

PRACTICE



UNCERTAINTIES

How effective are platelet rich plasma injections in treating musculoskeletal soft tissue injuries?

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Platelet-rich plasma (PRP) has become increasingly popular in sports medicine and orthopaedic practice as treatment for muscle, tendon, and ligament injuries, and has received media attention because of its promise as a regenerative therapy.^{1 2} PRP is an autologous preparation of a patient's whole blood, which is centrifuged or filtered, allowing separation of a fraction containing a supraphysiological concentration of platelets (fig 1). PRP can be applied on its own, or as an adjunct to surgery, allowing a high "dose" of growth factors and other bioactive proteins such as cytokines and chemokines to be delivered to the target tissue. This has the potential to improve repair and regeneration, although evidence from in vitro and animal studies has been conflicting.³⁻⁵

As an autologous preparation, PRP has been introduced into clinical practice without being subject to the stringent development required of new drugs. Many commercially available PRP preparation devices have US Food and Drug Administration (FDA) approval, although this is based on device performance and safety, not on a requirement for evidence of clinical efficacy.⁶

What is the evidence of uncertainty?

Lack of evidence of effectiveness

A 2014 Cochrane review identified 19 single centre randomised trials (1088 participants) that compared PRP with placebo, whole blood, dry needling, or no treatment for eight different soft tissue injuries, either as a direct treatment (for elbow lateral epicondylitis, patellar tendinopathy, and Achilles tendon

tendinopathy) or as an adjunct to surgery (anterior cruciate ligament reconstruction grafts and donor sites, rotator cuff repair, subacromial decompression, and Achilles rupture repair).⁷ Comparisons with other active treatments were not included. Most trials were judged to be at high risk of bias, with lack of standardisation of PRP preparation. Overall, there was no clinically significant improvement in pain and function with PRP. The authors of the Cochrane review concluded that there was insufficient evidence to support the use of PRP.

In our review of a further 10 randomised controlled trials (476 participants), we too had difficulty drawing clear conclusions about the efficacy of PRP, because of heterogeneous musculoskeletal conditions and outcome measures, underpowered studies, and poor reporting. Only half of these trials included analyses of PRP content and quality, and these showed marked differences in platelet concentration and white cell content; this is problematic, as different PRP preparations and application techniques could affect effectiveness.²

Possible harms

Autologous PRP is generally considered to carry a low risk of harm, but there are no high quality large scale clinical studies evaluating safety.⁸ Pooled data from the Cochrane review did not show a significant difference between PRP and comparator groups.⁷ Use of PRP may risk introducing infection, reported as an adverse event in two surgical randomised controlled trials.^{9 10} A recent PRP randomised controlled trial found that 2/160 (1%) of PRP samples were positive for microbial growth,

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This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the *Cochrane Library*. This paper is based on a research priority identified and commissioned by the National Institute for Health Research's Health Technology Assessment programme on an important clinical uncertainty. To suggest a topic for this series, please email us at uncertainties@bmj.com.

What you need to know

- Autologous platelet-rich plasma (PRP) is increasingly used to treat musculoskeletal soft tissue injuries, either on its own or as an adjunct to surgery
- Routine use is not recommended as there is insufficient evidence of clinical efficacy; instead, its use should be restricted to research settings
- Ensure patients receiving PRP are aware of the limited evidence of efficacy, so that they can make an informed decision about their care
- Clinicians should be aware of the concentration of PRP, and yield of bioactive proteins, produced by their selected preparation device

Search strategy and study selection

We used the same search strategy and eligibility criteria as a Cochrane review of PRP (randomised controlled trials of platelet-rich plasma (PRP) versus no PRP or placebo)⁷ in Medline and the Cochrane Library and Central Register Of Controlled Trials (up to 27 May 2015). We found a further 10 randomised controlled trials (476 participants), investigating PRP use for rotator cuff tendinopathy^{15,16} and surgical repair,^{9,20} acute hamstring injury,^{11,21} and elbow lateral epicondylitis.²²

although no clinical indicators of infection developed.¹¹ Infection risk may also vary with different PRP preparations as some have been shown to have antimicrobial properties in vitro.¹²

Is ongoing research likely to provide relevant evidence?

We searched the WHO International Clinical Trials Register and identified several ongoing randomised controlled trials evaluating PRP for a wide range of musculoskeletal soft tissue injuries. We are currently conducting the PATH-2 study, a randomised controlled trial to compare the effects on muscle-tendon function of a standardised PRP preparation versus dry needle injection (control) for non-operatively managed acute Achilles tendon rupture (ISRCTN54992179).

What should we do in the light of the uncertainty?

Routine use of PRP in clinical practice for musculoskeletal soft tissue injuries cannot be recommended given the lack of high quality clinical evidence supporting its efficacy. Thus the UK's National Institute for Health and Care Excellence (NICE) guidance for autologous blood injections, including PRP, for plantar fasciitis and tendinopathy states that it should “only be used with special arrangements for clinical governance, consent and audit or research,” even if there are no major safety concerns with use for these conditions.^{13,14}

We argue that patients should only be offered PRP for musculoskeletal soft tissue injuries within the context of well designed clinical trials, with informed consent, high quality verbal explanations, and supporting written information. Advise patients that there is currently insufficient evidence to show that it is effective treatment for musculoskeletal soft tissue injuries. Clinicians offering PRP should ask manufacturers for the evidence of the platelet and growth factor concentrations, the constitution, and the viability of their PRP product (platelet activation levels).

Contributors The idea for this article was formulated by KW in discussion with M Chew (associate editor, *BMJ*), DJK, and JA. DJK wrote the first draft of the paper, and KW and JA commented on it. All authors approved the final version and are the guarantors.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following interests: KW is chief investigator and JA and DJK are co-investigators on the PATH-2 trial evaluating platelet-rich plasma (PRP) as a treatment for acute Achilles tendon rupture. PATH-2 is funded by the Efficacy and Mechanism

Evaluation (EME) Programme, an MRC and NIHR partnership. KW receives royalties from Zimmer for previous orthopaedic implant design work.

The views expressed in this publication are those of the authors and not necessarily those of the MRC, NHS, NIHR or the Department of Health. PATH-2 uses the same PRP preparation device (supplied by Fannin UK) at all recruitment sites to standardise the intervention. No contract or agreements have been made with the manufacturer or supplier, nor will they have a role in the study design; data collection, access, analysis, or interpretation; writing of the report; or the decision to publish.

Provenance and peer review: Commissioned, externally peer reviewed.

Patient consent: Patient consent obtained.

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Recommendations for further research

Large multicentre randomised controlled trials with blinding of participants, outcome assessors, and where practical, clinical investigators—Patients with common high-burden musculoskeletal soft tissue injuries, receiving either platelet-rich plasma (PRP) or a placebo or inactive control intervention. Efficacy of PRP should be established before comparisons with other active interventions.

Outcome measures—Pain, patient reported function scales, physical performance tests, and return to sport, work, and social activities.

Trials should also evaluate:

- What cell and growth factor concentrations and platelet activation levels in PRP optimise clinical efficacy
- Optimal preparation process and delivery method for PRP (for example, whether injections need to be guided by imaging for some conditions)
- Specific timing or dose of PRP, or need for repeated injections
- Which validated clinical outcomes (such as recovery of musculoskeletal function) and outcomes important to patients (such as pain and longer term risk of re-injury) are the most appropriate
- The risk of adverse events, with careful monitoring and reporting of harms.

Large scale collaboration are needed to facilitate multicentre randomised controlled trials, expanding networks of clinicians and researchers.²³

How patients were involved in the creation of this article

A patient who previously had a tendon rupture and received PRP or a control treatment in a pilot randomised controlled trial gave feedback on the manuscript, which we incorporated in the revised paper. She highlighted the value of differentiating between clinical outcomes and outcomes important to patients, and the provision of clear verbal and written information to support patients.

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Figure

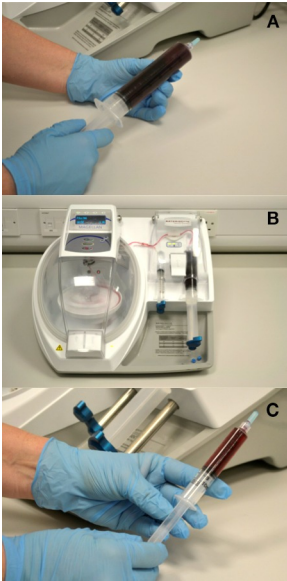


Fig 1 Making autologous platelet-rich plasma (PRP): a whole blood sample is taken (a) then a specialised centrifuge (such as the Magellan Autologous Platelet Separator System from Arteriocyte (b)) or filtration system is used to concentrate the platelets, and the resulting PRP is collected in a syringe for injection into the target tissue (c)