Autologous Blood Injection to Treat Achilles Tendinopathy? A Randomized Controlled Trial

Jake Pearson, David Rowlands, and Ruth Highet

Context: Achilles tendinopathy is a common and often debilitating condition, and autologous blood injection is a promising treatment option. Objective: To determine whether autologous blood injection added to standard management was effective in alleviating symptoms of Achilles tendinopathy. Design: A prospective randomized controlled trial. Setting: Private sports medicine clinic. Patients: 33 patients (18 women, 15 men) of mean age 50 y (SD 9) with 40 cases of Achilles tendinopathy of mean duration of 11 mo (SD 7). Intervention: Participants were randomized to blind peritendinous autologous blood injection added to standard treatment (eccentric-loading exercises) or standard treatment alone for 12 wk. Main Outcome Measure: Victorian Institute of Sport Assessment for Achilles (VISA-A) score and ratings of discomfort during and after the injection were measured at baseline and 6 and 12 wk. Analytically derived effect-size thresholds of 5 (small) and 15 (moderate) VISA-A units were used as the reference values for clinical inference. Results: Improvements in VISA-A of 7.7 units (95%CL: ± 6.7) and 8.7 units (± 8.8) were observed in the treatment and control groups, respectively, at 6 wk relative to baseline, with no clear effect of blood injection. At 12 wk VISA-A score improved to 18.9 units (± 7.4) in the treatment group, revealing a blood-injection effect of 9.6 units (± 11.5), relative to a comparatively unchanged condition in control (9.4 units; ± 9.0). Predictors of response to treatment were unremarkable, and a 21% rate of postinjection flare was the only noteworthy side effect. Conclusions: There is some evidence for small short-term symptomatic improvements with the addition of autologous blood injection to standard treatment for Achilles tendinopathy, although double-blinded studies with longer follow-up and larger sample size are required.

Keywords: rehabilitation, sport, injection therapy

Achilles tendinopathy is a common and often debilitating condition that most commonly involves the midportion of the tendon. Etiology usually links overuse or a sudden change in loading pattern to microscopic tearing, which engenders subsequent failure of the normal healing response, leading to the degenerative condition of tendinosis. Mechanical, age-related, genetic, and vascular factors are thought to contribute to this maladaptive response, with subsequent neovascular ingrowth suggested as a potential mediator of pain.

Most Achilles tendinopathy cases respond to a conservative treatment program based around eccentric strengthening, and a variety of adjunctive treatment options exist for those who do not respond adequately to this. A number of case series have reported promising results for autologous blood injections for tendinopathy around the elbow and knee. Autologous blood injection has been compared with corticosteroid injection for the treatment of plantar fasciopathy and lateral elbow tendinopathy, with autologous blood injection recommended as a potential treatment alternative. A recent high-quality double-blinded randomized controlled trial investigating the effect of platelet-rich-plasma (PRP) injection on Achilles tendinopathy found no difference from placebo saline injection, but there have been no published studies specifically investigating autologous blood injection for Achilles tendinopathy.

The aim of the current study, therefore, was to determine the short-term effectiveness of the addition of autologous blood injections to standard conservative management of mid-Achilles tendinopathy in clinical practice. Secondary aims were to determine potential clinical or radiological predictors of response and document the tolerability and safety of this technique.

Methods

Design

Thirty-three patients with 40 injured Achilles tendons were recruited and randomized to standard treatment plus autologous blood injection (treatment) or standard...
treatment alone (control). Bilateral tendinopathy cases were randomly allocated with 1 tendon to the treatment group and 1 to the control group. All patients had a baseline ultrasound scan to confirm the presence of tendinopathy and assess the presence and degree (nil = 0, mild = 1, moderate = 2, or severe = 3) of neovascularization. The ultrasound scans were performed with either a Siemens Antares (Mountain View, CA) or Toshiba Aplio (Otawara, Japan) machine using high-frequency linear probes and compound imaging. Both groups received instructions on a rehabilitation program and were seen for follow-up at 6 and 12 weeks. In addition, the treatment group was offered an autologous blood injection after the initial visit and, in some cases, when deemed clinically appropriate, a second injection after the 6-week visit (Figure 1). Offering a second injection to only clinically appropriate patients was intended to replicate real-life clinical practice. No placebo injection was performed; hence, neither patients nor treatment providers were blind to the treatment allocation.

**Patients**

Thirty-three patients with a total of 40 injured Achilles tendons who fulfilled the inclusion criteria were recruited through a specialist sports medicine clinic in 2008. Baseline patient characteristics are presented in Table 1. Ethical approval was obtained from the Central Regional Ethics Committee, New Zealand. An information sheet was provided and written consent obtained from all participants. For inclusion in the study, participants had to meet the eligibility criteria of a diagnosis of mid-Achilles tendinopathy (activity-related pain of gradual or semicute onset, postinactivity stiffness, and tenderness, swelling, and nodularity localized to the midtendon) with duration of symptoms of at least 3 months. Exclusion criteria included diagnostic uncertainty or concurrent presence of insertional pathology, anticoagulant therapy, systemic disease that may contribute to pathology; being an elite-level sportsperson; or having received any injection therapy for the tendon within the last 3 months.

**Table 1 Patient Characteristics**

<table>
<thead>
<tr>
<th>Total tendons</th>
<th>Treatment group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>(male, female)</td>
<td>20 (8, 12)</td>
<td>20 (7, 13)</td>
</tr>
<tr>
<td>Involved side</td>
<td></td>
<td></td>
</tr>
<tr>
<td>left</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>right</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Age, y</td>
<td>49 (8.8; 34–65)</td>
<td>51 (7.6; 42–70)</td>
</tr>
<tr>
<td>Duration of symptoms, mo</td>
<td>13 (10; 3–36)</td>
<td>9 (10; 3–36)</td>
</tr>
<tr>
<td>Baseline VISA-A score</td>
<td>54 (26; 16–94)</td>
<td>52 (25; 13–89)</td>
</tr>
</tbody>
</table>

Data presented as centralized distributions are mean (SD; range).

**Procedures**

Standard treatment focused on the Alfredson eccentric strengthening program, with identical prescription and encouragement provided to both groups. The exercises were explained and the technique demonstrated. A mild to moderate degree of pain while performing the exercises was endorsed, and instructions were given to progressively increase loading. Participants were permitted to continue with nonsurgical treatments already initiated but were told not to take nonsteroidal anti-inflammatory drugs (NSAIDs), as they may mask symptoms and interfere with the goal of tendon strengthening. Any activities that were clearly aggravating symptoms were discontinued for the treatment period, but patients were encouraged to remain active, often with alternative lower-impact forms of exercise.

The injection was performed with the patient prone. The subcutaneous and ventral peritendinous tissue were anesthetized using a 23-gauge needle and syringe containing 1 mL of 1% lignocaine via a medial approach under aseptic technique, centered at the point of maximal tenderness of the midtendon. The syringe was disconnected but the needle left in situ; a fresh needle was then used to obtain 3 mL of venous blood from the antecubital fossa. The blood-filled syringe was then immediately reconnected to the needle and injected peritendinously under low resistance. The patient was asked to massage the area for 5 min immediately afterward and return to eccentric exercises within 48 hours, once any postinjection pain had settled.

The primary outcome measure selected was the Victorian Institute of Sport Assessment for Achilles (VISA-A) questionnaire, completed at the initial (baseline) and 6- and 12-week visits. Secondary outcome measures were ratings of perceived discomfort during and after the injection. The treatment group was asked to rate on a Likert scale the degree of discomfort experienced during the injection procedure (4 options: no significant discomfort, mild discomfort, moderate discomfort, or severe pain) and over the 48 hours after injection, relative to preinjection (5 options: improved, no change, mild discomfort, moderate discomfort, or severe pain).

**Statistical Analyses**

Sample size was estimated by magnitude-based clinical inference. In the absence of empirical data, the smallest effect size of 0.2 times mean population variation (SD_between) in VISA-A score of 1714 was used as the value for smallest meaningful clinical change, with test–retest reliability (SD) calculated from Pearson \( r = .93, 14 \) where

\[
SD = \sqrt{(1-r)} \times SD_{\text{between}}
\]

The calculations resulted in \( N = 40 \).

The effect of autologous blood injection on VISA-A was estimated with mixed modeling (SAS Version 9.1, SAS Institute, Cary, NC). An intention-to-treat repeated-
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A measures model was constructed with time (baseline and 6 and 12 weeks) and group as the fixed effects. The standardized baseline VISA-A score was included in the model as a covariate. Furthermore, because there is some evidence suggesting that the degree of neovascularization might influence pain associated with the tendinopathy, we also included our neovascularization assessment as a second moderating covariate and present outcomes with and without this adjustment. Finally, whether 1 or 2 injections were administered was included as a third covariate, but this had no appreciable impact on the uncertainty or inference so was excluded. Measures of centrality and spread for participant descriptive data are means and SDs. Means for outcome data are least-squares means derived from the analysis.

We made inferences about the population values of statistics via magnitude-based clinical inference. Statistical precision is presented as 95% confidence limit (CL) or confidence interval (CI). To qualify the magnitude of outcomes, data were standardized and inferences about the population value determined using effect size (trivial 0.0–0.2, small 0.2–0.6, moderate 0.6–1.2, large 1.2–2.0, very large 2.0–4.0). The effect-size thresholds were derived from the analysis to provide an objective estimate of small (5 VISA-A units) and moderate (15 units) clinical-effect thresholds, where as defined by Cohen small effects are just perceptible, and moderate effects are clearly perceptible but not so great as to be defined as large. Likelihood-based clinical inference was provided from the probability of a small meaningful increase or decrease calculated from the 2-tailed t distribution, where outcomes were inferred as 1%, almost certainly not; 1% to 5%, very unlikely; 5% to 25%, unlikely; 25% to 75%, possible; 75% to 95%, likely; 95% to 99%, very likely; and 99%, almost certain. As defined by Hopkins et al, we adopted the suggested default probabilities for declaring an effect clinically beneficial when the likelihood is <0.5% (most unlikely) for harm and >25% (possible) or >75% (likely) for benefit. A clinically unclear effect is therefore possibly beneficial (>25%) with an unacceptable risk of harm (>0.5%).

Results

There were more female than male participants in the study (Table 1) and 7 cases of bilateral tendinopathy, all in female patients. One patient with bilateral tendinopathy withdrew soon after the baseline visit due to unrelated medical reasons and was not included in further analyses. Three other patients (4 tendons, 2 from each group) did not complete the study for unknown reasons, and 6 questionnaires were not recovered. Consequently, the final number of tendons available for analysis of VISA-A scores was 36 at 6 weeks and 28 at 12 weeks (Figure 1). No patients reported taking NSAIDs, but this was not formally recorded.

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**Figure 1** — Flow diagram of study design, cohort response, and time points for autologous blood injection and sampling.
Of the 19 tendons in the treatment group, 9 received 1 injection (baseline only) and 10 received 2 injections (baseline and 6 weeks). Criteria for offering a repeat injection were no severe pain after the initial injection, significant residual symptoms, a plateau or unacceptably slow rate of improvement, and willingness on the part of the patient to proceed.

The tendon response to conventional treatment and autologous blood injection is presented in Figure 2. There were likely small improvements in VISA-A score at 6 weeks, but the effect of blood injection was inconclusive. At 12 weeks, however, VISA-A increased further by a similar magnitude in the blood-injected tendons to yield an almost certainly meaningful moderate-size improvement relative to baseline (likelihood of clinically substantial benefit 100%, substantial harm 0.0%), but there was no clear change from 6 weeks in the control tendons; the net blood-injection effect was a likely small increase relative to control occurring between observations at weeks 6 and 12 (clinical likelihoods benefit/harm: 82.7%/0.4%; effect unadjusted for neovascularization 9.1 units 95% CL ± 11.6; clinical likelihoods benefit/harm: 75.7%/0.8%).

There was no clear association between age or duration of symptoms and baseline VISA-A score. Although outcomes were highly variable and nonuniformly distributed, improvement in VISA-A score from baseline to 6 and 12 weeks for all tendons trended lowest when the degree of neovascularization was moderate compared with nil, mild, or severe (data not shown).

![Figure 2](image)

**Figure 2** — Effect of conventional treatment for Achilles tendinopathy with (treatment) and without (control) autologous blood injection on VISA-A scores at 6 and 12 weeks. (A) Least-squares mean effect, where the vertical bars are the composite between-participants SD (gray bar = control) derived from the analysis. (B) Likelihood of clinical outcomes for VISA-A scores, where data points are the observed mean response and bars the 95% confidence intervals.
Most patients described the discomfort experienced during the injection (including local anesthesia) as mild (Figure 3A). One patient rated it as severe, which corresponds to a risk of 3% of severe discomfort experienced during the injection. There was greater variability in the change in discomfort over the 48 hours after the injection, but most patients rated this as mild or moderate (Figure 3B). Six patients rated this as severe, which corresponds to a risk of 21%. Anecdotally, in 3 of these patients this marked worsening of symptoms persisted for up to 2 weeks postinjection. There were no infections and no tendon ruptures.

Discussion

The current study is the first to our knowledge to evaluate the efficacy of peritendinous autologous blood injections for Achilles tendinopathy via a randomized controlled design. Our findings suggest that the addition of autologous blood injection to standard conservative management of Achilles tendinopathy could provide a small clinical reduction in symptoms over a 12-week period.

Our work adds to the promising results of previous case-series reports on the use of autologous blood injection in tendinopathy. The thresholds for small and moderate meaningful clinical effects of 5 and 15 calculated from the standard deviation of the study sample encompass the subjective value of 12 for the clinical threshold used in a recent PRP intervention.11 Furthermore, dose-response research is required to clarify objectively the value for meaningful clinical change in VISA-A; subjective thresholds are insufficient. Comparison of the treatment response in the current study with that in other intervention studies for Achilles tendinopathy can be limited by different outcome measures and follow-up durations. A recent randomized controlled trial on PRP11 reported a mean improvement in VISA-A of 21 in both groups in a patient demographic similar to our study over twice the duration (24 weeks). The responses at the 6- and 12-week marks were similar to those of our control group at the same time points. Randomized controlled trials on Aprotinin19 and shock-wave treatment20 have likewise reported improvements in VISA-A of 20 to 25 in both treatment and eccentric-exercise control groups over a 3- to 4-month period, all of which are within the range of estimate uncertainty in the current study (Figure 2). All these studies also had both groups of patients performing eccentric strengthening exercises. Direct comparison with the previous randomized controlled trials of autologous blood injection5–10 is difficult due to different outcome measures used; in addition, corticosteroid injection is an unsuitable comparison for Achilles tendinopathy due to concerns about an increased risk of rupture.

Patients in the current study were encouraged to continue their eccentric loading regimen once any postinjection flare in symptoms had resolved. Some patients appear to respond adequately to a single injection, whereas others may gain further benefit from 1 or more repeat injections. The 6-week period between injections was based on the estimated period for a reasonable tendon-healing response; a range of 4 to 6 weeks has been suggested by previous authors.5–8 While a 12-week follow-up is acknowledged as a short period for a relatively metabolically inactive tissue such as a tendon, in a rabbit model Taylor et al11 reported tendon-strength improvements 12 weeks after autologous blood injection. There may, however, be a longer delay before any change is clinically detectable.

In previous published reports on autologous blood injections, the injections were aimed either intratendinously under ultrasound guidance6–8 or, as performed in the current study, peritendinously without image guidance.5,8,10 Whether these different approaches result in a clinically important difference is unknown. Advocates of the intratendinous approach propose that placing the blood in areas of tendon disruption maximizes potential stimulation of tendon healing; it could also be argued, however, that the smaller blood components will spread into the affected area given the compromised tendon structure. Another obvious comparison is between the injections of whole blood versus PRP; however, no research to date has directly compared these. Comparison has already been made between the outcomes of this study and those of de Vos et al11 on (ultrasound-guided intratendinous) PRP injection for Achilles tendinopathy. If platelet-derived growth factors are indeed the active ingredient and more is better, then PRP should in theory be more effective; however, neither of these assumptions has been proven. A key practical advantage of the autologous blood-injection technique described here is its relative simplicity and lack of requirement for processing or technical equipment including ultrasonography.
We strongly considered performing a placebo injection in order to blind participants but did not due to the possibility of therapeutic benefits from the needling required. Consequently, there was no blinding of participants, introducing potential subjective bias; however, care was taken to minimize this by stating to participants that the efficacy of autologous blood injection is as yet unknown. Administering either 1 or 2 injections to the treatment group was intended to most accurately replicate clinical practice and therefore improve real-life applicability of findings, but it introduced a further variable that could influence outcomes. However, including the second injection as a covariate in the statistical analysis resulted in no appreciable impact on outcomes, providing some additional support that the observed improvement in VISA-A at 12 weeks could be placebo. Equally possible was that clinical judgment was correct and the patients required the repeat injection or, alternatively, that the clinical effect of injection is delayed longer than the follow-up duration. The separation of bilateral tendinopathies into different groups may complicate the data interpretation somewhat, but this effect was accounted for by including participant as a random effect. A further limitation of this study is the dropout rate, which at 30% was in the midupper range for clinical intervention trials of this type. Clearly, a larger number of participants and no dropouts would have resulted in greater statistical power, lowering the uncertainty of estimate.

We observed no clear relationship between the degree of neovascularization on ultrasound scan and the response to autologous blood injection, other than some indication that the response to treatment was least when neovascularization was graded as moderate. The lack of a validated grading system for neovascularization is acknowledged. While it would be useful to identify baseline predictors of response to treatment, the relationship between symptoms, neovascularization, and treatment response appears more complex, in keeping with the conclusions of de Vos et al.\(^2\)

The main side effect seen over the period studied was a 21% risk of severe worsening of pain over the 48 hours postinjection, although the rating scales used have not been previously validated. Previous case series with longer follow-ups have likewise reported no serious complications such as infections or ruptures. Any injection of whole blood continues to remain a doping offense in elite sportspersons,\(^23\) with a failure thus far to differentiate between the practice of intravenous infusion for oxygen-transfer enhancement and peritendinous or intratendinous injection for injury rehabilitation. The current cohort was a middle-aged to older patient group, and hence application to a younger population is cautioned.

Conclusion

We provide some evidence that the addition of autologous blood injection to standard conservative treatment for Achilles tendinopathy could result in a likely clinically small short-term mean improvement in VISA-A score. Nevertheless, we regard the current outcomes as pilot evidence, longer-term effects remain uncertain, and the method is currently technically prohibited for athletes subject to doping control. Further carefully constructed higher-powered double-blinded clinical trials are suggested to clarify a true physiological effect by eliminating the possibility of placebo, to compare injection techniques, and to determine the mechanism of action to validate and refine the intervention in clinical practice.

Acknowledgments

Pacific Radiology (Wellington, New Zealand) performed the ultrasounds free of charge to the patients.

References


12. Randomization plan generator (select first generator, use seed 21383, labels “treatment” and “control,” 2 blocks of 20 subjects each). http://www.randomization.com


