PREVENTION. CARE. RECOVERY.

Te Kaporeihana Āwhina Hunga Whara

Considered Judgement Form

This form is a checklist of issues that may be considered by the Purchasing Guidance Advisory Group when making purchasing recommendations.

Meeting date: 14 October 2014

Topic: Autologous Blood Injections for Musculoskeletal Disorders

Background and Purpose:

ACC Research was asked to review the evidence about the efficacy of autologous blood products in the treatment of musculoskeletal disorders and to summarise the best evidence for their use with a special focus on tendinopathies.

"Tendinopathy'" describes a range of conditions that affect tendons, causing pain, stiffness, and weakness. Sites commonly involved are the elbow extensor ('tennis elbow'), Achilles, and patellar tendons. Other names used include tendonitis and tendinosis. Conservative treatments for tendinopathies include rest, analgesics, anti-inflammatory medication, orthotic devices, eccentric exercise, and physiotherapy.

Autologous blood products are a therapy that is claimed to promote healing through the action of various growth factors extracted from the patient's blood on their affected tendon. This report focuses on two autologous blood products, autologous whole blood (ABI) and platelet-rich plasma (PRP).

Autologous whole blood injections involve withdrawing the person's own blood by standard venesection and injecting it into or around the affected tendon. Platelet-rich plasma, on the other hand, is derived from centrifuging the person's own whole blood and separating part of the centrifuged blood which has a higher concentration of platelets than seen in whole blood. About 2-3 mls of the whole blood or platelet-rich plasma is injected into or around the tendon, sometimes with ultrasound guidance and local anaesthetic is often used. "Dry needling" (repeatedly passing the needle through the tendon) may be performed before injection of the blood. Moreover, a "peppering" technique is sometimes used which involves inserting the needle into the tendon, injecting some blood, withdrawing without emerging from the skin, then slightly redirecting and reinserting into tendon and injecting again; this may be repeated many times.

The mechanism of action of these injections is proposed to be a healing response in the damaged tendons that is triggered by the growth factors in the blood. These growth factors are proposed to trigger stem-cell recruitment, increase local vascularity and directly stimulate the production of collagen. These therapies whilst appearing to be biologically plausable have not had a significant amount of basic science research performed. Currently there are commercially available systems for preparing PRP but no universally accepted protocol for PRP preparation. This is due to the wide variety of variables that in themselves have not been explored and significant variation in the characterisation of the PRP delivered by the various commercial systems.

1. Effectiveness, Volume of Evidence, Applicability /Generalisability and Consistency / Clinical impact	
Comment here on the extent to which the service/product/ procedure achieves the desired outcomes. Specific reference needs to be made to safety. Report number needed to treat and harm where possible, any issues concerning the quantity of evidence and its methodological quality and the extent to which the evidence is directly applicable or generalisable to the New Zealand Population, and the degree of consistency demonstrated by the available evidence. Where there are conflicting results, indicate how the group formed a judgement as to the overall direction of the evidence. Comment on the clinical impact e.g. size of population, magnitude of effect, relative benefit over other management options, resource implications, balance of risk and benefit.	**Evidence level** **(please refer to scale at end of form)**
EFFECTIVENESS: Systematic reviews included in the evidence based review Nine systematic reviews were included of various methodological quality	
The best quality systematic review (Sheth et al., 2012) included 23 randomised control trials (RCTs) and found that 6 RCTs showed a significant functional benefit for PRP, 15 showed no difference between PRP and control, and one showed a benefit for the control. The meta-analysis of improvement in pain found no significant difference in pooled VAS scores between PRP and control groups across the six included RCTs (SMD = –0.34 (95%CI: –0.75 to 0.06); p=0.10). The authors concluded that the current evidence is insufficient to conclude that any autologous blood product provides a clinical benefit in the treatment of orthopaedic conditions.	**1++**
Another systematic review (Taylor et al., 2011) about the use of PRP in ligament and tendon injuries located 4 RCTs investigating the use of PRP in a variety of ligament and tendon injuries and found mixed results: PRP was superior to steroid injection for tennis elbow in one; no different from saline injection in Achilles tendinopathy; and no benefit for ACL reconstruction in two studies.	**1+**
The remaining six systematic reviews (de Vos et al., 2010a; Hoksrud & Bahr, 2011; T. g. P. Krogh et al., 2012; Martin, 2011; Rabago et al., 2009; Sadoghi et al., 2013) and one rapid evidence-based review (National Institute for Health and Clinical Excellence, 2013) were all small (based on 5 RCTs at the most) and generally found that it was difficult to come to any conclusive recommendations due to the poor quality of the primary studies.	**1++** **1+** **1-**
EFFECTIVENESS: RCTs included in the evidence based review Nine RCTs were included that investigated the effects of ABIs and PRP on elbow tendinopathies. These studies were low to high quality and there was heterogeneity in methodologies between studies. Another eight RCTs with various quality looked at ABI and PRP use for Achilles tendinopathies, Rotator cuff disease, Patellar tendinopathies and Plantar fasciitis. Details of evidence are as below:	
<u>*Elbow tendinopathies, Lateral epicondylosis/epicondylitis*</u> Two RCTs looked at PRP:	
- PRP improved pain and function significantly more than corticosteroid injection at 2 years follow-up (Gosens, Peerbooms, van Laar, & den Oudsten, 2011)	**1++**
- No difference in terms of pain and functional improvement compared to corticosteroid injection and saline injection at 3 months follow-up (T. P. Krogh et al., 2013).	**1+**
Five RCTs looked at ABI:	
-No difference in terms of pain and functional improvement compared to corticosteroid injection and saline injection at 6 months follow-up (Wolf et al., 2011).	**1+**
-No difference in terms of pain and functional improvement compared to corticosteroid	**1-**

injection at 6 weeks follow-up (Omar, Ibrahim, Ahmed, & Said, 2012).	
-Autologous blood injections improved pain and function significantly more than corticosteroid injection (Dojode, 2012; Kazemi, Azma, Tavana, Rezaiee Moghaddam, & Panahi, 2010)	**1-** **1-**
-Autologous blood injection and extracorporeal shockwave treatment improved pain and function significantly more than corticosteroid injection at 1 yr follow-up (Ozturan et al., 2010).	**1-**
Two fair quality RCTs (Creaney et al., 2011; Thanasas et al., 2011) that autologous blood injections are no more efficacious than platelet-rich plasma for the treatment of elbow tendinopathies or lateral epicondylosis/epicondylitis.	**1+** **1+**
<u>*Achilles tendinopathy:*</u>	
One good quality RCT (Bell et al., 2013) and one poor quality RCT (Pearson, Rowlands, & Highet, 2012) found that the addition of autologous blood injections to a programme of eccentric exercise did not result in additional benefit in people with mid-portion Achilles tendinopathy when compared to dry needling and an eccentric exercise programme.	**1++** **1-**
One fair quality RCT found that the addition of platelet-rich plasma injection to a programme of eccentric exercise or combination of a saline injection and eccentric exercise did not result in additional benefit in people with mid-portion Achilles tendinopathy (de Jonge et al., 2011).	**1+**
<u>*Rotator cuff disease*</u>	
One fair quality RCT reported that platelet-rich plasma may improve pain (but not range of movement) more in rotator cuff disease compared to dry needling at 6 months follow-up (Rha et al., 2013).	**1+**
<u>*Patellar tendinopathy*</u>	
One fair quality RCT found that platelet-rich plasma may improve pain and function better than extracorporeal shockwave treatment in athletes at 1 year follow-up (Vetrano et al., 2013).	**1+**
<u>*Plantar fasciitis*</u>	
One poor quality RCT found that platelet-rich plasma injection may improve pain and function better than corticosteroid injection at 6 weeks follow-up (Omar et al., 2012).	**1-**
Two fair quality RCTs (Kiter et al., 2006; Lee, Ahmad, Lee, & Ahmad, 2007) found that there is no difference in terms of pain and functional improvement when comparing autologous blood injection with corticosteroid injection for plantar fasciitis at 6 months follow-up. Kiter et al (2006) also reported that no difference in terms of pain and functional improvement when comparing autologous blood injection with dry needling for plantar fasciitis at 6 months follow-up.	**1+** **1+**
External Peer Review Comments: *"It was highlighted by the external peer reviewer throughout this report that the detrimental long term effects of corticosteroid injections are not always discussed in the included RCTs. The impact of this is that although ABI and PRP products may appear superior to corticosteroid injections, this is not proof of their efficacy in that these products have less detrimental effects than a corticosteroid injection."*	
SAFETY Only half (n=6) of the systematic and related reviews discussed safety. Overall it appeared	

from the evidence included in this report that ABI and PRP injections are not associated with any serious adverse events. However the evidence is limited with no long-term follow-up studies. The most common side-effect is additional pain at the site of the autologous blood product injection of a few days duration. No infections or tendon ruptures were reported.

2. Cost

Where possible and reported in the published research literature any economic analysis of the new treatment is considered. Where possible the following will be considered; total costs of the new intervention and number of claimants likely to be affected are considered, along with comparison with the cost of current treatments or interventions, actuarial assessment of the impact of the intervention on scheme liability (including direct and indirect impact e.g. other services and access), expected "accrued benefit" in terms of quality of life, longer life or speedier return to the workforce, implications of cost to the wider health sector.

- Variable costs depending on whether imaging is used to guide placement of injection.
- ABI likely to be cheaper as no centrifuging required (and no associated machinery)
- Information available on costs from the world wide web ranged from US$ 450 for three PRP injections to US$ 500-1000 per injection

3. Equity

The extent to which the intervention reduces disparities in health status; in particular equity of access and health outcome. The extent to which the intervention supports the objectives of the Maori access strategy and will encourage access to assessment, treatment and rehabilitation services for those groups where there is evidence of that access is problematic.

No equity issues were identified.

4. Consistency with the intent of the IPRC Act

Purchasing decisions made by ACC must be consistent with and reflect consideration of factors described in the IPRC Act, Schedule 1, clause 2(1 and 2) and these decisions must be defensible against this statutory requirement in respect of individual claimants.

5. Possible Purchasing Options

List the possible purchasing options.

The options are:

1. Purchase,
2. Don't purchase, or
3. Purchase on a case by case basis on the decision of the Corporate Medical Advisor (or equivalent).

6. Evidence Statements

Summarise the advisory group's synthesis of evidence relating to this service, product or procedure, taking the above factors into account, and indicate the evidence level that applies.

Lateral epicondylitis

There is conflicting evidence from two RCTs that platelet-rich plasma injections are more efficacious than corticosteroid injections for lateral epicondylitis

There is conflicting evidence from five RCTs that autologous blood injections are more efficacious that corticosteroid injections for lateral epicondylitis.

There is moderate evidence from two fair quality RCTs that autologous blood injections are no more efficacious than platelet-rich plasma for the treatment of lateral epicondylitis.

Achilles tendinopathy

There is moderate evidence from two RCTs that the addition of autologous blood injections to a programme of eccentric exercise did not result in additional benefit in people with mid-portion Achilles tendinopathy when compared to the combination of dry needling and an eccentric exercise programme.

There is limited evidence from one fair quality RCT that the addition of platelet-rich plasma injection to a programme of eccentric exercise did not result in additional benefit in people with mid-portion Achilles tendinopathy.

There is limited evidence from one fair quality RCTs that the addition of platelet-rich plasma injection to a programme of eccentric exercise did not result in additional benefit in people with mid-portion Achilles tendinopathy compared to the combination of saline injection and eccentric exercise.

Rotator cuff disease

There is limited evidence from one fair quality RCT that platelet-rich plasma may improve pain (but not range of movement) more in rotator cuff disease compared to dry needling at 6 months follow-up.

Patellar tendinopathy

There is limited evidence from one fair quality RCT that platelet-rich plasma may improve pain and function better than extracorporeal shockwave treatment in athletes with patellar tendinopathy at 1 year follow-up.

Plantar fasciitis

There is limited evidence from one poor quality RCT that platelet-rich plasma injection may improve pain and function better than corticosteroid injection at 6 weeks follow-up.

There is moderate evidence from two fair quality RCTs that there is no difference in terms of pain and functional improvement when comparing autologous blood injection with corticosteroid injection for plantar fasciitis at 6 months follow-up.

There is limited evidence from one fair quality RCT that there is no difference in terms of pain and functional improvement when comparing autologous blood injection with dry needling for plantar fasciitis at 6 months follow-up.

Safety

No serious adverse events have been reported in the literature, however, there are frequent reports of transient increased pain post-injection and other minor side-effects

7. Purchasing Recommendations

What recommendation(s) does the advisory group draw from this evidence?

'Strong' recommendations should be made where there is confidence that, for the vast majority of people, the intervention/action will do more good than harm (or more harm than good). The recommendation should be clearly directive and include 'should/ should not' in the wording.

'Conditional' recommendations, should be made where the intervention/action will do more good than harm, for most patients, but may include caveats eg on the quality or size of the evidence base, or patient preferences. Conditional recommendations should include 'should be considered' in the wording.

Autologous blood injections should not be purchased for the patients with the following musculoskeletal disorders because its effectiveness has not been established: Lateral epicondylitis - conflicting evidence Achilles tendinopathy - conflicting evidence Rotator cuff disease – conflicting evidence Patellar tendinopathy - insufficient evidence	**Strong**

Plantar fasciitis - conflicting evidence	
Briefly justify the strength of the recommendation Current evidence does not support the effectiveness of autologous blood injection for musculoskeletal disorders. The evidence is inadequate in quantity and quality. There are also significant heterogeneity of populations studied, number of injections given, outcome measures used, and follow-up times across the included studies which surmounts to conflicting evidence and thus strong evidence not to purchase this item. Therefore based on evidence from the literature it is suggested that ACC should not purchase autologous blood products for musculoskeletal conditions.	

PGAG discussions:

First ABIs are being funded via the prior approval mailbox under "guided injection" with the substance being injected not specified. When an application for funding a second injection of autologous blood then these are turned down.

Levels of evidence:

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

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