of America non-traumatic epicondylitis (both medial and lateral) had an annual compensable workers' compensation claims incidence of 11.8 per 10,000 full-time employees, resulting in an average of 205 lost working days per claim, and an average annual direct cost of more than $9 million (6).

Management

First line treatment for epicondylitis can include: rest or 'watchful waiting', activity or equipment modification, nonsteroidal anti-inflammatory medication, bracing or physical therapy. If these treatments fail to improve pain and tenderness, second-line treatments such as cortisone injections, prolotherapy, autologous whole blood (AWB) injections, platelet rich plasma (PRP) injections and needling of the extensor tendon origin can be prescribed. If patients continue to report pain and dysfunction despite these measures, surgery is then considered (7).

Treatments in the form of injections using AWB or PRP are increasingly being used in clinical practice (8). Autologous whole blood injections involve taking a small amount of blood from the patient and re-injecting it into and around a damaged tendon or joint; whereas PRP therapy involves separating the plasma from whole blood using a centrifuge and then injecting the plasma component back into the patient (8). Both of these preparations are generally prepared at point-of-care, and can be administered with or without ultrasound guidance (8).

The rationale for the use of such treatments is that blood contains different growth factors and other cytokines that stimulate healing of bone and soft tissue, in the case of PRP these components are in a concentrated form (9). In terms of therapeutic dose, PRP has been benchmarked at a concentration of 3 to 5 times greater than that of whole blood (10, 11). The therapeutic dose of autologous whole blood appears to be based on a blood volume of approximately 2-3 ml (12).

Regulatory status

In Australia two PRP preparation systems are currently registered on the Australian Registry of Therapeutic Goods: Magellan® and Terumo SmartPReP®. In terms of regulatory status PRP or AWB injections have not specifically been approved by the Medicare Benefits Schedule (MBS), although practitioners have been known to utilise item numbers such as 13703 "Administration of blood, including collection from donor" in order to receive a subsidy on the therapy (8).

Intended purpose of the review

The Transport Accident Commission (TAC) and Victorian WorkCover Authority (VWA) requested a review of the evidence to determine whether PRP or AWB is an effective treatment compared to placebo in patients with epicondylitis. This report sought to answer the following questions:

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

METHODS

Methods are outlined briefly below. More detailed information about the methodology used to produce this report is available in Appendices 1 and 2 that are located in the Technical Report accompanying this document.

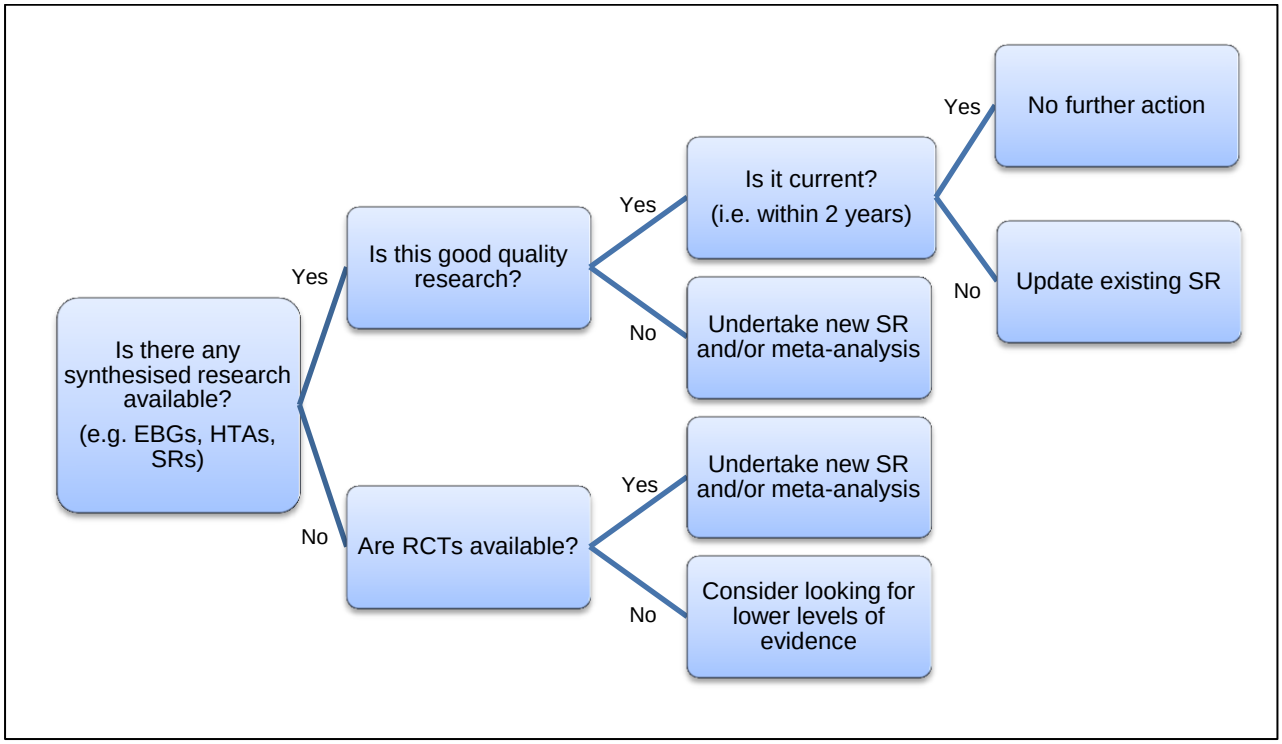
A comprehensive search of Medline, Embase, the Cochrane Library, All EBM, and CINAHL was undertaken in April 2014 to identify relevant synthesised research (i.e. evidence-based guidelines (EBGs), systematic reviews (SRs), health technology assessments (HTAs)), randomised controlled trials (RCTs) and controlled clinical trials (CCTs). Reference lists of included studies were also scanned to identify relevant references. Searchers were limited to publications between 2003 and April 2014. Search strategies for all databases are in Appendix 3 of the technical report.

Studies identified by the searches were screened for inclusion using specific selection criteria (see Appendix 2 Technical Report, Table A2.1). In this review studies were only included if they were SRs, RCTs or CCTs that investigated the effects of PRP or AWB compared with placebo in patients with epicondylitis. Evidence that met the selection criteria were reviewed to identify the most up-to-date and comprehensive source of evidence, which was then critically appraised to determine whether it was of high quality using the Cochrane Risk of Bias method and Grade (see Appendix 6 and 7 Technical report). Two reviewers

conducted all screening and selection independently, results were compared and any discrepancies discussed and resolved.

The available evidence was mapped (see Table 1), and the algorithm in Figure 1 was followed to determine the next steps necessary to answer the clinical questions.

Figure 1. Further action required to answer clinical questions



Data on characteristics of all included studies were extracted and summarised (see Appendix 5 Technical Report and Table 2.

SEARCH RESULTS

In total three studies were identified (see Table 1). Searches of Medline, Embase, the Cochrane Library, All EBM, and CINAHL resulted in 2617 potentially relevant references. After screening using specific selection criteria (see Appendix 2 Technical Report, Table A2.1), three RCTs were identified (see Appendix 4 Technical Report Table 1).

Table 1. Evidence map of identified studies by study-type

Synthesised Studies		Primary studies	TOTAL
EBGs	SRs & HTAs		
0	0	3 RCTs	3

STUDY RESULTS

DESCRIPTION OF STUDIES

Three RCTs published between 2011 and 2013 were identified. The number of patients recruited by each study was 19 (13), 40 (14) and 230 (15). Two studies were conducted in the USA (13, 15), and one in Denmark (14). Two studies compared PRP injections with placebo: 0.5% bupivacaine injection (15) or 0.9% saline injection (14). One study compared AWB with saline injection plus lidocaine (13). Krogh (2013) and Wolf (2011) also compared PRP and AWB with glucocorticoid injections. This evidence review has not described the characteristics or results of the glucocorticoid arm as it was beyond the scope of the review.

A summary of the included studies (including the population, intervention and comparators, outcomes and results) can be found in Table 2, and in greater detail in the Technical Report (Appendices 5 and 6).

Population

PRP vs Placebo

Both studies recruited adult patients with lateral epicondylitis with a history of elbow pain of more than three months. Epicondylitis was diagnosed as pain at the lateral epicondyle by palpation and during resisted extension of the wrist. The study by Mishra (2014) specifically included patients who had failed conventional therapy (either local steroid injections, physical/occupations therapy or non-steroidal anti-inflammatory medications). Both studies excluded patients with a history of elbow surgery or inflammatory diseases (e.g. rheumatoid arthritis) in addition to patients who had received local steroid injections within last 6 weeks (15) or 12 weeks (14). Mishra (2014) excluded patients with a platelet counts outside the normal range of 150-400 x 1000/µl.

AWB vs Placebo

The study by Wolf (2011) recruited patients with a diagnosis of lateral epicondylitis (diagnostic criteria not specified) who had not been treated with any injectable therapies in the previous six months. This study excluded patients with: a history of elbow surgery on the lateral side, compressive neuropathy, inflammatory arthritis, autoimmune disease or chronic regional pain.

Intervention and comparators

PRP vs Placebo

For the PRP studies different platelet concentrations were used. In Krogh (2013) the platelet concentration was 8 times that of whole blood while in Mishra (2014) it was 5 times the concentration. Both studies used a peppering technique injecting approximately 3mls into the common wrist and finger extensor origin, although the number of tendon perforations was different: five for Mishra (2014) and seven for Krogh (2013). In Mishra (2014) the injection site was blocked using 0.5% bupivacaine with epinephrine prior to administering PRP, while Krogh (2013) used lidocaine to block the site..

The control groups were different between studies with Mishra (2014) using 2-3mls 0.5% bupivacaine and Krogh (2013) using 3ml 0.9% saline.

Only the study by Krogh (2013) used an ultrasound guided injection technique to administer the interventions.

AWB vs Placebo

Wolf (2011) injected patients with either 3mls of AWB with lidocaine or saline with lidocaine under the extensor origin with multiple passes of the needle in a fan like fashion.

Outcomes

PRP vs Placebo

- Pain

  Although both studies assessed pain on resisted wrist extension, Mishra (2014) used a 100-mm visual analogue scale (VAS) while Krogh (2013) used change from baseline scores for the pain domain of the Patient Rated Tennis Elbow Evaluation (PRTEE).

  The primary outcome for Mishra (2014) was “successful treatment” defined as ≥25% improvement from baseline in VAS. This study also reported mean percentage improvement in VAS and post-hoc analysis using “successful treatment” defined as ≥50% improvements in VAS at 24 weeks. The outcome of “successful treatment” was only assessed in patients that did not require pain medication beyond 48 hours and did not require escape therapy (escape therapy not defined).

  #### Patient Rated Tennis Elbow Evaluation (PRTEE)

  Both studies measured the PRTEE (14, 15). The PRTEE consists of two domains: 5 questions relating to pain and 10 questions relating to function, each using a numeric rating scale from 0 to 10.

- Other outcomes

  Other outcomes of interest included elbow tenderness (15) and adverse events (14, 15).

Patient follow up ranged from short terms 4-12 weeks (14, 15) and long term 24 weeks (15) and 12 months (14). For Mishra (2014) the original design of the study was for 12 weeks follow-up, however a protocol change in the middle of the study increased the follow-up to 24 weeks. At the time of this change patients initially enrolled in the 12 week protocol had already passed their 24 week follow-up. The results of this study are presented at 12 weeks (n=225) for both cohorts, and at 24 weeks for those enrolled after the protocol change (n=136).

AWB vs Placebo

The primary outcome measure in Wolf (2011) was the "Disabilities of the Arm, Shoulder, and Hand (DASH) scores. The DASH Outcome Measure is scored in two components: the disability/symptom section (30 items, scored 1-5) and the optional high performance Sport/Music or Work section (4 items, scored 1-5). It is unclear whether both components were scored. Other outcome measures were pain using a visual analogue scale, a disease specific questionnaire, and the PRFE (now known as the PRTEE).

Analysis

The significance level used for analysis was set at $p \leq 0.05$ in Krogh (2013) and Wolf (2011). For Mishra (2014) a significance level of $p \leq 0.025$ was used for successful treatment; as the hypothesis tested was a based on a 1-sided test, where the proportion of successfully treated patients with PRP would be greater than controls. All other analyses were set at a significance level of $p \leq 0.05$.

RISK OF BIAS

Selection bias

PRP vs Placebo

The randomisation process in both studies was not clearly defined. In the study by Krogh (2013) a 'shuffling envelope' method was used to randomise patients and sealed envelopes were used to conceal allocation. Despite using an adequate method for concealment of allocation the potential for selection bias in Krogh (2013) was high, particularly if there was prior knowledge as to what treatment arms were in the envelopes and how well they were shuffled prior to randomisation.

Overall the risk of selection bias in Mishra (2014) is unclear as both the method of randomisation, "computerised protocol" was not described and allocation concealment was not reported. Furthermore it is unclear whether selection bias was present for the 24 week cohort as baseline characteristics were not presented for this particular group.

AWB vs Placebo

In Wolf (2011) the potential for selection bias was low as patients were randomised using a centrally generated random numbers tables. Allocation to treatment was concealed using sealed opaque envelopes.

Performance bias

PRP vs Placebo

In Krogh (2013) although patients were blinded to treatment the treating physician was not. This has the potential to introduce bias if the treating physician differentially treats patients according to which intervention they receive. In Mishra (2013) the risk of bias was minimised as patients and treating physicians were blinded to treatment.

AWB vs Placebo

Wolf (2013) blinded the patients to the treatment but did not blind the treating physician thus there is a high risk of performance bias.

Detection bias

PRP vs Placebo

For Mishra (2014) and Krogh (2013) there was a low risk of bias as outcome assessors were blinded to treatment.

AWB vs Placebo

The study by Wolf (2011) used self-reported questionnaires for outcome assessment; given that patients were blinded to treatment the risk of bias is low.

Attrition Bias

PRP vs Placebo

There is a high risk of attrition bias in both PRP studies (14, 15). For Krogh (2013), follow-up was 3, 6 and 12 months, however only 3-month data are reported, due to a >50% drop out of the study population. Only an intention to treat analysis (ITT) at 3 months is presented. Per protocol and ITT analyses for 6 and 12 months are only presented in an appendix and not discussed in the results as only 11 of the 40 patients remained.

In Mishra (2014) there is a high risk of attrition bias with 15% of patients dropping out for the 12 week cohort and 12% of patients for the 24 week cohort. The number of dropouts at 12 weeks was 50% higher in the placebo group. For the 24 week cohort the proportion of dropouts for each group could not be confirmed, as the denominator for each of the groups was not reported. For both cohorts intention to treat analysis was not performed.

AWB vs Placebo

The potential for attrition bias in Wolf (2011) is high as there was a 17% dropout rate and no intention to treat analysis was performed on these patients. Intention to treat analysis was performed however on patients who had switched intervention groups (n=1 from each group). Reasons for dropping out of the study were not reported.

Reporting bias

PRP vs Placebo

There is potential for reporting bias in the Mishra (2014) with post hoc changes applied to the primary outcome "treatment success". The outcome was initially defined as ≥25% improvement in VAS on resisted wrist extension and then changed to a 50% or greater improvement for the 24 week cohort. The potential for reporting bias in Krogh (2013) was low as data for relevant outcomes were presented for all time points.

AWB vs Placebo

The potential for reporting bias in Wolf (2011) was low as data for all relevant outcomes were reported for all time points.

Other Bias

There is a potential conflict of interest in both Krogh (2013) and Mishra (2014) as both studies are sponsored by Biomet Biologics, which are the makers of a PRP separation device. Furthermore the primary author A.K Mishra receives royalties for patents from Biomet and ThermoGenesis and owns stock in BioParadox and ThermoGenesis. Other authors receive research support from Biomet.

EFFECTS OF INTERVENTIONS

For all outcomes the quality of evidence from the available RCT's is low to very low (see Table 3).

Pain

PRP vs placebo

Both studies reported no significant difference in pain between PRP and placebo at 3 months: PRTEE pain scores [PRP vs. placebo: -2.7 (95% CI, -8.8 to 3.5, p = 0.395)] (14); mean percentage improvement in VAS on resisted wrist extension (55.1% PRP vs 47.4% placebo, p=0.163 (15) and treatment success (≥25% reduction in VAS) (75.2% PRP vs 65.9% placebo, p = 0.203) (15).

At 24 weeks Mishra (2014) reported a significant difference in mean percentage improvement in VAS in the PRP group compared to placebo [71.5% PRP vs 56.1% placebo, p=0.019). There was no significant difference between success rates defined as ≥25% reduction in VAS at this time point (83.9% PRP vs 68.3%, p = .037, 1-sided; p = .056, 2-sided). However when success rates were defined as ≥50% improvement in VASs, significant differences between PRP and placebo were observed (82.1% PRP vs 60.1% placebo, p= .008, 1-sided; p = 0.015, 2-sided).

AWB vs Placebo

In this study the PRFE pain component scores showed a significant improvement over time in both groups. There was no significant difference in PRFE pain scores between AWB and placebo (p=0.378) (13).

There was no significant difference for VAS pain scores and PRFE pain scores between groups at any time point (13).

PRTEE/PRFE

PRP vs placebo

Krogh (2013) reported no significant difference in PRTEE disability score between PRP and placebo at three months [PRP vs placebo -9.0, (95% CI -21.2 to 3.1, p = 0.144)]. For PRTEE scores, no significant difference between PRP and placebo at 12 (27.05 PRP vs 28.88 placebo) and 24 weeks (16.17 PRP vs 21.06 placebo) were also reported by Mishra (2014).

AWB vs Placebo

There were significant improvements in PRFE functional scores at 6months for all groups (p=0.046). However comparisons between treatment groups showed that functional scores were significantly better for saline compared to AWB at 6 months (1.5 Placebo vs 0.6 AWB, p = 0.048)(13).

Other Outcomes

PRP vs placebo

There was no significant difference between the groups with regards to adverse events (14, 15). No significant differences, in local tenderness, were observed at 4, 8, or 12 weeks; although the PRP group reported significantly less local tenderness at 24 weeks (54% placebo vs 29% PRP, p=0.009) (15). Krogh (2013) reported no serious adverse events and no infections for any of the treatments; although 4 patients in the PRP arm and 3 in the placebo arm presented to the department with concerns about the level of persistent pain. Furthermore 3 out of the 4 PRP patients also reported reduced movement of elbow.

AWB vs Placebo

Although Wolf (2011) reported significant differences between baseline and 6 month DASH scores for both AWB and placebo ($p<0.00$), no significant difference was observed when AWB and placebo were compared ($p=0.188$)

Table 2. Summary of Studies.

Reference	Inclusion, exclusion criteria (for P.I.C.O)	Study design	Conclusion/recommendation	Direction of effects
Krogh (2013) Randomised, double-blind, placebo controlled trial for treatment of lateral epicondylitis, comparing platelet rich plasma, glucocorticoid and saline.	**POPULATION/CLINICAL INDICATION** **Included:** Adults with lateral epicondylitis symptoms for more than 3 months. **Excluded:** Age younger than 18 years, glucocorticoid injection within the past 3 months, previous tennis elbow surgery, inflammatory diseases (eg, rheumatoid arthritis, psoriatic arthritis, or inflammatory bowel disease), neck pain, shoulder pain on the ipsilateral side, and other chronic widespread pain syndromes. **INTERVENTION** Ultrasound-guided injection of PRP with the elbow bent to 90^{o}. **COMPARATOR** Glucocorticoid and saline. **OUTCOMES** The primary efficacy outcome was changes in pain intensity after 3 months using the pain section of the Patient-Rated Tennis Elbow Evaluation (PRTEE) questionnaire. The secondary end points included changes in functional disability using the functional section of the PRTEE, US changes in color Doppler signal and tendon thickness, adverse events, and any additional pain caused by the injection therapy itself.	RCT	The effect of PRP or glucocorticoid injection on pain and disability at a primary end point of 3 months (no attrition) was not statistically different from saline injection.	*Neutral (no difference in pain reduction or improve functionality between control groups)*
Wolf (2011) A prospective, blinded, randomized, controlled trial comparing saline, corticosteroid, and autologous blood injections for lateral epicondylitis.	**POPULATION/CLINICAL INDICATION** **Included:** Adults with clinically diagnosed lateral epicondylitis who had not been treated with an injection in the previous 6 months. **Excluded:** Patients with a history of surgery on the lateral side of the elbow, compressive neuropathy, inflammatory arthritis or autoimmune disease or chronic regional pain syndrome. **INTERVENTION** Injection of PRP. **COMPARATOR** Corticosteroid and saline. **OUTCOMES** Disabilities of the Arm, Shoulder, and Hand (DASH) scores as the primary outcome measure and Visual Analog Scale (VAS) and Patient-Rated Forearm Evaluation (PRFE) scores as the secondary outcome, at 2 weeks, 2 months and 6 months.	RCT	Study did not show a significant difference in DASH, VAS and PRFE pain scores among the 3 groups for all time points. The PRFE functional score were significantly better for saline compared with blood injection at 6 months. However, differences between saline and corticosteroid groups and between the blood and corticosteroid groups were not significant.	*Negative (improve functionality in saline compared to blood injection).*

Reference	Inclusion, exclusion criteria (for P.I.C.O)	Study design	Conclusion/recommendation	Direction of effects
Mishra 2014 Double-blind, prospective, randomized controlled trial to evaluate the clinical value of tendon needling with PRP in patients with chronic tennis elbow compared with an active control group (dry needling).	**POPULATION/CLINICAL INDICATION** **Included:** Pain by palpation at the lateral epicondyle of the elbow, baseline elbow pain ≥50 mm/100 mm using a visual analog scale (VAS) during resisted wrist extension, history of elbow pain for at least 3 months, pain unresponsive to 1 of 3 conventional therapy programs (local steroid injections, physical/occupational therapy, nonsteroidal anti-inflammatory medications). **Excluded:** Pregnancy, age <18 years, history of anemia, history of bleeding disorder, history of carpal tunnel syndrome on the affected side within 1 year before randomization, cervical radiculopathy, systemic disorders such as diabetes, rheumatoid arthritis, or hepatitis, uncooperative patient or patient with neurological disorders who is incapable of following directions or who is predictably unwilling to return for follow-up examinations, previous surgery for elbow tendinosis, active bilateral elbow tendinosis within 4 weeks before randomization, hypothyroidism, history of any blood disorder, hemoglobin <11 g/dL, hematocrit <33%, platelet count outside of the normal range of 150 to 400 × 1000/uL, participation in a workers' compensation program or planning to apply for the program and/or any ongoing, pending, or planned legal action as a result of elbow pain, history of arthritis or fracture of the affected elbow, received local steroid injections within 6 weeks, physical/occupational therapy within 4 weeks, or nonsteroidal anti-inflammatory medications within 1 week of randomization, intolerance to acetaminophen. **INTERVENTION** Injection of PRP. **COMPARATOR** Dry needling. **OUTCOMES** The primary outcome measure was defined based on the VAS with resisted wrist extension (VASRWE) and the Patient-Rated Tennis Elbow Evaluation (PRTEE; formerly known as the Patient-Rated Forearm Evaluation Questionnaire) and extended wrist examination were secondary measurements of outcome.	RCT	In conclusion, the primary endpoint of at least 25% improvement in VAS pain scores was not statistically significant at 12 weeks. The pain score and elbow tenderness improvement at 24-week might be significant if the minimum improvement was set at 50%.	*Positive/Neutral (PRP more effective than dry needling in terms of pain reduction)*

Table 3. Summary of Findings.

PRP vs Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Placebo**	Corresponding risk **PRP**				
Pain - PRTEE 12 weeks PRTEE (Patient Rated Tennis Elbow Evaluation) - Pain Domain. Scale from: 0 to 50. Follow-up: mean 12 weeks	The mean pain - PRTEE 12 weeks in the control groups was **-3.3 Pain score 0-50**	The mean pain - PRTEE 12 weeks in the intervention groups was **2.7 lower** (8.8 lower to 3.5 higher)		40 (1 study)	⊕⊕⊖⊖ **low**[1,2,3,4]	Not significant
Pain -Successful Outcome VASRWE <=25% 12 weeks VASRWE - Visual Analogue Scale Resisted Wrist Extension Follow-up: 12 weeks	**65 per 100**	**76 per 100** (62 to 92)	**RR 1.16** (0.95 to 1.41)	164 (1 study)	⊕⊖⊖⊖ **very low**[1,3,4,5,6,7]	P value reported in the study was not significant
Pain -Successful Outcome VASRWE <=25% and <=50% at 24 Weeks VASRWE - Visual Analogue Scale Resisted Wrist Extension Follow-up: 24 weeks	Insufficient data to calculate	Insufficient data to calculate		0 (1 study)	⊕⊖⊖⊖ **very low**[1,3,4,5,6,8]	SD or SE not reported
Function - PRTEE Functional Domain Score PRTEE (Patient Rated Tennis Elbow Evaluation) - Functional Domain. Scale from: 0 to 100. Follow-up: mean 12 weeks	Mean PRTEE functional domain score in the control groups was **-7.6 Function Score 0-100**	Mean PRTEE functional domain score in the intervention groups was **9.0 lower** (21.2 lower to 3.1 higher)		40 (1 study)	⊕⊕⊖⊖ **low**[1,2,3,4]	Not significant
Function- PRTEE total score at 12 and 24 weeks PRTEE (Patient Rated Tennis Elbow Evaluation) - Total Score	Insufficient data to calculate	Insufficient data to calculate		0 (1 study)	⊕⊖⊖⊖ **very low**[1,3,4,5,6]	SD or SE not reported

CI: Confidence interval; **RR:** Risk ratio; **SD:** Standard deviation; **SE**: Standard Error

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Sparse data both studies had sample size < 200, Sample size for Krogh (2013) was n=40, Mishra (2014) n= 164 for 12 weeks, sample not reported for 24 weeks
[2] The quality of the methods such as randomisation and blinding was not adequately performed, it is unclear what impact this has on the overall results.
[3] Only one study reported this outcome
[4] Unable to explore as there is less than 10 studies
[5] Outcome was only based on a subset of patients i.e. patients not requiring pain medication beyond 48 hrs and not requiring escape therapy - representing 58% of the total study population
[6] For the subgroup analysed it is unclear whether the intervention groups were similar at baseline.

[7] Results were not significant, confidence intervals were not considerably wide
[8] Wolf (2011) had very small sample size - n=10 in AWB group and n=9 in control group.

AWB vs Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Placebo**	Corresponding risk **AWB**				
Pain - PRFE Pain and Function 6 months Patient Rated VAS pain score Follow-up: mean 6 months	Insufficient data to calculate	Insufficient data to calculate		19 (1 study)	⊕⊖⊖⊖ **very low**[1,2,3,4,5,]	
DASH - Disability of the Arm and Shoulder and Hand scale Scale from: 0 to 100. Follow-up: mean 6 months	The mean DASH in the control groups was**10** **Scale 0-100**	The mean DASH in the intervention groups was **10 higher** (2.36 lower to 22.36 higher)		19 (1 study)	⊕⊖⊖⊖ **very low**[1,2,3,4,5,6]	Not Significant

CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Sparse Data <200, Wolfe 2011 n=19
[2] Six patients dropped out of the study no intention to treat analysis was performed
[3] The quality of the methods such as blinding was not adequately performed, it is unclear what impact this has on the overall results.
[4] Only one study has compared AWB with Placebo
[5] Could not be explored as less than 10 studies
[6] Large confidence intervals

DISCUSSION

OVERALL EFFECTIVENESS

PRP vs Placebo

Short term effectiveness

Overall the evidence shows that in the short term PRP is no better than placebo in alleviating pain and improving functional outcomes with Mishra (2014) and Krogh (2013) showing no significant between group differences in pain using the VAS on resisted wrist extension (15) and PRTEE pain scores (14, 15). These results however are based on two low quality studies with relatively small sample sizes, one of which was adequately powered (14) and the other which was not (15). In the case of Mishra (2014) there was a 15% dropout rate; while Krogh (2013) had no drop outs at 3 months.

Long term effectiveness

The long-term effectiveness of PRP is unclear with only one study reporting results at 24 weeks (15). This trial reported significantly better pain outcomes for PRP on percentage change in VAS on resisted wrist extension and "success rate" (≥50% improvement in VAS pain score) compared to placebo. For PRTEE, which encompasses functional and pain outcomes, no difference between groups at 24 weeks was observed.

Along with these conflicting results there is further uncertainty regarding these data as the analysis was based on a cohort of patients representing 50% of the total study population. Another concern is that the primary outcome "success rate" (≥25% improvement in VAS pain score) is only based on a subset of patients i.e. patients not requiring pain medication beyond 48 hours and not requiring escape therapy. At 12 weeks this subgroup represented 58% of the study population; the sample size of this subgroup was not reported at 24 weeks. Furthermore, given that the sample size of the 24 week cohort deviates considerably from the initial sample size; it is unclear whether the integrity of the randomisation was maintained; as the authors did not report on whether the PRP and placebo groups were similar at baseline for confounding factors such as baseline pain scores, forearm function and age.

Long term follow up data was not reported by Krogh (2013) as there were significant drop outs after 12 weeks with only 11 of the 40 patients remaining at 12 months. In this study the main reason for dropping out was that patients were not satisfied with the level of pain relief they were receiving.

Safety

There were no serious adverse events with regards to the safety of PRP in either of the studies.

Conflict of interest

There is a potential conflict of interest in both studies (14, 15) are sponsored by Biomet Biologics, which are the makers of a PRP separation device. Furthermore the primary

author in Mishra (2014) receives royalties for patents from Biomet and ThermoGenesis and owns stock in BioParadox and ThermoGenesis. Other authors receive research support from Biomet.

AWB vs Placebo

Based on the finding of one small study there is no significant difference between AWB and placebo with regards to improvement in pain. With regards to PRFEE functional score patients in the placebo group showed significant improvement compared to those receiving AWB at 6 months (13). It is unclear if there is any safety issues associated with AWB as this was not addressed in the study. These findings however are limited, given the small sample size and that patients that were lost to follow up were not included in the final analysis.

Considerations for both AWB and PRP studies

The value of specific outcome measures needs to be considered when assessing the effect of PRP. For example the primary outcome was different across studies; for example, Mishra's (2014) was treatment success (defined as ≥25% improvement in VAS pain score); Krogh's (2013) was PRTEE and Wolf's (2011) was the DASH. There is also difficulty in interpreting results when there are inconsistencies across different measures. For example Mishra (2014) reported a significant improvement in pain for PRP over placebo using the VAS on resisted wrist extension but no significant difference in PRTEE. In this case it is unclear whether the resisted wrist extension pain should have more weighting than the PRTEE (a tool which was specifically developed to assess forearm pain and disability in patients with lateral epicondylitis (16)). Furthermore Mishra (2014) did not report whether there was any consistency between the results of the VAS and the PRTEE pain domain.

Another issue to consider is the different protocols for PRP between Mishra (2014) who used a leukocyte-enriched PRP with platelets 5 x baseline, unactivated preparation; and Krogh (2013) who used no enrichment with a platelet concentration 8 x baseline, unactivated. There is a lack of clarity around the therapeutic dose of PRP, currently based on a 3-5 x baseline concentration from *in vitro* studies (10, 11). It is also unclear what effect higher PRP concentrations and leukocyte enrichment has on patient outcomes. Furthermore the protocol on Krogh (2013) injected lidocaine outside the tendon around the peritendon; and although it was not injected intratendinously, there is some concern that the presence of lidocaine in the area could have a negative effect on tendon healing. (14). This may also be the case for Wolf (2011) where lidocaine was also added to PRP and placebo.

It's unclear whether the effect of PRP is different for different patient groups, e.g. patients with more severe epicondylitis or patients who have failed previous treatments. For example Mishra (2014) recruited patients who had failed previous treatment whereas Krogh (2013) and Wolf (2011) did not. Furthermore the study by Krogh (2013) recruited patients with above average severity (mean duration 23 months) while Mishra (2014) and Wolf did not report on these data.

There is also the possibility that the placebo injections could be more than an inactive treatment as the placebo techniques in all three studies included perforations into the common tendon origin similar to the active interventions.

CONCLUSION

Although it would appear that PRP and AWB is no more effective than placebo in the short term, there is insufficient evidence to confirm this. Based on the available evidence the long-term effectiveness of these treatments is unclear given the very low quality of the RCT's. Overall further high quality and independent evidence is needed to demonstrate the effectiveness of PRP and AWB.

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