# Platelet-rich plasma injection for adults with acute Achilles tendon rupture: the PATH-2 RCT

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# Scientific summary

## The PATH-2 RCT

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# Scientific summary

## Background

Achilles tendon rupture (ATR) accounts for 20% of all tendon ruptures, and leads to significant health-care and societal costs. The current treatment strategies are (1) surgical repair or (2) immobilisation in a cast or boot. The mechanical and biological properties of healed tendons appear to never match those of the original intact tendons, leading to a high risk of re-rupture (3–5%) or reduced function and a loss of, on average, 63–108 days of work.

Platelet-rich plasma (PRP) is an autologous, supraphysiological concentration of platelets that also contains other blood cells. Platelets play an important role at various stages of the repair process of tendon injury. On activation, platelets release an ordered sequence of growth factors, cytokines and an array of bioactive proteins over the lifespan of the platelets. Subsequently, this leads to recruitment of leucocytes, local stem cells and tenocytes to initiate the healing process. Different methods of PRP preparation result in biological component variability, which may influence its efficacy.

In published studies, there is substantial variation in the validity and type of outcomes measured, as well as inconsistency in the observed effect size of PRP. The underpowered and inadequately designed studies suggest that no definite conclusions can be made on PRP application as an adjunct to standard care in the management of ATR. Prior to the PRP in Achilles Tendon Healing (PATH-2) trial, the authors of a meta-analysis of PRP for orthopaedic conditions concluded that there was a need for adequately powered studies using disease-specific and patient-important outcomes to investigate the effect of PRP (Sadoghi P, Rosso C, Valderrabano V, Leithner A, Vavken P. The role of platelets in the treatment of Achilles tendon injuries. *J Orthop Res* 2013;**31**:111–18).

## Objectives

- To evaluate the clinical efficacy of PRP among patients with acute ATR using an objective measure of mechanical muscle–tendon function.
- To evaluate the secondary outcome measures of patient-reported function, pain, participant goal attainment and quality of life.
- To determine the key components of PRP that may contribute to its mechanism of action.
- To identify the tissue-level parameters that PRP may alter to exert its effects in an exploratory biopsy substudy.

## Methods

### *Design*

A multicentre, parallel-group, participant- and outcome assessor-blinded randomised controlled trial comparing PRP with a placebo (imitation) injection in adults with acute ATR. Two substudies were embedded in the main study to contribute to the understanding of the PRP mechanism in tendon healing:

- substudy 1 – PRP and whole-blood analysis
- substudy 2 – immunohistochemistry analysis of ultrasound-guided needle biopsies from 16 participants at one centre (Oxford).

### *Setting*

The trial was conducted in the trauma and orthopaedic surgery departments of 19 NHS hospitals in England and Wales.

### Participants

Patients aged ≥ 18 years with an acute ATR attending an outpatient trauma or orthopaedic clinic within 12 days of sustaining the injury and suitable for non-surgical management were eligible for the trial.

The following patients were excluded:

- those with insertional or musculotendinous junction rupture
- those with previous tendon or ankle injury
- those with deformity to either lower leg
- those with a history of diabetes mellitus
- those with known platelet or haematological disorder
- those using systemic cortisone or anticoagulant treatment
- those with lower-limb gangrene/ulcers or peripheral vascular disease or hepatic or renal impairment
- pregnant or breastfeeding females
- those receiving radiotherapy or chemotherapy
- those with inadequate venous access
- those unable to participate in the trial or attend follow-up.

### Interventions

Participants were individually randomised to receive either PRP injection or placebo (dry-needle insertion to the tendon rupture gap), preceded by local anaesthetic, in a 1 : 1 allocation ratio. A central computer-based randomisation system utilising minimisation, stratified by centre and age group (< 55 years or ≥ 55 years), with a probabilistic element of 0.8 to reduce predictability, was provided by the Oxford Clinical Trials Research Unit. Immediately after randomisation, up to 55 ml of venous blood was taken from participants in the PRP group and up to 5 ml was taken in the placebo group. Both interventions were delivered using the same technique by a surgeon or extended-scope physiotherapist while maintaining a participant's blinding. Post injection, the remaining blood and PRP samples were sent to a central laboratory for substudy 1 analysis. Sixteen participants (nine in the PRP group and seven in the placebo group) in one centre (Oxford) received an ultrasound-guided biopsy for substudy 2 assays. All participants received standardised rehabilitation in terms of the duration of ankle immobilisation and non-weight-bearing, and all were referred for physiotherapy.

### Follow-up

Blinded outcome assessments were carried out at 4, 7, 13 and 24 weeks post randomisation. Following signed consent being obtained, baseline data were collected and the participant was randomised; in most cases, the injection treatment took place on the same visit. Primary outcome data were collected at a 24-week face-to-face appointment. At every time point, trial follow-up was carried out wherever possible by blinded assessors unaware of treatment allocation.

### Outcome measures

Muscle–tendon function assessed by the Limb Symmetry Index (LSI) of work (joules) during the heel-rise endurance test (HRET) at 24 weeks was the primary outcome. Movement of the heel during the HRET in each leg was captured using a computer-controlled linear encoder. The work LSI was calculated as follows: (injured limb measurement/uninjured limb measurement) × 100.

Secondary outcomes were the maximum heel-rise height and number of repetitions during the HRET and the patient-reported outcomes of function and symptoms [measured using the Achilles tendon Total Rupture Score (ATRS)], quality of life [measured using the Short Form questionnaire-12 items (SF-12) version 2 acute], pain (measured using the visual analogue scale and subscale from ATRS) and participant goal attainment [measured using the Patient-Specific Functional Scale (PSFS)].

In substudy 1, whole-blood and PRP samples were analysed for cell count, platelet activation and growth factor concentrations [i.e. platelet-derived growth factor (PDGF), insulin-like growth factor 1 (IGF-1), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and transforming growth factor beta (TGF-β)]. In substudy 2, 16 participants in one centre had needle biopsy under ultrasound guidance

at 6 weeks. Analysis included tissue morphology, proliferation, apoptosis, vascularity, metabolic indicators and collagen ratio.

### Analysis

The target sample size was 230 participants to provide 80% power. For the primary outcome, analysis included a modified intention-to-treat (mITT) population, defined as all randomised intention-to-treat participants with available work LSI data. Multivariate linear regression was used to investigate the effect of PRP on ATR recovery. Sensitivity analyses were carried out using imputation of values for missing HRET data to examine the robustness of the conclusions made from the analyses to address the primary aims of the trial.

A mITT population was also used for secondary outcome analyses. Linear mixed-effects regression models were used to allow the data collected at all follow-up time points to be taken into account, adjusting for pre-injury baseline scores when applicable. Data quality and effect of treatment received were assessed using complier-average causal effect (CACE) analysis in place of the originally planned per-protocol analysis. Complication events reported by participants were explored at two levels: serious adverse events and adverse events (AEs).

For the two substudies, analyses were primarily descriptive, and the relationship between various biomarkers and clinical outcomes was explored.

## Results

A total of 230 participants were recruited between July 2015 and September 2017. Of these, 114 were randomised to receive the PRP injection and 103 (90%) of these received the allocated treatment; 116 were allocated to, and received, placebo. At 24 weeks, 201 out of 230 participants (87.4%) completed the HRET to provide the work LSI primary outcome, and 216 out of 230 (93.9%) completed the patient-reported outcomes. One participant withdrew from the trial. The average age of participants was 45 years; 75% were male, with 69% of injuries occurring during sporting activity. The baseline characteristics of the participants in the intervention groups were well matched.

### Clinical trial results

There was no difference between the PRP and placebo groups at 24 weeks in the work LSI. In the PRP group ($n = 101$), the work LSI was 34.9%, compared with 38.3% in the placebo group ($n = 100$) [adjusted mean difference –3.872, 95% confidence interval (CI) –10.454 to 2.710; $p = 0.231$]. Statistical model adjustment by stratification factors and the predefined prognostic variables had no impact on the results attained. Sensitivity analyses accounting for participants with zero measurements for the uninjured limb (unable to lift the heel at all) in the HRET, individuals missing heel-rise repetitions, individuals missing the entire HRET data sets and compliance (i.e. CACE) showed that the results were robust.

There was no difference in secondary outcome results at 24 weeks: ATRS [PRP ($n = 107$), mean 64.9; placebo ($n = 109$), mean 65.6; adjusted mean difference –0.543; 95% CI –4.899 to 3.813; $p = 0.807$] and PSFS (PRP, $n = 109$, mean 7.198; placebo, $n = 107$, mean 7.495; adjusted mean difference –0.297; 95% CI –0.868 to 0.274; $p = 0.291$). ATRS-related pain scores were not different between the two groups in the follow-up period (PRP, $n = 109$, mean 7.661; placebo, $n = 107$, mean 7.449; adjusted mean difference 0.212; 95% CI –0.563 to 0.987; $p = 0.592$). Although no differences in the SF-12 physical component score were identified between the treatment groups (adjusted mean difference 0.805, 95% CI –1.269 to 2.879; $p = 0.447$), mean SF-12 mental component scores were lower in the PRP group than in the placebo group at 24 weeks (adjusted mean difference –2.714, 95% CI –5.242 to –0.187; $p = 0.035$). There was no difference between the PRP group and the placebo group in any of the patient-reported secondary outcomes at 4, 7 and 13 weeks. Daily pain over the 2 weeks after injection was not different between the groups (PRP, $n = 87$, mean 9.5; placebo, $n = 93$, mean 13.6; adjusted mean difference –4.019; 95% CI –10.302 to 2.265; $p = 0.210$). The two groups had similar AE rates related to their Achilles rupture or injection. The number of participants reporting at least one complication of any type related to their Achilles rupture or injection was 84 out of

113 (74%) for the PRP group and 90 out of 116 (78%) for the placebo group. The numbers of participants experiencing a re-rupture [PRP, 6/113 (5.3%); placebo, 4/116 (3.5%)] and deep-vein thrombosis [PRP, 6/113 (5.3%); placebo, 5/116 (4.3%)] were also similar.

### Substudy 1 results

Whole-blood cell counts (red blood cells, white blood cells and platelets) showed that the two groups were relatively well matched at baseline. Cell count analysis of PRP samples showed wide variation in cell counts. The mean platelet count was 852.6 × $10^9$/l [standard deviation (SD) 439.0 × $10^9$/l], with a wide range from 6.0 to 2903.0 × $10^9$/l. The mean white blood cell count was 15.1 × $10^9$/l (SD 10.3 × $10^9$/l), with a range of 1.7 to 65.3 × $10^9$/l. Red blood cells were reduced remarkably (0.9 × $10^{12}$/l, SD 1.5 × $10^{12}$/l, range 0.1 to 9.0 × $10^{12}$/l). The quality of the PRP samples in the majority of preparations was high, with low levels of basal activation, and they were capable of activation and degranulation. TGF-β, VEGF, PDGF, IGF-1 and FGF mean concentrations (133.4 ng/ml, 0.984 ng/ml, 55.49 ng/ml, 78.2 ng/ml and 112.5 pg/ml, respectively) were high, as expected. Overall, PRP samples were therefore shown to be functional, with the majority of platelets in the PRP preparations shown to be capable of activation and degranulation. Parameters of baseline whole blood taken before intervention in both groups did not correlate with the primary outcome measure at 24 weeks. PRP cell counts did not correlate with the primary outcome measure. None of the growth factor concentrations showed any correlation with the work LSI.

### Substudy 2 results

All biopsy results except one showed evidence of healing at 6 weeks; collagen fibre density was lower in the PRP group. This did not correlate with differences in cellularity or vascularity as these parameters were similar in both groups, suggesting equivalent healing processes.

## Conclusions

### *Implications for health care*

The main finding of the PATH-2 trial is that there was no evidence of benefit for PRP application in acute ATR in terms of objective and subjective efficacy outcomes. The effect size estimates of the primary outcome and end point and the consistency with patient-reported secondary outcomes during the follow-up strongly support the validity of the conclusion that PRP does not improve the outcome of ATR management. Although a health economic analysis was not carried out, applying PRP in ATR management would add to the cost of standard care for no clinically measured improvement in the outcome. It is a no-value intervention in ATR management.

### *Recommendations for research*

The implication of the PATH-2 trial is that the indication for PRP application in other soft-tissue injuries should be validated by similar robust clinical trials. The extent of functional asymmetry between injured and uninjured legs in this trial was substantial. Optimising recovery of tendon–muscle function during rehabilitation is therefore a recommended area of future investigation. An extended follow-up of PATH-2 participants at 2 years has started to evaluate longer-term patient-reported outcomes.

## Trial registration

This trial is registered as ISRCTN54992179.

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